Measurement of Cerebrovascular Reactivity in Pediatric Patients With Cerebral Vasculopathy Using Blood Oxygen Level-Dependent MRI

Jay S. Han, MSc; David J. Mikulis, MD; Alexandra Mardimae, MSc; Andrea Kassner, PhD; Julien Poublanc, MSc; Adrian P. Crawley, PhD; Gabrielle A. deVeber, MD; Joseph A. Fisher, MD; William J. Logan, MD

Background and Purpose—Cerebrovascular reactivity (CVR) is an indicator of cerebral hemodynamics. In adults with cerebrovascular disease, impaired CVR has been shown to be associated with an increased risk of stroke. In children, however, CVR studies are not common. This may be due to the difficulties and risks associated with current CVR study methodologies. We have previously described the application of precise control of end-tidal carbon dioxide partial pressure for CVR studies in adults. Our aim is to report initial observations of CVR studies that were performed as part of a larger observational study regarding investigations in pediatric patients with cerebral vascular disease.

Methods—Thirteen patients between the ages of 10 and 16 years (10 with a diagnosis of Moyamoya vasculopathy and 3 with confirmed, or suspected, intracranial vascular stenosis) underwent angiography, MRI, and functional blood oxygen level-dependent MRI mapping of CVR to hypercapnia. The results of the CVR study were then related to both the structural imaging and clinical status.

Results—Sixteen blood oxygen level-dependent MRI CVR studies were performed successfully in 13 consecutive patients. Twelve of the 13 patients with angiographic abnormalities also had CVR deficits in the corresponding downstream vascular territories. CVR deficits were also seen in 8 of 9 symptomatic patients and 2 of the asymptomatic patients. Notably, in patients with abnormalities on angiography, the reductions in CVR extended beyond the ischemic lesions identified with MR structural imaging into normal-appearing brain parenchyma.

Conclusions—This is the first case series reporting blood oxygen level-dependent MRI CVR in children with cerebrovascular disease. CVR studies performed so far provide information regarding hemodynamic compromise, which complements traditional clinical assessment and structural imaging. (Stroke. 2011;42:1261-1269.)

Key Words: BOLD MRI ■ cerebral hemodynamic ■ cerebrovascular reserve ■ CVR ■ intracranial stenosis ■ moyamoya disease ■ MRI ■ pediatric ■ vasculopathy

Structural imaging of the brain with CT, MRI, MR angiography, and conventional angiography is capable of identifying areas of parenchymal injury and large vessel occlusion. However, these imaging modalities provide no information about hemodynamics, an important element in understanding the pathophysiology of vascular diseases.

Cerebrovascular reactivity (CVR), defined as a change in cerebral blood flow in response to a vasodilatory stimulus, reflects the vasodilatory reserve capacity of the cerebral resistance vessels.1 Focal narrowing of a main cerebral supply vessel decreases the downstream cerebral perfusion pressure, which results in compensatory vasodilation. Reductions in CVR are therefore interpreted as an encroachment on the finite compensatory vasodilatory capacity that, when exhausted, can result in a reduction in perfusion, or “steal phenomenon,” in response to a global vasodilatory stimulus. Indeed, in adults, paradoxical reductions in blood flow to vasodilatory stimuli have been shown to be associated with an increased risk of stroke in the affected vascular area.2–4 However, CVR studies have not been routinely performed in children at risk of stroke. This may be due in part to the level of cooperation required for voluntary respiratory maneuvers, a reluctance to administer systemic vasodilatory agents, and, more importantly, a disinclination to expose children to ionizing radiation.

We have developed a noninvasive method for mapping CVR that combines a standardized (ie, precise, repeatable) method of controlling end-tidal partial pressure of CO2...

Received September 21, 2010; accepted October 28, 2010.
From the Departments of Anesthesia (J.S.H., A.M., J.A.F.) and Medical Imaging (J.S.H., D.J.M., J.P., A.P.C.), University Health Network, Toronto, Ontario, Canada; the Department of Physiology (J.S.H., J.A.F.), University of Toronto, Toronto, Ontario, Canada; and the Departments of Medical Imaging (A.K.) and Pediatric Neurology (G.A.d.V., W.J.L.), The Hospital for Sick Children, Toronto, Ontario, Canada.
Correspondence to David J. Mikulis, MD, The Toronto Western Hospital, University Health Network, 399 Bathurst Street, 3MC-431, Toronto, Ontario, Canada M5T 2S8. E-mail david.mikulis@uhn.on.ca
© 2011 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.110.603225
1261
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Visit</th>
<th>Clinical Presentation</th>
<th>Angiography Result</th>
<th>MRI Result</th>
<th>CVR Result</th>
<th>CVR Deficits in Normal Brain</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Occasional headaches</td>
<td>Occluded left ICA, diminished left MCA, right PCA calibre</td>
<td>High signal abnormalities in the occipital lobes consistent with NF-1</td>
<td>Exhausted cortical and subcortical CVR in left MCA and left PCA territory extending into angiographically normal tissue</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 months follow-up from initial CVR study; 8 months postleft-sided indirect EC-IC bypass</td>
<td>Clinically asymptomatic</td>
<td>Ocluded left MCA, filling of pial collaterals through STA</td>
<td>Stable, no change</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Involuntary hand movements</td>
<td>Diminished caliber left ICA, left MCA, and left ACA</td>
<td>Bilateral hemispheric white matter T2 hyperintensities</td>
<td>Diminished CVR left MCA territory</td>
<td>Yes</td>
<td>. . .</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>F</td>
<td>Left MCA stenosis</td>
<td>Initial CVR study</td>
<td>Progressive headache, right arm weakness</td>
<td>Diminished caliber left MCA at M1/M2 junction</td>
<td>Normal</td>
<td>Diminished CVR left MCA territory</td>
<td>Yes</td>
<td>. . .</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>F</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Asymptomatic</td>
<td>Diminished left MCA</td>
<td>Bilateral hemispheric white matter T2 hyperintensities</td>
<td>Left MCA, left ACA territory diminished CVR with paradoxical reactivity; extending beyond T2 findings</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>F</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Bilateral headaches, slurred speech, right foot weakness, left facial droop</td>
<td>Bilateral stenosis at the origins of ACA, MCA with no collaterals</td>
<td>Focal left hemispheric T2 hyperintensities</td>
<td>Exhausted CVR with steal in left ACA, left MCA, and left PCA territories</td>
<td>Yes</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Resolution of previous symptoms; new onset of daily periodic left arm and leg numbness and palsy</td>
<td>Increasing right ACA and right MCA stenosis and with even greater worsening of the left ACA and left MCA stenosis</td>
<td>Unchanged</td>
<td>Improved CVR on the left side, worsened CVR on right side extending beyond T2 abnormalities</td>
<td>Yes</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinically stable</td>
<td>Unchanged</td>
<td>Ischemic changes in the posterior right superior frontal gyrus</td>
<td>CVR improved in right hemisphere and left hemisphere remains stable</td>
<td>Yes</td>
<td>. . .</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Visit</th>
<th>Clinical Presentation</th>
<th>Angiography Result</th>
<th>MRI Result</th>
<th>CVR Result</th>
<th>CVR Deficits in Normal Brain</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>13</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Asymptomatic</td>
<td>Occluded left MCA</td>
<td>Multiple T2 hyperintensities</td>
<td>Diminished left MCA territory CVR with steal</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>F</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Transient episodes of right hand numbness</td>
<td>Bilaterally reduced caliber of ICAs</td>
<td>Left hemispheric white matter hyperintensity</td>
<td>Diminished CVR with steal bilaterally in ACA and MCA territories</td>
<td>Yes</td>
<td>Rhabdomyosarcoma/ radiation therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 months follow-up from last CVR study</td>
<td>Asymptomatic</td>
<td>No change</td>
<td>Stable, no change</td>
<td>Improved CVR in ACA and MCA territories</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Bilateral arm and leg weakness, headaches</td>
<td>Bilateral distal ICA stenosis</td>
<td>Old hemorrhage in putamen</td>
<td>Diminished CVR with steal bilaterally in ACA and MCA territories</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>M</td>
<td>Left MCA stenosis</td>
<td>Initial CVR study</td>
<td>Headaches</td>
<td>Left MCA stenosis</td>
<td>Focal bilateral T2 hyperintensities</td>
<td>Diminished Reactivity left MCA territory</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>F</td>
<td>Possible MCA stenosis</td>
<td>Initial CVR study</td>
<td>Headaches</td>
<td>Normal Angiogram</td>
<td>Bilateral hemispheric white matter T2 hyperintensities</td>
<td>Normal</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Headaches</td>
<td>Occluded left MCA</td>
<td>Focal bilateral T2 hyperintensities</td>
<td>Diminished CVR with steal in left ACA, left MCA, and left PCA territories</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Headaches</td>
<td>Occluded left ICA, diminished left MCA calibre</td>
<td>Focal bilateral T2 hyperintensities</td>
<td>Diminished CVR with steal in left MCA territory</td>
<td>Yes</td>
<td>NF-1</td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>M</td>
<td>Moyamoya disease</td>
<td>Initial CVR study</td>
<td>Left body hemisensory loss</td>
<td>Occluded right ICA</td>
<td>Normal</td>
<td>Exhausted CVR with steal in right ACA and right MCA territories</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

CVR indicates cerebrovascular reactivity; M, male; F, female; MCA, middle cerebral artery; EC-IC, extracranial–intracranial; PCA, posterior cerebral artery; STA, superficial temporal artery; ACA, anterior cerebral artery; ICA, internal carotid artery; NF-1, neurofibromatosis Type 1.
PETCO2 and end-tidal partial pressure O2 (PetO2) as the vasoactive stimulus and blood oxygen level-dependent (BOLD) MRI to assess changes in regional blood flow. The use of this method has been reported in adults with cerebrovascular disease5,6 and in a single pediatric patient with subclavian steal syndrome.7 We report here our experience with BOLD MRI CVR in our first 13 consecutive patients of a larger observational study on the pathophysiology of stroke in children.

Patients and Methods

Ethics and Consent
Institutional Review Board approval was obtained for this study. The entire protocol was reviewed with each subject and informed consent was obtained from the patient and the patient’s parents, as applicable.

Eleven patients were symptomatic: headaches (5), motor and/or sensory deficits (4), and both headaches and motor and sensory deficits (2). Two patients were asymptomatic and were undergoing a battery of screening tests requested by the referring neurologist when they were recruited for this study. All patients had undergone catheter angiography, MR angiography, or both. Thirteen patients (8 males; age range, 10 to 17 years; median age, 14 years) underwent at least 1 CVR study. Three patients underwent additional follow-up CVR (refer to the Table for time course and the “Discussion” for patient details). Of the 13 patients, 10 had diagnosis of moyamoya disease, 2 had confirmed, and 1 suspected idiopathic intracranial vascular stenosis (however, a repeat MR angiogram performed at our institution showed normal vasculature).

Magnetic Resonance Imaging
MRI was performed on a 3.0-T scanner (Signa HDX platform; GE Healthcare, Milwaukee, WI) with an 8-channel phased-array head coil. For coregistration with the MRI CVR measures, T1-weighted anatomic images were acquired using a 3-dimensional spoiled gradient echo pulse sequence (whole brain coverage; matrix: 256×256; slice thickness: 2.2 mm; no interslice gap). BOLD MRI CVR data were acquired with a T2*-weighted single-shot gradient echo pulse sequence with echoplanar readout (field of view: 24×24 cm; matrix: 64×64; TR: 2000 ms; TE: 30 ms; flip angle: 85°; slice thickness: 5.0 mm; interslice gap: 2.0 mm, number of temporal frames=254).

Respiratory Protocol
PetCO2 and PetO2 were controlled using a model-based prospective end-tidal targeting approach.8 A computer-driven gas blender supplied sequences of gas concentrations to sequential rebreathing circuit (RespirAct; Thornhill Research Inc, Toronto, Canada). Subjects breathed from the circuit through a plastic face mask secured to the subject’s face using transparent medical dressing (Tegaderm; 3M, St Paul, MN) to assure an airtight seal. The end-tidal sequences

Figure 1. ICA Occlusion. Patient 13, Table. A, Three-dimensional time of flight circle of Willis MR angiography demonstrating stenotic right middle cerebral artery (MCA; arrow); axial T2 fluid-attenuated inversion recovery demonstrating normal-appearing brain parenchyma in left MCA territory; cerebrovascular reactivity (CVR) map demonstrating reduced CVR and vascular steal (blue) in the right MCA territory. B, End-tidal partial pressure of CO2 (PetCO2) and blood oxygen level-dependent (BOLD) signal time course data. Positive correlation. C, PetCO2 and BOLD signal time course data. Negative correlation (steal phenomenon).
consisted of iso-oxic (mean ± SD; PetO₂ = 100 ± 2 mm Hg) step changes in PetCO₂ from baseline to PetCO₂ 40 ± 1 mm Hg (normocapnia) for 60 seconds, then to PetCO₂ 50 ± 1 mm Hg (hypercapnia) for 60 seconds, return to normocapnia for 100 seconds, then repeat hypercapnia for 180 seconds, and return to normocapnia for 110 seconds. Tidal gas concentrations were continuously sampled from the mask and analyzed for PCO₂ and PO₂. Data were digitized and recorded using customizable software (LabView; National Instruments Corporation, Austin, TX). The same software was configured to automatically identify end-tidal values of PCO₂ and PO₂.

BOLD MRI CVR Mapping
MRI and PetCO₂ data were imported into MRI data analysis software, AFNI Version 12. Each patient’s overall BOLD MRI signal was time-aligned with the PetCO₂ waveform. The BOLD MRI signal from each voxel was then correlated to the PetCO₂. Each correlation between PetCO₂ and BOLD MRI signal was calculated with the value color-coded from a spectrum with red to yellow indicating high to slight correlation (Figure 1B), colorless indicating no correlation (ie, no change in BOLD signal with changes in PetCO₂), and a range of light blue to dark blue indicating slight to a strong negative correlation (Figure 1C). A decrease in BOLD signal represents a redistribution of blood flow away from the corresponding vascular territory during a global vasodilatory stimulus, or “vascular steal” (Figures 1A and 1C). Voxels were then overlaid the patient’s anatomic scans to generate CVR maps.

Assessment of Angiography, Structural Imaging, and Clinical Status
All structural MRI and MR or conventional angiograms acquired at our, or the referring, institution were reviewed with a staff neuroradiologist (D.J.M.). Clinical histories were obtained from the referring pediatric neurologist (G.A.d.V. and W.J.L.).

Results
The clinical presentations and the results of angiography, structural MRI, and CVR studies are summarized in the Table.

Angiography Versus Initial CVR
Twelve patients with angiographic abnormalities had a reduced CVR in the corresponding parenchymal territories (see Figure 1 for sample case; Patient 13 in Table). The one patient who had a normal angiogram had a normal CVR study (Figure 2A; Patient 10 in Table).

Clinical Presentation and CVR
All 6 patients who presented with focal neurological deficits (motor and/or sensory deficits) demonstrated reductions in CVR in the corresponding brain territories. In the 5 patients who presented with nonfocal neurological deficits (head-
aches), 4 demonstrated reductions in CVR in vascular territories supplied by abnormal vessels as identified by angiography. The single patient who presented with headaches and a normal angiographic study also had a normal CVR study (Figure 2A). The remaining 2 asymptomatic patients also demonstrated concordance between abnormal angiographic findings and reductions in CVR.

Structural Imaging Versus Initial CVR
All but 1 of the 13 patients in this study had ischemic changes in the brain parenchyma identified with structural MRI. In each of these patients, the mapped reductions in CVR extended beyond the ischemic lesions into normal-appearing brain parenchyma.

Effect of Surgical Intervention on CVR
Three of the patients in this study underwent follow-up CVR studies. Two of these patients were imaged after surgical intervention. The first patient (Patient 1, Table) had a diagnosis of neurofibromatosis Type 1 and presented with generalized headaches without focal neurological signs. Time-of-flight MR angiography and conventional angiography both revealed stenosis of the cavernous portion of the left internal carotid artery and total occlusion of the supraclinoi-d internal carotid artery and M1 segment of the left middle cerebral artery with a reduction in the calibre of the left posterior cerebral artery. The initial CVR study showed reduced reactivity in the left hemisphere. The patient subsequently underwent a left-sided indirect extracranial to intracranial arterial bypass. After surgery, the patient noted fewer episodes of headaches. A subsequent CVR study showed improvement in CVR in the left middle cerebral artery and posterior cerebral artery territories despite the persistence of the middle cerebral artery stenosis.

The second patient (Patient 5, Table) initially presented with bilateral frontal headaches, right leg weakness, left facial droop, and slurred speech. MR angiography showed severe stenosis at the origin of the anterior cerebral artery and middle cerebral artery with no collateral blood supply (Figure 3, 1a). The patient’s initial CVR study demonstrated vascular steal involving the anterior cerebral artery, middle cerebral artery, and posterior cerebral artery territories in the left hemisphere (Figure 3, 1c). A left indirect extracranial to intracranial arterial bypass was performed. Postoperatively, the patient

Figure 3. Imaging studies from Patient 5, Table. 1, Initial studies. 1a, Coronal view of 3-dimensional time of flight MR angiography demonstrates severe bilateral distal internal carotid artery stenosis (arrows) extending into the anterior cerebral artery (ACA) and middle cerebral artery (MCA); posterior circulation vessels are excluded from maximum intensity projection reconstruction. 1b, Normal T2 fluid attenuated inversion recovery (FLAIR). 1c, Cerebrovascular reactivity (CVR) demonstrates severe loss of reserve with steal (blue) in the left MCA and ACA watershed territories. 2, Post left-sided indirect extracranial to intracranial arterial (EC-IC) bypass. 2a, Increasing right ACA and MCA stenosis and with worsening of the left ACA and MCA stenosis on MR angiography. 2b, T2 FLAIR acquisition is unchanged. 2c, CVR demonstrates reduced but preserved reactivity in the previously operated left hemisphere but newly exhausted vascular reserve with steal phenomenon in the right hemisphere. 3, Post right-sided indirect EC-IC bypass. 3a, MR angiography remains unchanged. 3b, T2 FLAIR acquisition remains unchanged. 3c, CVR shows improved reactivity in the right hemisphere; CVR in the left hemisphere is unchanged.
was well until approximately 1 year later, when she began to develop transient episodes of left arm and leg numbness and paralysis lasting for approximately 15 to 20 minutes. A repeat CVR study at this time showed improved CVR in the left middle cerebral artery territory but not in the anterior cerebral artery territory. However, it also showed newly developed exhausted vascular reserve capacity with steal in the right hemisphere (Figure 3, 2c). The patient subsequently underwent a second indirect extracranial to intracranial arterial bypass, this time on the right side. Postoperatively, the patient developed transient episodes of left arm and leg numbness, which eventually resolved. A CVR study obtained 1 year later revealed stable reactivity in the left hemisphere and improved right hemispheric vascular reserve (Figure 3, 3c) despite no change in intracranial vasculature on angiography (Figure 3, 3a).

The third patient (Patient 7, Table) had a history of a right-sided cranial rhabdomyosarcoma that had been treated with radiation at the age of 3 years. At the age of 14 years, the patient presented with transient episodes of right-handed numbness. Angiography revealed bilaterally occluded internal carotid arteries at the supraclinoid segment. There was however good collateralization through both posterior communicating arteries. The CVR study showed reductions in CVR bilaterally in the anterior cerebral artery and middle cerebral artery territory (Figure 4E). Given the patient’s mild symptoms and the presence of good collateralization, a decision was made to continue to follow the patient clinically. The patient’s symptoms improved over time and eventually stopped. The patient returned 2 years later for follow-up neurovascular imaging. Despite angiographic findings demonstrating no change in the intracranial vasculature (Figure 5A), the repeat CVR study showed bilateral improvement in vascular reactivity (Figure 5C), consistent with the patient’s clinical improvement.

**Discussion**

We report our initial experience from a case-series study undertaken to investigate the role of CVR mapping in the battery of neurological tests for the investigation of neurovasculopathy affecting children. We found that similar to adults, children with angiographically proven vessel abnormalities also demonstrated impaired CVR in the vascular territories supplied by the affected vessel(s). In some cases, the areas of abnormal CVR extended beyond that indicated by structural imaging into contiguous normal-appearing brain parenchyma. Also striking were the results obtained in the postoperative follow-up studies of 3 patients. Whereas follow-up angiographic studies demonstrated worsening or unchanged vascular stenosis, the CVR studies showing improvement in vascular reserve were consistent with the clinical course for each patient. The improvements in CVR...
were likely due to the augmentation of cerebral blood flow through either surgical revascularization (if performed) or as a result of the development of collateral circulation, as seen in the follow-up CVR in the third patient. These findings indicate that conventional angiography is limited in assessing the impact of stenosis or occlusion at the tissue level. Our unpublished data indicate that approximately 80% of carotid occlusions have normal CVR suggesting that revascularization would have no impact on improving flow.

To date, there have been few investigations into the role of CVR in guiding the treatment of children with vascular diseases. Using acetazolamide and single positron emission CT, So et al compared pre- and postrevascularization CVR studies in clinically symptomatic children with moyamoya disease. They found that patients with abnormal preoperative CVR demonstrated improvement in both clinical status and CVR after revascularization, likely due to the augmented cerebral blood flow. Interestingly, the authors also found that patients with persistent reductions in CVR postoperatively were found to be at a higher risk for developing ischemic attacks and recommended reoperating if that were the case. In the current series, CVR mapping provided information as to the efficacy of surgical revascularization in 2 patients with moyamoya disease. In 1 patient, surgical revascularization resulted in an improvement in both the clinical status and CVR on follow-up. In the second patient, a left hemispheric indirect surgical revascularization improved the middle cerebral artery but not the anterior cerebral artery CVR deficit. Repeated CVR studies allowed us to observe, for the first time, the development of abnormal CVR in a vascular territory coinciding with the onset of new neurological symptoms and the improvement of CVR and symptoms after the second surgical vascular bypass (Figure 3, 3c).

Measuring CVR in Children

We were able to solicit sufficient cooperation to successfully perform the CVR studies in this group of children aged >10 years. The rise in PCO2 was tolerable, because the children were able to increase their minute ventilation in response to any shortness in breath they may have experienced. Increasing respiratory rate with our system did not affect the stability of targeted PetCO2 levels (which were maintained within 1 mm Hg) or PetO2 which was maintained at normoxia. The latter was constrained within narrow limits to avoid the confounding effects of changes of arterial PO2 on BOLD signal. With the repeatability of the stimulus (PetCO2 values for all tests in all subjects were within 1 mm Hg), we were able to compare CVR studies (1) in patients over time (like in the 3 patients who had returned for follow-up examination); and (2) between patients.

Commonly used methods of high spatial cerebral blood flow imaging such as positron emission tomography (PET), Tc-99m HMPO, and Xenon-133 single photon emission CT are all associated with a risk of radiation exposure, which should be minimized, especially in children and in young people. Recent literature even suggests that the brain is more susceptible to radiation than previously thought. In our study, the changes in BOLD MRI signal used as a surrogate for regional blood flow changes provided adequate spatial resolution without the risk of radiation exposure. However, the long duration required for examination may be problematic in younger uncooperative children, although in this study, a 10 year old was examined successfully.

Conclusions

In our first 13 consecutive studies of children with neurovascular disease, CVR provided complementary information to structural imaging with respect to the severity and distribution of hemodynamic compromise. Further studies will be required to assess the role of this information for clinical management.

Acknowledgments

We thank the Toronto Western Hospital MRI technologists, particularly Eugen Hlasny, David Johnstone, and Keith Ta, for their contributions to the data acquisition. We also thank respiratory therapist Stephanie Dorner for her assistance in acquiring data.

Disclosures

J.A.F., D.J.M., and J.S.H. 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.

References
Measurement of Cerebrovascular Reactivity in Pediatric Patients With Cerebral Vasculopathy Using Blood Oxygen Level-Dependent MRI
Jay S. Han, David J. Mikulis, Alexandra Mardimae, Andrea Kassner, Julien Poublanc, Adrian P. Crawley, Gabrielle A. deVeber, Joseph A. Fisher and William J. Logan

*Stroke*. 2011;42:1261-1269; originally published online April 14, 2011; doi: 10.1161/STROKEAHA.110.603225

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/42/5/1261

Data Supplement (unedited) at:
http://stroke.ahajournals.org//subscriptions/

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/
Abstract

Measurement of Cerebrovascular Reactivity in Pediatric Patients With Cerebral Vasculopathy Using Blood Oxygen Level-Dependent MRI

Jay S. Han, MSc; David J. Mikulis, MD; Alexandra Mardimae, MSc; Andrea Kassner, PhD; Julien Poublanc, MSc; Adrian P. Crawley, PhD; Gabrielle A. deVeber, MD; Joseph A. Fisher, MD; William J. Logan, MD

背景及目的：脑血管反应性（CVR）是脑血液动力学的一个评价指标。在成人，大量研究表明，受损的 CVR 可增加脑血管病患者发生卒中的风险；在儿童，此类研究较少，可能是由于 CVR 的检测方法复杂且有一定危险性所致。在之前的研
究中，我们已应用监测呼吸末二氧化碳分压的方法检测过成人 CVR 的变化。本文属于对儿童脑血管病患者大规模观察研
究的一部分，旨在报道该研究初期的成果。

方法：对 13 名 10-16 岁的患者 (10 例诊断为 moyamoya 病，3 例为确诊的或疑似的颅内血管狭窄) 进行血管造影术、MRI 检查，同时应用血氧水平依赖性功能磁共振成像，通过激发患者的高碳酸血症状态检测 CVR。此 CVR 研究结果既
与脑部的结构成像有关，又与患者的临床状态有关。

结果：13 例患者均各自成功进行 1 次 CVR 检测，其中 3 例又随访 1 次。13 例患者中有 12 例血管造影术显示存在颅内血
管异常，这些患者同时出现了相应受损血管供血区的 CVR 下降；1 例血管造影术示颅内血管正常的患者，其 CVR 正常。13 例患者中，6 例有局灶性神经系统症状者均存在 CVR 降低；5 例无局灶性神经系统症状但伴有头痛的患者中，4 例血
管狭窄伴 CVR 下降；1 例颅内血管正常伴 CVR 正常；2 例血管狭窄但无任何临床症状的患者 CVR 下降。值得注意的是，血
管狭窄的患者，其 CVR 的下降显著超出了结构磁共振成像所示的缺血区域，延伸到了缺血以外的正常脑实质。

结论：本文是有关儿童脑血管病患者血氧水平依赖性功能磁共振成像 CVR 研究的首次系列报道。本研究目前结果显示儿
童脑血管病患者存在脑血流动力学的异常，该结论补充了儿童脑血管病传统临床评估及结构磁共振成像的不足。

关键词：脑血液动力学；脑血管储备；CVR；颅内狭窄；moyamoya 病；MRI；儿科；血管病变

(Stroke. 2011;42:1261-1269.)