Impact of Extracranial–Intracranial Bypass on Cerebrovascular Reactivity and Clinical Outcome in Patients With Symptomatic Moyamoya Vasculopathy

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Background and Purpose—The purpose of this study was to evaluate in symptomatic moyamoya patients the effect of surgical revascularization on impaired cerebrovascular reactivity (CVR) and its relationship to clinical outcome.

Methods—Brain revascularization was performed using a direct superficial temporal artery to middle cerebral artery bypass or indirect encephalo-dural–arterial synangiosis. CVR was measured pre- and 3 months postoperatively using blood oxygen level-dependent MRI during iso-oxic hypercapnic changes in end-tidal carbon dioxide. Outcomes were assessed by MRI, clinical examination, and modified Rankin Scale scores.

Results—Fifty-five hemispheres were revascularized in 39 patients (superficial temporal artery to middle cerebral artery in 47, encephalo-dural–arterial synangiosis in 8). Surgery reversed CVR impairment in 52 hemispheres (94.5%) and in 36 of 39 patients (92.3%; Fisher exact test, \( P < 0.001 \)), and this was predictive of a patent extracranial–intracranial bypass. New, clinically silent perioperative hemorrhages, cortical foci of ischemia, or new white matter T2 hyperintensities were detected after 11 surgeries (20%), but no new lesions arose after 3 postoperative months. One patient had a clinical perioperative stroke (1.8%). In clinical follow-up, 37 of 39 patients (95%) had stable or improved modified Rankin Scale scores and 2 patients (5.1%) worsened. No patients with patent bypasses or CVR improvements exhibited new clinical symptoms, but failure of CVR improvement corresponded to a poorer long-term outcome (Fisher exact test, \( P < 0.001 \)).

Conclusions—Cerebral revascularization surgery is a safe and effective treatment for reversing preoperative CVR defects and may prevent recurrence of preoperative symptoms. Moreover, CVR measurements may be useful in long-term follow-up and for predicting bypass patency. (Stroke. 2011;42:3047-3054.)

Key Words: cerebrovascular reactivity ◊ EC-IC bypass ◊ hemodynamics ◊ MR imaging ◊ stroke

Moyamoya vasculopathy is a progressive intracranial arterial steno-occlusive disease of unknown etiology characterized by stenosis of the supraclinoid internal carotid arteries and a network of abnormal neovascularized distal collateral vessels.1 This yields fragile moyamoya vessels that may be prone to hemorrhage. Also, patients may develop transient ischemic attacks (TIAs) and, ultimately, ischemic strokes. Thus, treatment of symptomatic moyamoya vasculopathy focuses on improving cerebral perfusion. Therapies include pharmacological vasodilators, corticosteroids, antiplatelet agents,1,2 and surgical revascularization.3,4 The latter is achievable either by directly anastomosing an external carotid artery branch to a cortical artery or indirectly by placing a vascularized tissue pedicle in direct contact with the brain, leading to an ingrowth of new blood vessels to the cortex. Both procedures remain controversial in patients with atherosclerotic disease5 but both are commonly used for stroke prevention in moyamoya patients.3

Surgical revascularization is rational if the patients’ symptoms are due to hemodynamic impairment and are not of embolic origin.4 One method of differentiating between the 2 etiologies is through measurements of cerebrovascular reactivity (CVR). CVR, defined as an increase in cerebral blood flow (CBF) in response to a given vasodilatory stimulus, is assumed to reflect the ability of the cerebral vasculature to augment CBF when cerebral perfusion pressure is reduced. CVR can be measured by blood oxygen level-dependant (BOLD) MRI at the time patients are subjected to vasoactive stimuli comprising using hypercapnic changes in end-tidal carbon dioxide (PetCO2).6 In patients with atherosclerotic...
disease, impairments in CVR are believed to be associated with a high risk of future ischemic events, although the role of surgery in reducing this risk is unresolved. CVR impairments are also noted in patients with moyamoya vasculopathy. Many of these patients exhibit persistent clinical symptoms due to intracerebral hemorrhage, TIAIs, or minor or major strokes despite best medical therapy. Although CVR defects might be correctable by surgical revascularization, there have been no systematic appraisals of whether surgically correcting CVR deficits is associated with clinical benefit.

We studied patients with moyamoya vasculopathy who also displayed preoperative clinical symptoms despite ongoing medical therapy with antiplatelet agents and who also exhibited a BOLD MRI CVR deficit in the symptomatic hemisphere to determine whether such patients might benefit from cerebral revascularization. Our data indicate that cerebral revascularization surgery is a safe and highly effective treatment for reversing preoperative CVR defects and may prevent symptom recurrence. Moreover, CVR measurements may be useful in long-term follow-up and for predicting bypass patency.

Materials and Methods

Ethics and Consent
This study was approved by the research ethics board at the University Health Network, Toronto, Ontario, Canada.

Patient Selection and Surgery
Data were collected prospectively between September 2001 and December 2010 in a database incorporating demographic, clinical, imaging, CVR, and treatment information. Inclusion criteria were: angiographically demonstrated moyamoya vasculopathy, ongoing clinical symptoms (TIA or minor strokes) despite best medical management, impairment in BOLD CVR in the middle cerebral artery territory ipsilateral to the clinically symptomatic brain, and at least 1 additional CVR study 3 months postoperatively. Best medical management consisted of a minimum of 30 days of antiplatelet agents in all patients and antiplatelets + warfarin in 2 patients before the onset of any clinical symptoms. Revascularization surgery was performed using either a direct superficial temporal artery to middle cerebral artery bypass or indirect encephalo-dural–arterial synangiosis. Encephalo-dural–arterial synangiosis was performed if superficial temporal artery to middle cerebral artery was not deemed to be technically achievable.

BOLD CVR and MRI
The CVR protocol using standardized iso-oxic (constant end-tidal partial pressure of O₂; PetO₂) hypercapnic changes in PetCO₂ combined with BOLD MRI has been reported in detail previously. BOLD MRI measures changes in CBF indirectly. Increased CBF results in dilution of intravascular deoxyhemoglobin, generating increased signal on T2*-weighted images. MRI was performed either on a 1.5- or a 3.0-Tesla scanner (Signa; GE Healthcare, Milwaukee, WI) with an 8-channel phased array head coil. For either on a 1.5- or a 3.0-Tesla scanner (Signa; GE Healthcare, Milwaukee, WI) with an 8-channel phased array head coil. For

Control of PetCO₂ and PetO₂
PetCO₂ and PetO₂ were controlled prospectively using algorithms described by Slessarev et al by means of an automated gas delivery system consisting of a computer-driven gas blender and sequential gas delivery breathing circuit (RespirAct; Thornhill Research Inc, Toronto, Canada). We targeted the following sequence (attained values in brackets): normocapnia (60 seconds at PetCO₂=40 mm Hg, SD=1 mm; PetO₂=100 mm Hg, SD=2 mm), Hypercapnia (60 seconds at PetCO₂=50 mm Hg, SD=1 mm; PetO₂=100 mm Hg, SD=2 mm), normocapnia (100 seconds), hypercapnia (180 seconds), and normocapnia (110 seconds).

Data Processing
PetCO₂ and PetO₂ values were selected automatically from the continuous raw pCO₂ and pO₂ tracings. The peak of the waveforms at the highest and lowest values were selected during exhalation. All values were confirmed post hoc by visual inspection and corrected if necessary. MRI and PetCO₂ data were then imported into the software AFNI. The BOLD MRI data were temporally aligned with the point of maximum statistical correlation with the subject’s PETCO₂ waveform (eg, Figure 1A). The correlation between PetCO₂ and BOLD MRI signal for each voxel was color-coded and overlaid on the patient’s anatomic scans to generate whole brain CVR maps with a red–red–orange–yellow spectrum with red indicating highest correlation, 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 strong negative correlation (paradoxical reactivity; eg, Figure 1B).

Follow-Up Imaging
Pre- and postoperative MRIs and MRIs at most recent follow-up were reviewed to identify new hemorrhagic or ischemic lesions or new focal T2 fluid-attenuated inversion recovery hyperintensities ipsilateral to the surgery. Bypass patency was evaluated in all patients using either digital subtraction angiography (Figure 2A–B) or CT angiography (Figure 1D). Patients who underwent a direct extracranial–intracranial (EC-IC) bypass had a follow-up BOLD MRI study performed 3 months postsurgery, whereas those who underwent indirect revascularization had a follow-up CVR study 6 months postsurgery. Many patients underwent additional imaging at subsequent follow-up visits, including BOLD MRI CVR studies and routine MRI with fluid-attenuated inversion recovery and diffusion-weighted imaging sequences.

Normalization of a preoperative CVR defect was defined as complete reversal of the impaired BOLD MRI CVR map to levels obtained in the unaffected contralateral hemisphere or, in the case of bilateral moyamoya, in age-matched control subjects. Improvement was defined as increased reactivity as compared with the preoperative CVR.

Functional Outcome
All patients were prospectively assigned a modified Rankin Scale (mRS) score preoperatively, postoperatively, and on clinical follow-up. A change in functional outcome was defined as a change between the preoperative and postoperative or last follow-up mRS scores.

Results
Between September 2001 and July 2010, 196 patients underwent 263 EC-IC bypass surgeries by a single surgeon (M.T.). Of these, 102 patients underwent a total of 136 EC-IC bypass procedures for moyamoya vasculopathy. A total of 39 patients fulfilled the inclusion criteria for this study (Methods). Exclusions were due to inability or refusal to undergo
both pre- and postoperative MR CVR and bypass patency studies (12 patients), hemodynamics assessed using positron emission tomography or CT techniques rather than BOLD MRI CVR (18 patients), decision to operate based on angiographic and clinical criteria alone (9 patients), and patients with impaired CVR whose presenting ischemic symptoms (stroke or TIA) occurred before starting optimal medical management with antiplatelet agents and who preferred revascularization to medical therapy alone (24 patients).

The demographics and surgical interventions of the 39 enrolled patients are provided in the Table. The clinical presentations consisted of 18 (46.2%) with prior ischemic stroke, 10 (25.6%) with prior brain hemorrhage, 8 (20.5%) with TIA, 2 (5.1%) with progressive cognitive decline, and 1 (2.6%) with seizures. The mean age of this cohort was 34.5 years (range, 15–67 years); 27 were female. All exhibited impairments in at least 1 middle cerebral artery territory on their BOLD MRI CVR maps. Bilateral surgeries were performed in 16 patients due to bilateral CVR impairments (eg, Figure 1). Thus, a total of 55 hemispheres underwent revascularization (47 direct and 8 indirect EC-IC bypasses). No patients were lost to follow-up.

MRI CVR studies were performed 3 months after each procedure, including in 15 of 16 patients who underwent bilateral surgeries. In 1 patient with bilateral moyamoya involvement, MRI CVR was performed only after both procedures were completed.

**Figure 1.** BOLD MRI CVR maps and MR and CT angiograms of a representative patient with bilateral Moyamoya before (left) and after (right) surgery. A, Left, Paradoxical BOLD MRI signal response. PetCO2 waveform (red) with a negative correlation BOLD MRI signal waveform (blue) indicating a reduction in CBF (vascular steal). Right, Normal BOLD MRI signal response. PetCO2 waveform (red) with positive correlation with BOLD MRI waveform (blue) indicating an increase in CBF with hypercapnia. B, CVR map demonstrating loss of reactivity and accompanying vascular steal (blue) in both MCA territories (left) and normalization postbilateral EC-IC bypass in the same patient (right). C, Pre- and postoperative 3-dimensional time-of-flight MR angiograms demonstrating bilateral stenotic supraclinoid ICAs with reduced MCA signal preoperatively (left) and bilateral EC-IC bypasses postoperatively (right). D, Pre- and postoperative CT angiograms of the same patient. Arrows indicated patent bypasses. BOLD indicates blood oxygen level-dependent; CVR, cerebrovascular reactivity; PetCO2, end-tidal carbon dioxide; MCA, middle cerebral artery; EC-IC, extracranial–intracranial; ICA, internal carotid artery.

**EC-IC Bypass Is Effective in Improving Preoperative CVR Defects**

Revascularization surgery produced a complete normalization or improvement of the CVR defect in 52 of 55 preoperatively impaired hemispheres (94.5%; 17 normalized, 35 improved; Figures 1B and 2D; “Methods”).
Forty-four of 47 hemispheres in 34 patients that were revascularized with a direct superficial temporal artery to middle cerebral artery bypass exhibited a patent bypass (94%). Within this group, 42 of 44 hemispheres (95.5%) exhibited normalization or improvement of ipsilateral CVR. Of the 3 patients with hemispheres in which a bypass was not patent, 2 demonstrated a CVR improvement but both had undergone a prior successful contralateral bypass surgery and possessed a competent circle of Willis on angiography. Thus, overall, 31 of 34 patients who received at least 1 patent direct EC-IC bypass showed normalization or improvement of CVR, suggesting that this procedure is highly effective in improving preoperative CVR defects (Fisher exact test, \( P < 0.001 \)). Additionally, 5 patients underwent indirect encephalo-dural–arterial synangiosis revascularization of 8 hemispheres. All exhibited new EC-IC connections on follow-up angiography and an improvement (6 hemispheres) or normalization (2 hemispheres) of preoperative ipsilateral hemispheric CVR deficits. Overall, direct or indirect revascularization surgery improved or normalized pre-existing CVR defects in 36 of 39 patients (92.3%, Fisher exact test, \( P < 0.001 \)).

In this small sample of patients, a normalized or improved CVR was completely predictive of a patent EC-IC bypass (100% positive predictive value), and no patients without CVR improvement had patent bypasses (100% negative predictive value). Further work may be required to determine whether MRI BOLD CVR measurements can replace post-operative imaging of bypass patency in long-term follow-up.

**Contralateral Improvement in CVR After EC-IC Bypass**

Of the 39 patients, 16 underwent bilateral surgeries. However, an additional 12 exhibited bilateral CVR impairments on their preoperative study but after a unilateral EC-IC bypass, the preoperative CVR defect normalized bilaterally (eg, Figure 2). Such patients uniformly exhibited a patent anterior communicating artery.

**EC-IC Bypass Surgery and Silent MRI-Detectable Postoperative Events**

All operated patients underwent anatomic MR brain imaging at the time of their postoperative CVR studies at 3 months and, when possible, at subsequent follow-up visits. The mean imaging follow-up duration was 14.8 months (range, 3–82 months). Lesions were classified as: new hemorrhages (Figure 3B), new cortical foci of ischemia (Figure 3C), or new white matter T2 hyperintensities suggestive of an ischemic demyelination pathology (Figure 3D).

In the 55 operated hemispheres of which 52 bypasses were patent, a total of 11 ipsilateral new events (20.0%) were detected in 8 patients on follow-up. All of these events were clinically silent, that is, they were undetected by the patient or by clinical examination. Four consisted of new cortical foci of ischemia, 3 were new white matter T2 hyperintensities, and 4 were new small hemorrhages. One of these events (new ischemic infarct) developed in a patient whose bypass was not patent. In the patients who developed new ischemic or hemorrhagic lesions, all but 1 initially presented with an ischemic event. The remaining patient developed a new small hemorrhage after initially presenting with a hemorrhage. The initial presentation of patients that developed T2 hyperintensities varied, consisting of each of the following: 1 seizure, 1 ischemic, and 1 hemorrhagic event. Thus, there was no obvious relationship between the patients’ initial presentations and the types of stroke detected by MRI. There were no new silent strokes in any of the 27 patients who had MRI scans subsequent to their initial 3-month postoperative follow-up.

**Association of CVR Improvement With Symptom Recurrence**

There were no clinically evident ischemic or hemorrhagic complications in any of the operated hemispheres. However,
### Table. Patient Demographics and Outcomes

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(Continued)
1 patient with extensive bilateral moyamoya and severe bilateral CVR impairments had an intraoperative stroke in his left hemisphere at the time of undergoing surgery on the right. Thus, the incidence of clinical perioperative strokes in this cohort was 1.8%.

Patients were assigned mRS before, within 72 hours, and at last follow-up after surgery. By 72 hours, mRS was improved after 4 (7.8%), unchanged after 46 (90.2%), and worsened after 1 (1.8%) procedures. The latter was the patient who had an intraoperative stroke contralateral to the surgical side.

Of patients with improved or resolved CVR defect, none exhibited new clinical symptoms during a clinical follow-up period averaging 22.3 months (range, 3–123 months). However, of the 3 patients in whom surgery failed to improve CVR in their clinically symptomatic vascular territories, 1 exhibited a silent new ischemic infarct peripherally and 2 had fatal brain hemorrhage 2 and 3 years postoperatively. Thus, a lack of improvement in CVR corresponded to a poorer long-term clinical outcome (Fisher exact test, \( P<0.001 \)).

At last follow-up (average, 22.3 months; range, 3–123 months), 17 of 39 patients (43.6%) exhibited at least a 1-point improvement in the mRS score as compared with postoperative mRS, 20 (51.3%) remained stable (no change in mRS), and 2 patients (5.1%) worsened (1 died of intracerebral hemorrhage, 1 experienced progressive cognitive decline). The patients who worsened had nonpatent bypasses, suggesting this to be a poor prognostic indicator (Fisher exact test, \( P<0.001 \)).

**Discussion**

Impaired CVR has been deemed to represent a risk of impending stroke in patients with atherosclerotic carotid stenosis.\(^7\)\(^8\) CVR measurements using various techniques have also been used to assess patients with moyamoya vasculopathy.\(^18\)\(^19\) However, the impacts of brain revascularization on CVR and the relationship between CVR and clinical outcome have not been systematically evaluated. The present study selected a narrow patient population, those with moyamoya vasculopathy refractory to best medical management and who exhibited compromised CVR in the symptomatic brain area. Our data suggest that in these patients, brain revascularization is safe and effective at reversing the CVR defect. Moreover, measurements of CVR with BOLD MRI predict bypass patency and possibly clinical response to treatment, making this technique a useful means with which to evaluate patients pre- and postoperatively.

Due to the nature of our study (a case series) and to the complex natural history of moyamoya vasculopathy, our data cannot be used to conclude causality between bypass surgery and prevention of clinical symptom recurrence. However, symptom recurrence in believed to be common in moyamoya patients. For example, Hallemeier et al\(^20\) reported a 65% 5-year risk of ischemic events in medically treated moyamoya patients, an 82% risk in patients with bilateral involvement and ischemic symptoms, and a 30% to 65% risk of hemorrhage recurrence. The patient population in the current study is a further subset that, in addition to clinical symptoms, exhibited CVR impairments. Although our patient population could represent an even higher risk group than that analyzed by Hellemeyer et al, none of our patients who exhibited CVR improvements in their symptomatic hemisphere exhibited further clinical strokes or TIA’s, a benefit that may be attributable to the surgery. However, given that most of our patients presented with strokes, and many stroke symptoms cluster in time and improve over months, surgical benefit should be tested in a more comprehensive, controlled trial.

Other studies have suggested an advantage of surgery over medical management in moyamoya patients. For example, Kraemer et al\(^21\) reported a stroke risk in the first year after an initial ischemic event of 45% and 80% in surgically and medically treated patients, respectively. Moreover, studies have confirmed using mRS scores that 94.8% to 97% of patients experience either clinical improvement or stabilization on follow-up,\(^22\) as confirmed in our study (94.9%
improvement or stabilization). Our data are consistent with prior studies in suggesting a benefit of surgery over medical management in moyamoya patients. However, in addition, we demonstrate that CVR measurements may be useful to predict the clinical response to treatment. Nonetheless, despite our encouraging results in this small patient sample, the clinical impact of revascularization surgery should be evaluated in larger trials. This is particularly important in the context of our findings that 20% of surgeries resulted in clinically silent, MRI-detectable perioperative events indicating silent ischemia or hemorrhage. The fact that none occurred >3 months postoperatively may indicate that they represent perioperative events rather than representing further strokes due to progression of the moyamoya vasculopathy.

It is unclear whether these MRI findings have clinical significance, but they serve as a reminder that all surgeries bear risks that should be ideally evaluated in comprehensive trials.

We believe that MRI BOLD measurements of CVR may complement traditional angiographic studies in evaluating moyamoya patients. Whereas angiography is essential in the diagnosis, angiographic findings do not always predict clinical symptoms, because some patients with profound features of moyamoya such as bilateral carotid occlusions may be asymptomatic, whereas others with lesser impairments may have profound symptoms. Of these, some symptoms may be due to emboli, whereas others may be hemodynamic. Measurements of CVR may help differentiate between such patients and identify a subgroup that may benefit the most from treatment by revascularization.

The study of CVR requires both a vasodilatory stimulus such as an elevation of arterial CO2 or lowering pH and an imaging method (to measure associated changes in CBF). This may be achieved by various means such as the administration of acetazolamide, breath-holding, CO2 inhalation, and end-tidal forcing. However, with the exception of end-tidal forcing, which is difficult to apply, particularly in the MR environment, these methods are incapable of delivering a standardized repeatable CO2 stimulus, introducing a stimulus-related variability in the CVR results. In contrast, the administration of a standard stimulus generates data that can be compared in a single subject over time and between groups of subjects enrolled in studies.

A variety of imaging techniques may be used to assess CVR, including xenon-CT, single photon emission CT, positron emission tomography, and perfusion CT. However, these involve an inherent exposure to radiation. Additionally, each modality bears its own limitations such as limited resolution (single photon emission CT), the need for contrast agents (CT), or limited availability (positron emission tomography). In perfusion CT, the generation of measured perfusion parameters requires an arterial input function, which can be problematic in patients with bilateral or extensive vessel disease. However, in MRI BOLD imaging, the signal is due to endogenous intravascular paramagnetic deoxyhemoglobin. Increases in CBF results in the dilution of intravascular deoxyhemoglobin, which generates an increased signal on T2-weighted (BOLD) images thereby providing an indirect measure of CBF. Thus, the use of BOLD MRI to image changes in CBF is an alternative that does not expose patients to radiation or require exogenous contrast agents and is independent of arterial input functions.

Conclusions
In patients with moyamoya vasculopathy refractory to medical management who also exhibit compromised CVR, brain revascularization is safe and effective in reversing the CVR defect. Moreover, measurements of CVR with BOLD MRI predict bypass patency and clinical response to treatment, making this technique a useful means with which to evaluate patients pre- and postoperatively. Cerebral revascularization that results in CVR improvements may be useful in preventing recurrence of strokes and TIAs.

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Impact of Extracranial–Intracranial Bypass on Cerebrovascular Reactivity and Clinical Outcome in Patients With Symptomatic Moyamoya Vasculopathy

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