Monitoring of Cerebral Vasodilatory Capacity With Transcranial Doppler Carbon Dioxide Inhalation in Patients With Severe Carotid Artery Disease

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Background and Purpose—Cerebral vasodilatory capacity (CVC) testing with transcranial Doppler has been shown to be useful in the assessment of stroke risk in patients with symptomatic and asymptomatic internal carotid artery (ICA) stenosis and occlusion, but whether hemodynamic status improves, deteriorates, or remains the same over time is uncertain.

Methods—Thirty-five patients with ≥80% carotid artery stenosis or complete occlusion underwent CVC testing at baseline and 6 months later. CVC was assessed by measuring the increase in ipsilateral middle cerebral artery mean flow velocity in response to 5% inhaled CO2. Continuous tracings of left and right middle cerebral artery flow velocity, heart rate, respiratory rate, and PCO2 were recorded and then analyzed offline. One-way analysis of variance was used to compare baseline CVC in symptomatic and asymptomatic patients with control subjects. A paired t test was used to compare CVC before and after revascularization. Also, χ2 analysis was used to compare rates of cerebrovascular events in patients with low compared with normal CVC over the 6-month period and in 14 patients whose ICAs were revascularized.

Results—Patients with high-grade stenosis or occlusion of the ICA who had ICA disease had an average CVC of 2.4±1.9%/mm Hg PCO2; control subjects averaged 4.2±1.1%/mm Hg PCO2. (P=0.01). In the revascularization group, CVC increased from an average of 1.4±1.7%/mm Hg PCO2 at baseline to an average of 2.8±1.0%/mm Hg PCO2 after revascularization, significantly different from the spontaneous change in the natural history group over 6 months (P=0.003). Over the 6-month follow-up period, in the natural history group and in the treatment group after revascularization, 4 ischemic events occurred, all in patients with abnormal CVCs; abnormal CVC was associated with ischemic events (Fisher’s exact test, P=0.03).

Conclusions—In a timeframe pertinent to clinical decision making and clinical trial outcomes, cerebral hemodynamic status may not be constant. A higher ischemic risk may be present in patients with severe carotid artery disease whose CVC is poor at baseline, becomes poor over 6 months, or fails to normalize after revascularization. (Stroke. 2003;34:945-949.)

Key Words: autoregulation ■ cerebral blood flow ■ cerebrovascular reactivity ■ ultrasonography, Doppler, transcranial

Cerebral hemodynamic testing provides a measurement tool that reflects the relationship between the common stroke subtype of large-vessel atherostenosis and its potential pathophysiological underpinning, cerebral perfusion failure. Positron emission tomography (PET) studies have demonstrated that as perfusion pressure falls, cerebral blood flow (CBF) is maintained by autoregulatory vasodilation of cerebral arterioles, imaged as increased cerebral blood volume (CBV).1-3 If cerebral perfusion pressure falls low enough, as occurs in some cases of internal carotid artery (ICA) stenosis or occlusion, CBF begins to decrease, and oxygen extraction fraction (OEF) increases to maintain tissue oxygen metabolism.4 At later stages of cerebral hypoperfusion, sometimes referred to as misery perfusion,5 a vulnerable hemodynamic state exists in which any further drop in perfusion will produce ischemia. Previous human studies of CBF and brain function in the setting of ICA balloon test occlusions showed that in a CBF range of 30 to 40 cm³ · 100 g⁻¹ · min⁻¹, reversible brain dysfunction may occur, but with CBF of <30 cm³ · 100 g⁻¹ · min⁻¹, brain dysfunction is likely to be persistent unless normal flow is restored.6 Patients with symptomatic carotid artery occlusion with increased OEF have been shown to have a 7-fold-increased risk for subsequent ipsilateral stroke.7

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Cerebral hemodynamic status can also be assessed with transcranial Doppler ultrasound (TCD), which measures blood flow velocity in the middle cerebral artery (MCA). As long as the MCA diameter remains constant, changes in MCA flow velocity will reflect arteriolar vasomotor activity. When a pharmacological vasodilator is administered (e.g., intravenous acetazolamide or inhaled CO₂), the MCA flow velocity increases as a result of vasodilation of arterioles downstream in the vascular bed. The capacity of cerebral arterioles to respond to a vasodilator is thought to reflect the normal autoregulatory ability of cerebral arterioles. In a state of low perfusion pressure, the arterioles cannot dilate further, and the cerebral vasodilatory capacity (CVC) decreases or disappears, indicating a state of exhausted cerebrovascular reserve and misery perfusion. Similar to the way that increased OEF predicts hemodynamic failure stroke in patients with carotid artery occlusion, severely impaired CVC has been shown to predict stroke in patients with symptomatic and asymptomatic carotid artery occlusion and stenosis.

Despite the recent studies supporting the predictive value of hemodynamic testing in patients with large-vessel disease, the natural history of cerebral hemodynamics in such patients is not well characterized. Both improvement and deterioration in cerebral hemodynamic status have been reported. If hemodynamic status is variable over time, the risk to patients with severe large-vessel stenosis may correspondingly increase or decrease. Furthermore, treatment with revascularization may improve CVC, but whether failure to increase CVC confers a persistent ischemic risk has not been addressed. In this prospective study, we sought to assess whether CVC changed with revascularization and whether CVC remained stable over 6 months without revascularization. We hypothesized that there would be a significant increase in CVC in patients in whom revascularization took place compared with patients who were not revascularized. We further hypothesized that over a 6-month period, whether patients were revascularized or not, low CVC would correlate with a higher risk of ischemic events.

**Materials and Methods**

**Subjects**

Thirty-five patients with severe carotid artery disease (≥80% stenosis or complete occlusion diagnosed by color Doppler, MR angiography, or catheter arteriography) were recruited from the inpatient and outpatient stroke services at Columbia-Presbyterian Medical Center and followed up for 6 months. These patients were designated the natural history (NatHX) group. Status of the carotid arteries was also assessed at the 6-month follow-up point. Patients with significant pulmonary disease or with technically poor temporal windows were excluded from the study. Race or ethnicity, education level, and presence or absence of hypertension, diabetes, and cigarette smoking were recorded. The NatHX patients and 9 roughly age-matched, healthy control subjects with no cerebrovascular-large-vessel disease underwent TCD cerebral vasodilatation testing at time T₀ (baseline) and at follow-up 6 months later. Patients with symptomatic carotid artery disease could be followed up in the NatHX group if they had either complete occlusion or stenosis for which no treatment was planned. At the 6-month follow-up visit, patients were interviewed and examined by a neurologist for symptoms or signs of intervening stroke or transient ischemic attack (TIA). Fourteen additional patients, recruited from the same population as the NatHX group, made up the revascularization (Rx) group. The Rx group had CVC performed before and 1 to 2 months after revascularization. Rx patients were also monitored for clinical outcomes for 6 months after revascularization by office visit or validated telephone contact. The study was approved by the Columbia-Presbyterian Medical Center Institutional Review Board. Signed, informed consent was obtained for all procedures.

**Vasoreactivity Measurements**

All patients and control subjects underwent continuous bilateral TCD monitoring (Pioneer TC 4040, Nicolet Biomedical) of the MCA at an insonation depth of 50 to 56 mm. Ultrasound probes were held in place with an adjustable head frame (Spencer Technologies). End-tidal partial pressure of carbon dioxide (PcO₂) was measured continuously with an inline capnometer (Datex-Ohmeda) connected via a snorkel mouthpiece, with the nasal airway occluded by a nose clip. Continuous tracings of left and right MCA flow velocity, heart rate, respiratory rate, and Pco₂ were recorded by the Doppler machine on separate channels and used for offline analysis. After 2 minutes of baseline measurements, subjects breathed a mixture of 5% CO₂ and air (Carbigen) for 2 minutes. Blood pressure was measured at baseline and during CO₂ inhalation. CVC was calculated as percent rise in the ipsilateral MCA mean flow velocity (MFV) per 1 mm Hg Pco₂, once the MFV curve plateaued at its highest level during the 2-minute inhalation period. The contralateral CVC was measured as a control. After the MFV returned to baseline for at least 2 minutes, a second 2-minute CO₂ inhalation CVC measurement was obtained for reliability measurements. There could be no more than a 10-bpm heart rate difference between the baseline and CO₂ inhalation periods. “Normal” CVC was defined as a rise in MCA MFV of >2.0%/mm Hg Pco₂, corresponding to 2 SD below the control group mean. Reliability of CVC measurements was determined by calculating the mean difference, variation coefficient, correlation coefficient, and percent error for the following components of the protocol: Instrumental reliability was tested by comparing resting MFV at the beginning and the end of testing sessions for all subjects, controlling for Pco₂; reliability of the CO₂ inhalation technique was determined by comparing 2 CVC measurements during the same testing period in the control group, and intrarater and interrater reliabilities for CVC calculations were determined from control group data.

**Statistical Analysis**

One-way analysis of variance was used to compare baseline CVC in symptomatic and asymptomatic patients with that of controls. A paired t test was used to compare CVC before and after revascularization. Nonparametric (χ²) analysis was used to compare rates of cerebrovascular events in patients with low versus normal CVC during the 6-month study period or in the 6-month postrevascularization period in the Rx patients. Student’s t test was used to compare baseline vasoreactivity between the NatHX group and control subjects and to compare changes in CVC over 6 months. A paired t test was used to compare CVC before and after revascularization in the Rx group, and a 2-sample t test was used to compare changes in CVC between the NatHX and Rx groups. All probability values were 2-tailed and considered significant at α=0.05.

**Results**

In the NatHX group, there were 35 patients (23 men, 12 women) ranging in age from 28 to 84 years (mean, 66 years). Fourteen patients had ≥80% stenosis, and 21 had complete occlusion of the ICA. Sixteen patients could be classified as symptomatic (stroke or TIA in the 2 years before the study), and 19 patients were asymptomatic. The 14 patients in the Rx group had a mean age of 55 years. Ten were symptomatic and 4 were asymptomatic by the above criteria. Seven underwent standard carotid endarterectomy, 4 had ICA angioplasty (2 intracranial, 2 extracranial), 1 had subclavian carotid bypass for subclavian occlusion, and 2 had spontaneous recanalization after ICA dissection. There was no significant difference
in age between the NatHx and Rx groups. The 9 subjects in the control group had a mean age of 52 years, which was not statistically different from the that of the NatHx or Rx group. The 6-month follow-up data were available for 32 patients in the NatHx group (follow-up response rate, 91%). Three patients evaluated at baseline, 2 with ICA stenosis and 1 with carotid occlusion, did not return for their follow-up TCD. Exclusion of their data from the final analysis did not change the overall results of the study. No patient with stenosis went on to complete occlusion during the study period as assessed by follow-up Doppler or MR angiography. There was no loss to follow-up among the control subjects. In the Rx group, all patients had CVC and clinical assessment at 1 to 2 months. One patient was unable to be contacted for clinical follow-up at 6 months. The 32 remaining subjects in the NatHx group, all 14 in the Rx group, and all 9 control subjects were able to complete the protocol without difficulty. All patients’ CVC curves plateaued within 2 minutes, suggesting that there was good equilibration between measured end-tidal CO₂ and arterial PCO₂ within 2 minutes.

Patients with high-grade stenosis or occlusion of the ICA had an average ipsilateral CVC of 2.4±1.9%/mm Hg Pco₂ at baseline; control subjects averaged 4.2±1.1%/mm Hg Pco₂ (P=0.01). CVC in the contralateral ICA in patients with unilateral ICA disease averaged 3.8±2.6%, which was not statistically different from the control group. Dividing patients into those with and without symptoms showed that baseline CVCs were 1.7±1.3% and 3.1±2.2%/mm Hg Pco₂ respectively. These groups were significantly different from each other and from control subjects (F3,39=6.79, P=0.003; see Figure 1). There was no difference in average CVC between patients with symptoms >2 years before and those who were never symptomatic from their carotid disease.

Comparison of baseline with follow-up CVC measurements showed that on average neither control subjects nor the NatHx group had altered hemodynamics over 6 months. On an individual basis, however, hemodynamic status changed in 5 of the 32 patients. Of the 12 NatHx patients with an abnormal CVC at baseline (<2.0%/mm Hg Pco₂), 1 had a normal CVC at 6 months. Of the 20 patients who had a normal baseline CVC at baseline, 4 had an abnormal CVC at 6 months. Two of 11 patients with an abnormal CVC at both baseline and 6 months and 1 of the 4 whose CVC fell into the abnormal range at the 6-month point had ischemic events during the 6-month observation period. One of these had ipsilateral stroke producing mild hemiparesis; 1 had recurrent ipsilateral TIAs (speech difficulty and face numbness); and the third had recurrent episodes of postural lightheadedness attributed to bilateral carotid artery disease. CVC for these patients was 1.43%, 3.35%, and 1.24%/mm Hg Pco₂ at baseline and 0.41%, 2.00%, and 1.51%/mm Hg Pco₂, respectively, at follow-up. Of note, 1 of the patients whose CVC became abnormal who did not have an ischemic event had a third CVC assessment at 1 year and was found to have a normal CVC once again. Re-examination of her carotid artery at that point disclosed spontaneous improvement of flow in the ICA, thought to be due to local collateralization.

In the Rx group, there was a significant rise in CVC after revascularization, increasing from an average of 1.4±1.7%/mm Hg Pco₂ at baseline to an average of 2.8±1.0%/mm Hg Pco₂ after revascularization (P=0.008). Eight of 10 patients with an abnormal CVC before revascularization achieved normal CVC after revascularization; 3 patients were normal both before and after revascularization; 2 had abnormal CVCs before and after revascularization; and 1 patient was in the low-normal range before revascularization and had an abnormal CVC 1 month after revascularization (see Figure 2). The improvement in hemodynamic status in the revascularization group was statistically different compared with the lack of change in CVC over 6 months in the NatHx group (P=0.003). Among the 14 Rx patients, 1 had an ischemic event 2 months after revascularization. That patient was 1 of the 3 whose CVC was abnormal after revascularization.

Considering outcomes in both the NatHx and Rx groups, none of the 26 patients whose CVC was in the normal range at both baseline and follow-up (NatHx group) or who had normal postrevascularization CVC (Rx group) had an ischemic event; 4 of the 20 with an abnormal CVC during the 6-month NatHx period or in the 6 months after revascularization had ischemic events. Abnormal CVC was therefore associated with ischemic event (Fisher’s exact test, P=0.03; see the Table).

Bilateral high-grade stenosis or occlusion was present in 6 patients in the NatHx group. This group’s average CVCs were lower than those for patients with unilateral disease:
1.0±1.4% versus 2.3±1.0%/mm Hg PCO\textsubscript{2}, respectively. Two of the 4 patients with ischemic events had bilateral carotid disease, but presence of bilateral disease alone did not predict outcome.

Reliability analysis showed excellent instrumental consistency on the basis of repeated measurements of resting MFV: mean difference, –1.75 cm/s; variation coefficient, 7.3%; correlation coefficient, 0.99; and percent error, 0.3%. Reliability for CO\textsubscript{2} inhalation test-retest yielded a mean difference of 0.9%/MFV increase per 1 mm Hg PCO\textsubscript{2}, a variation coefficient of 11.3%, a correlation coefficient of 0.87, and a percent error of 4.4%. Intrarater reliability for CVC measurements yielded a mean difference of 0.3%/MFV increase per 1 mm Hg PCO\textsubscript{2}, a variation coefficient of 4.1%, a correlation coefficient of 0.99, and a percent error of 1.1%. Intrarater reliability for CVC measurements yielded a mean difference of 0.6%/MFV increase per 1 mm Hg PCO\textsubscript{2}, a variation coefficient of 8.5%, a correlation coefficient of 0.89, and a percent error of 1.8%. The variability we obtained with our methods is similar to that published in similar studies.\textsuperscript{18

### Discussion

Our study demonstrates that CVC in patients with severe carotid artery disease remains generally stable over 6 months. Patients are at higher risk for ischemic events, however, if their CVC is low at baseline and after 6 months, becomes abnormal over a 6-month period, or does not return to normal with revascularization. In our study, 20% of such patients with low CVC had ipsilateral stroke or TIA.

The predictive value of cerebral hemodynamic testing has been demonstrated in several settings in patients with carotid artery disease\textsuperscript{7,11,13,19} and may be used increasingly in clinical settings to guide treatment algorithms.\textsuperscript{20} Hemodynamic testing can be particularly useful in patients with asymptomatic carotid stenosis, total carotid occlusion, and intracranial large-vessel stenosis for whom revascularization treatment remains unproven or controversial.\textsuperscript{21–25} Even in patients with symptomatic carotid artery stenosis who would normally undergo revascularization regardless of hemodynamic state,\textsuperscript{26,27} medical conditions may intervene that pose increased surgical risk. Hemodynamic assessment in such patients may help weigh natural history risk against treatment risk. In a recent study of symptomatic carotid stenosis, CO\textsubscript{2} reactivity testing was shown to predict recurrent stroke in patients awaiting endarterectomy.\textsuperscript{28} What has not been established by the predictive value studies is the influence of the natural history of cerebral hemodynamics in patients with large-vessel disease, leaving uncertain whether a given hemodynamic status at 1 time point carries a constant risk for the future. Of the 4 patients in our study who had ischemic symptoms in the 6-month follow-up period, 2 had an abnormal CVC at baseline, 1 had an abnormal CVC only at the 6-month follow-up, and 1 failed to attain normal CVC after revascularization.

Both spontaneous worsening and improvement in cerebral hemodynamic status over time have been reported. In a recent PET study of 7 medically treated patients with symptomatic carotid artery occlusion and normal OEF, CBF and cerebral metabolism (CMRO\textsubscript{2}) decreased and OEF rose over 2 to 5 years, suggesting that hemodynamic status can worsen over time.\textsuperscript{14} In a similar longitudinal PET study of 10 patients with symptomatic unilateral ICA occlusion and increased (abnormal) OEF, average OEF and CBF improved over 1 to 5 years, while CMRO\textsubscript{2} remained unchanged, suggesting that hemodynamic state may improve over time.\textsuperscript{15} A long-term increase in CVC is also suggested by our finding that patients who were not recently symptomatic had higher average CVCs than those who had symptoms within 2 years. Hemodynamic improvement was also reported to be common in an older TCD study.\textsuperscript{16} In that study, however, only a small portion had severely impaired vasoreactivity, and only 4 of 55 patients (7%) improved from the exhausted CVC state in the first 6 months, closer to our own findings in this study. Another difference in our study compared with prior studies is that we included not only patients with typical extracranial atherosclerotic carotid disease but also patients with either ICA dissection or intracranial ICA stenosis. In fact, 3 of 4 ischemic events occurred in patients with intracranial ICA stenosis, although the presence of intracranial stenosis alone did not predict ischemic events. It would appear, in any case, that in our patient group hemodynamic impairment was equally likely to contribute to the pathophysiology of carotid disease regardless of the location and cause of the obstruction. Hemodynamic investigation of a larger set of patients with nonatherosclerotic carotid disease and of intracranial stenosis alone may increase our understanding of stroke risk in these conditions.

The results of this study suggest that hemodynamic testing with TCD can be useful in monitoring both the natural history of carotid disease and the effectiveness of revascularization treatment. Although our study had a relatively short follow-up period and a small number of events, 6 months is a common interval clinically for serial assessment in patients with carotid artery disease. This interval also falls within a common range of outcome measurement points in stroke clinical trials and stroke recovery studies.\textsuperscript{29–31} A dynamic test such as CVC allows us to better define the relationships between low perfusion pressure and the autoregulatory mechanisms that attempt to compensate for a low flow state. Just as other stroke risk factors may change over time to alter the risk of stroke, so may the risk factor of cerebral hemodynamics change. As treatment options expand for carotid artery stenosis and occlusion, it becomes increasingly important to assess the functional consequences of carotid artery disease and its treatment and not rely only on the degree of stenosis or the presence of occlusion to guide our management strategies.

| Rate of Ischemic Events in Patients With Low Compared With Normal CVC |
|---------------------|-----------------|-----------------|
|                      | n    | Mean (SD) | Ischemic Event, n (%) |
| Low CVC*             | 20   | 1.03% (1.07) | 4 (20) |
| Normal CVC           | 26   | 3.39% (1.13) | 0 (0) |

*≤2.0% increase in ipsilateral MCA MFV per 1 mm Hg PCO\textsubscript{2}
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