Cerebrovascular CO₂ reactivity after carotid artery occlusion

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Cerebral blood flow (CBF) was measured in 39 men at normocapnia and after 5% CO₂ inhalation using the xenon-133 technique. Twenty-three patients had unilateral carotid artery occlusion with no angiographic evidence of contralateral carotid artery stenosis or ophthalmic collateral flow. Eleven of these patients had undergone extracranial-intracranial (EC-IC) bypass surgery. Sixteen age-matched normal men underwent CBF measurements at normocapnia and hypercapnia to provide control data. Mean hemispheric CBF was not different between hemispheres ipsilateral and contralateral to the carotid artery occlusion either in the patients who had undergone bypass surgery or in those with carotid artery occlusion alone. Considering all patients with carotid artery occlusion, mean CO₂ reactivity was decreased in the hemisphere ipsilateral to the occlusion as compared to the contralateral hemisphere in both groups. Based on data from normal individuals, a hemispheric difference in CO₂ reactivity of more than 0.94%/mm Hg PaCO₂ or a global CO₂ reactivity of less than 0.66%/mm Hg PaCO₂ was considered abnormal for an individual patient. Six of 23 patients with carotid artery occlusion (three with an EC-IC bypass) had global or hemispheric abnormalities in CO₂ reactivity. Patients with impaired CO₂ reactivity were not distinguishable from other patients by neurological examination, presence of transient ischemic attacks, or evidence of infarction on computerized tomography scanning. This test was safe and simple to perform and may be a useful means of detecting impaired cerebrovascular collateral reserve capacity. If impaired CO₂ reactivity after carotid artery occlusion proves to be associated with a high risk of subsequent stroke, the test would provide a physiological basis for selecting a subgroup of patients who could be helped by cerebral revascularization.

KEY WORDS • carotid artery occlusion • xenon-133 • cerebral blood flow • CO₂ reactivity • autoregulation

The risk of stroke after carotid artery occlusion has been estimated to be 5% per year, with 51% of patients suffering ongoing transient ischemic attacks (TIA's) in the territory of the occluded artery. It has been suggested that many of the strokes occurring after carotid artery occlusion are ischemic and not embolic. Some support for this belief can be derived from studies with positron emission tomography (PET) in patients with carotid artery occlusion which have shown ipsilateral increased cerebral blood volume in many patients, associated with increased O₂ extraction in those with bilateral carotid artery occlusion and orthostatic TIA's. When studied with PET, the results of extracranial-intracranial (EC-IC) bypass procedures have been variable: small numbers of patients showed decreased cerebral blood volume, improved O₂ extraction, increased cerebral metabolic rate for oxygen, and increased regional cerebral blood flow. These studies have supported the hypothesis that EC-IC bypass could produce neurological improvement and/or diminish the risk of subsequent ischemic infarction in some patients. The finding by the EC-IC Bypass Study Group that superficial temporal-middle cerebral artery (STA-MCA) bypass did not decrease the risk of subsequent stroke after carotid artery occlusion has increased interest in a physiological method by which patients with impaired cerebrovascular collateral reserve capacity could be detected, in the hope of identifying a subgroup of patients with carotid artery occlusion who might benefit from revascularization. Positron emission tomography is not generally available and measurement of cerebral blood flow (CBF) is the only available alternative for physiological assessment of patients with cerebrovascular occlusive disease.
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Use of resting CBF to evaluate patients for bypass surgery or to assess its effects has been unrewarding because of the lack of information regarding flow-metabolism relationships. It has not been possible to identify ischemia based on low CBF values alone. The improvement in CBF documented by several investigators after a bypass procedure has been attributed to the natural recovery of the brain after infarction. Several recent publications have proposed measurement of CBF at rest and during hypercapnia as an index of cerebrovascular collateral reserve capacity in patients with carotid artery occlusion. The rationale for this dynamic test is that cerebral vessels dilate to preserve CBF distal to a flow-limiting arterial lesion. If the cerebral circulation is maximally dilated, it has a decreased capacity to dilate further in response to hypercapnia. Published data evaluating this test have established that the mean CO₂ reactivity in hemispheres ipsilateral to carotid artery occlusion is lower than the mean CO₂ reactivity of contralateral unaffected hemispheres of the same patients or hemispheres of normal individuals. The CO₂ reactivity may vary with age and atherosclerotic status. It is not known what level of CO₂ reactivity of an individual patient with carotid artery occlusion is abnormal based on data from comparable individuals of the same age without cerebrovascular disease. Cerebrovascular CO₂ reactivity was measured in 23 men with unilateral carotid artery occlusion without contralateral carotid artery stenosis and in 16 age-matched men in a control group to evaluate this test as a method of detecting patients with impaired cerebrovascular collateral reserve capacity.

Clinical Material and Methods

Between 1983 and 1986, 46 patients at Hunter Holmes McGuire Veterans Administration Hospital had angiographic confirmation of unilateral carotid artery occlusion. Six patients were excluded from study because of severe neurological disability. Seventeen declined studies, did not tolerate CO₂ administration, or had significant unrepaired contralateral carotid artery stenosis. The remaining 23 patients with unilateral carotid artery occlusion underwent measurement of CBF. The study group was highly selective in that patients with cerebral infarction within 6 months, severe disability, bilateral carotid artery occlusion, or high-grade stenosis contralateral to the occlusion were omitted from this analysis.

Table 1 gives the mean age, blood pressure, and neurological status of the three groups of patients. All patients with carotid artery occlusion presented with TIA's, amaurosis fugax, or stroke and then underwent cerebral angiography. Eleven patients had undergone STA-MCA bypass surgery within 12 months after their initial neurological event. The selection of patients for bypass procedures was dependent upon referral practices and was, therefore, not random. For this reason, no conclusions based on comparisons between these two groups have been made, although data were analyzed separately. Age was not significantly different among the three groups. Mean blood pressure was higher in those with cerebrovascular disease than in normal individuals. The studies were conducted more than 6 months after the suspected carotid artery occlusion. All patients with carotid artery occlusion underwent a neurological examination by a neurologist or neurosurgeon and the degree of disability was graded as none, mild, moderate, or severe. Patients were interviewed in detail regarding present or past neurological symptoms from the time of their initial presentation. Five patients had experienced TIA's since the date of the suspected carotid artery occlusion. In two cases, symptoms originated from the nonoccluded carotid artery. Three patients had moderate disability and all others were unimpaired or mildly impaired.

All patients underwent arteriography at the time of their initial presentation. Postoperative angiography of those subjected to EC-IC bypass surgery showed patency of the bypass in all cases. All arteriograms were reviewed and the source of collateral flow to the occluded hemisphere was considered ophthalmic or via the circle of Willis. All patients had undergone com-

| TABLE 1 |
| Clinical summary of the three groups studied* |
| Factor | Normal Group | Carotid Occlusion | Carotid Occlusion + Bypass |
| no. of cases | 16 | 12 | 11 |
| mean age (yrs) | 62.2 ± 7.6 | 65.1 ± 7.35 | 62.9 ± 6.8 |
| mean blood pressure (mm Hg) | 87 ± 12 | 93.3 ± 18 | 102 ± 16 |
| transient ischemic attacks | 0 | 3 | 2 |
| no or mild impairment | 16 | 10 | 10 |
| moderate impairment | 0 | 2 | 1 |
| infarction on CT scan | — | 5 | 4 |
| ophthalmic collaterals on angiograms | — | 0 | 0 |
| interval from initial presentation to CBF study (mos) | 21.8 ± 11 | 31 ± 11 |
| unilateral impairment of CO₂ reactivity (mean > 0.94%/mm Hg PaCO₂) | 0 | 2 | 1 |
| bilateral impairment of CO₂ reactivity (mean < 0.66%/mm Hg PaCO₂) | 0 | 1 | 2 |

* Mean values are given ± standard deviation. CT = computerized tomography; CBF = cerebral blood flow.
puterized tomography (CT) after carotid artery occlusion. These scans were also reviewed and the location and size of areas of infarction were documented. All patients with carotid artery occlusion and normal patients underwent cerebrovascular Doppler ultrasound studies of both extracranial carotid arteries at the time of CBF measurement. Particular attention was directed to the STA in those patients who had an EC-IC bypass. The results of extracranial Doppler studies were compared with previous arteriograms.

A Novo Cerebrograph Model 10A with 10 detectors was used to measure CBF. The detectors were positioned in a standard manner for each patient over the temporoparietal area. Blood pressure was monitored by an exercise monitor and end-tidal CO₂ concentration was continuously recorded. End-tidal xenon-133 (¹³³Xe) was collected by face mask and patients were allowed a 5-minute period to accommodate to the face mask while an unchanging end-tidal CO₂ concentration was documented. Then 20 mCi of ¹³³Xe was administered intravenously and CBF was measured. After conclusion of the first CBF study, residual radioactivity was quantitated and 5% CO₂ was administered in room air for 8 minutes before the second CBF measurement, for which 30 mCi of ¹³³Xe was used. Data from five detectors over each hemisphere were combined for measurement of hemispheric flow. A noncompartmental index of blood flow, termed “CBF 15,” was calculated using the software supplied with the Novo Cerebrograph. Average blood flow from all 10 detectors was used as a measure of global CBF. The percent change in hemispheric flow was calculated as: 100 times hypercapnic hemispheric flow minus baseline hemispheric flow, divided by baseline global flow. This number was then divided by the change in PaCO₂ to obtain percent change per torr. Five patients could not tolerate CO₂ due to a perceived shortness of breath and the study was ended. Systolic blood pressure increased by 17.5 ± 15.3 mm Hg with CO₂ inhalation and there was a mean sustained rise in PaCO₂ of 15 ± 3.4 mm Hg. All values are expressed as the mean ± standard deviation.

Results

Table 1 gives the incidence of hypodense areas on the CT scans. Such areas representing infarction were found in nine patients. On angiography, all patients demonstrated filling of the MCA ipsilateral to carotid artery occlusion from the contralateral carotid artery, and no patient showed filling of the ipsilateral MCA via ophthalmic collateral vessels. Only two patients had angiographic stenosis of the contralateral internal carotid artery, but these were not judged by angiography

or Doppler studies to be flow-limiting (< 50%). Normal patients demonstrated bilateral patency of the extracranial carotid arteries on Doppler studies, and in all patients with angiographic unilateral carotid artery occlusion Doppler studies confirmed unilateral occlusion and contralateral patency. The STA’s were patent in all patients who had undergone STA-MCA bypass.

Table 2 illustrates the mean hemispheric CBF during normocapnia for the three groups. The mean end-tidal CO₂ concentration at rest was 33.8 ± 5 mm Hg for normal individuals, 35.3 ± 4.3 mm Hg for those with carotid artery occlusion, and 35.6 ± 3.6 mm Hg for those with carotid artery occlusion plus bypass. Some hyperventilation was usual due to the mask. Baseline CBF measurements for each patient were corrected to a PaCO₂ of 40 mm Hg by the CO₂ reactivity found for that patient. The mean corrected global CBF’s of the normal, carotid artery occlusion, and occlusion plus bypass groups were not significantly different (Student’s t-test). Mean hemispheric CBF was not statistically different between the right and left hemispheres of normal individuals or between hemispheres ipsilateral and contralateral to carotid artery occlusion of either occlusion group. Nine patients with evidence of infarction on CT scans showed no mean differences in CBF between the infarcted and unaffected hemispheres (mean CBF = 1.14 ± 2.99 ml/100 gm/min).

Table 2 also shows the mean hemispheric response to hypercapnia in each group. Although the global CO₂ reactivity of those with carotid occlusion was not statistically different from normal individuals, hemispheric differences in CO₂ reactivity were found. While normal subjects showed no significant difference in CO₂ reactivity between the right and left hemispheres (2.6% ± 0.89%/mm Hg PaCO₂ on the right vs. 2.6% ± 1.09%/mm Hg PaCO₂ on the left), patients with carotid artery occlusion and no bypass had significantly lower CO₂ reactivity on the side ipsilateral to the occlusion (2.13% ± 1.03%/mm Hg PaCO₂ vs. 2.46% ± 1.47%/mm Hg PaCO₂ (p < 0.05, paired t-test)). Patients with occlusion and bypass showed a CO₂ reactivity of 2.25% ± 1.51%/mm Hg PaCO₂ on the same side as the occlusion and 2.4% ± 1.86/mm Hg PaCO₂ on the opposite side. These differences approached statistical significance (p = 0.07, paired t-test). Reactivity to CO₂ was less in the hemispheres with evidence of infarction on CT scans than in the contralateral hemisphere but did not reach statistical significance (mean CO₂ reactivity = 0.33% ± 0.61%/mm Hg PaCO₂, p = 0.1; one-sided paired t-test). In five of nine cases, infarction was in the hemisphere contralateral to the carotid artery occlusion.

Age-matched men from the same patient population were used to judge the variability in CBF and CO₂ reactivity occurring naturally. The mean difference in CBF between the right and left hemispheres of normal subjects was 0.26 ± 1.07 ml/100 gm/min. The mean difference in CO₂ reactivity was 0.11% ± 0.41%/mm Hg PaCO₂. The mean global CO₂ reactivity of normal subjects was 2.6% ± 0.97%/mm Hg PaCO₂. Values that
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TABLE 2
Mean hemispheric cerebral blood flow (CBF, ml/100 gm/min) during normocapnia*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Normal Group (16 cases)</th>
<th>Carotid Occlusion + Bypass (11 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>baseline CBF (corrected to PaCO₂ of 40 mm Hg)</td>
<td>40.43 ± 7.63</td>
<td>40.66 ± 7.6</td>
</tr>
<tr>
<td>CO₂ reactivity (% increase in CBF/ mm Hg PaCO₂)</td>
<td>2.6 ± 0.89</td>
<td>2.6 ± 1.09</td>
</tr>
<tr>
<td>global CBF</td>
<td>40.51 ± 7.55</td>
<td></td>
</tr>
<tr>
<td>global CO₂ reactivity</td>
<td>2.6 ± 0.97</td>
<td></td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation.
† Significant side-to-side difference (p < 0.05, paired t-test).
‡ Side-to-side difference approaching statistical significance (p = 0.07, paired t-test).

were two standard deviations from these means were defined as abnormal. By this definition, a side-to-side difference in CBF of more than 2.4 ml/100 gm/min or in CO₂ reactivity of more than 0.94%/mm Hg PaCO₂, or a global CO₂ reactivity of less than 0.66%/mm Hg PaCO₂ are abnormal. Five patients with carotid artery occlusion (three with and two without bypass) had significantly lower CBF in the hemisphere ipsilateral to the occlusion than in the contralateral hemisphere. Three patients (all with side-to-side differences in CBF) showed a significantly lower CO₂ reactivity in the hemisphere ipsilateral to carotid artery occlusion than in the contralateral hemisphere (mean 1.3% ± 0.1%/mm Hg PaCO₂). None of these three patients had TIA's. One was moderately disabled and two were unimpaired. The disabled patient had a large unilateral infarct on the CT scan (for reasons to be discussed, the study is considered invalid in this patient). The other two patients had normal scans. One patient had undergone STA-MCA bypass and two had not. Three additional patients, one in the carotid occlusion group and two with occlusion plus bypass, showed bilateral impairment of CO₂ reactivity (< 0.3%/mm Hg PaCO₂ in all cases). One of these patients had active TIA's in the hemisphere contralateral to carotid artery occlusion, with 40% stenosis of the contralateral internal carotid artery. The other two patients had no TIA's. All had mild or no neurological disability.

Discussion

These studies have shown that a significant number of patients (20%) with unilateral carotid artery occlusion had abnormal cerebrovascular CO₂ reactivity unrelated to the patient's neurological status or the presence of TIA's. Age-matched control individuals were chosen concurrently to ascertain normal values rather than use normal values for young men in general or the CO₂ reactivity of the hemisphere contralateral to the occlusion.²,¹² The test was simple to perform and safe. The clinical utility of this test depends upon whether abnormal CO₂ reactivity is the result of maximal cerebral vasodilation in response to a proximal flow limitation or from insensitivity to CO₂. Studies of cerebral blood volume after carotid artery occlusion are consistent with the hypothesis that impaired CO₂ reactivity is the result of maximal cerebral vasodilation. Gibbs, et al.,⁷ using PET, found that cerebral blood volume was greatly increased in patients with orthostatic ischemic symptoms and bilateral carotid artery occlusion; this observation was associated with increased oxygen extraction in these patients. In that study, 28% of the group of patients with unilateral carotid artery occlusion and no orthostatic TIA's were found to have significant increases in cerebral blood volume with no increase in the O₂ extraction ratio. This group of patients is similar to our group who showed a 20% incidence of abnormalities in CO₂ reactivity.

In some patients with carotid artery occlusion, decreased CO₂ reactivity is probably the result of insensitivity to CO₂. Decreased CO₂ reactivity of chronically infarcted brain has been shown experimentally.¹⁷ Bullock, et al.,³ reported decreased CO₂ reactivity in patients early after minor infarction. In patients without carotid artery occlusion, they found a relationship between diminished CO₂ reactivity and evidence of infarction in the CT scan.³ Despite the small sample size (nine subjects) in our study, decreased CO₂ reactivity approaching statistical significance was found by CT scan in infarcted hemispheres, regardless of the side of occlusion. These data suggest that in patients with acute infarction or with evidence of infarction on CT scan, the test may not be a valid index of cerebrovascular collateral reserve capacity.

Whether due to decreased response to CO₂ or maximal cerebral vasodilation, abnormalities in CO₂ reactivity after carotid artery occlusion have been consistently found by others. McHenry¹¹ and Dyken, et al.,³ have shown a lower mean global CO₂ reactivity in patients with carotid artery occlusion than in comparable patients with cerebral atherosclerosis and chronic infarction but without occlusion. Impairment of CO₂ reactivity ipsilateral to carotid artery occlusion has been found to be more severe in patients with angiographic evidence of collateral compromise than in those without.
Norrving, et al.,\textsuperscript{12} considering a normal response to CO\textsubscript{2} inhalation to be any value over 0.75 ml/mm Hg PaCO\textsubscript{2}, found a much higher incidence of impaired CO\textsubscript{2} reactivity in the affected hemisphere of patients with ophthalmic collateral flow than in those with filling of the hemisphere ipsilateral to the occlusion through the circle of Willis. Powers, et al.,\textsuperscript{16} noted a significant relationship between impaired cerebral hemodynamics and impaired angiographic collateral flow in patients with carotid artery stenosis. Carbon dioxide reactivity has been found lower in the hemispheres of patients with bilateral carotid artery occlusion than in normal individuals, in asymptomatic hemispheres contralateral to carotid artery occlusion, or in hemispheres ipsilateral to carotid artery occlusion.\textsuperscript{2,3} Bullock, et al.,\textsuperscript{3} found that CO\textsubscript{2} reactivity was significantly lower in hemispheres ipsilateral to carotid artery occlusion in patients with ongoing TIA’s than in hemispheres ipsilateral to carotid artery occlusion in those without ongoing symptoms, a finding we did not duplicate.

Based on the relatively high incidence of abnormalities in CO\textsubscript{2} reactivity (20%) found in patients who had no angiographic or clinical evidence of impaired cerebrovascular collateral reserve capacity (including those with bilateral carotid artery occlusion or orthostatic TIA’s), we think this test can be used to identify a subgroup of patients who have maximal cerebral vasodilation distal to carotid artery occlusion. The test is safe and simple to perform, and equipment is accessible to most hospitals. The test should be cautiously interpreted in those individuals with evidence of infarction on CT scanning. The clinical significance of this test cannot be determined until long-term follow-up data are obtained in a group of patients with carotid artery occlusion to determine if there are differences in the natural history of those with and without impaired CO\textsubscript{2} reactivity. If impaired CO\textsubscript{2} reactivity after carotid artery occlusion is associated with an increased risk or severity of subsequent infarction, this test would provide a physiological basis for selection of a subgroup of patients with carotid artery occlusion who might be helped by surgical revascularization.

References

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