Noninvasive Assessment of CO₂-Induced Cerebral Vasomotor Response in Normal Individuals and Patients With Internal Carotid Artery Occlusions

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To evaluate the CO₂-induced vasomotor reactivity of the cerebral vasculature, relative changes of blood flow velocity within the middle cerebral artery were measured by transcranial Doppler ultrasonography during normocapnia and various degrees of hypercapnia and hypocapnia. We studied 40 normal individuals and 40 patients with unilateral and 15 patients with bilateral internal carotid artery occlusions. When blood flow velocity changes as percent of normocapnic values were plotted against end-tidal CO₂ volume percent, a biasymptotic curve (a tangent-hyperbolic function) gave the best fit of the scattergram. The distance between the upper and lower asymptotes was defined as cerebral vasomotor reactivity. In the normal individuals, mean±SD vasomotor reactivity was 85.63 ±15.96%. In patients with internal carotid artery occlusions, vasomotor reactivity was significantly lower than normal on both the occluded (mean 45.2%, median 50.4%; p<0.0001) and the nonoccluded (mean±SD 67.7 ±13.3%, p<0.01) sides in the unilateral group and on both sides (mean±SD 36.6 ±15.9% and 44.9 ±24.6%, p<0.0001) in the bilateral group. The difference between vasomotor reactivity for symptomatic and asymptomatic unilateral occlusions was also highly significant (mean 37.6% and 62.9%, p<0.006). Vasomotor reactivity was also significantly lower in patients with low-flow infarctions on computed tomography than in patients with normal scans (mean±SD 36.7 ±25% and 60.2 ±16.9%, p<0.008). A striking association of low-flow infarctions, ischemic ophthalmopathy, and hypostatic transient ischemic attacks was found with vasomotor reactivities of <34% or even paradoxical reactions. Transcranial Doppler ultrasonographic evaluation of cerebral vasomotor reactivity is a new, feasible, noninvasive, and reproducible technique that allows selection and quantification of patients with true cerebrovascular insufficiency. (Stroke 1988;19:963–969)

The adverse effects of extracranial arterial occlusive disease on cerebral blood flow (CBF) and intracranial hemodynamics have previously been somewhat overestimated. Including small vessel disease,1-2 the predominant mechanism of stroke is thromboembolic rather than a low blood flow effect.3-6 A small subgroup of patients, however, experience transient ischemic attacks (TIAs), permanent stroke(s), and/or progressive ischemic eye disease due to critically reduced CBF.6-8 These patients represent true cases of cerebrovascular insufficiency in the strict sense in that CBF cannot be sufficiently maintained even with recruitment of all available mechanisms for compensation. Such patients may benefit from therapeutic measures to improve large vessel flow, such as extracranial-intracranial bypass surgery, carotid endarterectomy, or other recanalization techniques, but these patients would not be expected to benefit from any form of anticoagulation treatment.

Identification of this subgroup of stroke-prone individuals is based on the detection of an exhausted cerebrovascular reserve.9 Methods of detection have included angiography, regional cerebral blood flow (rCBF) techniques, and positron emission tomogra-
phy. Transcranial Doppler ultrasonography (TCD) (EME TC-2 64 device, Eden Medizinische Elektro-
nik, Überlingen/Bodensee, FRG) is a new method
that measures blood flow velocity within the basal
cerebral arteries from outside the skull. Compared
with the above-mentioned techniques, however,
TCD is safer (noninvasive, nonradioactive) and less
expensive and is very sensitive to the time resolu-
tion of blood flow changes.10,11

The purpose of our study was to examine the effect
of CO2 stimulation on blood flow velocity in the
middle cerebral artery (MCA) and to evaluate its
potential as an indicator of cerebral arterial reserve.
We used TCD to quantify MCA blood flow velocity
under normocapnic, hypercapnic, and hypocapnic
conditions in diseased and nondiseased individuals.

Theoretical Background

Intactness of vasomotor reserve implies that a
drop in perfusion pressure can be counterbalanced
by vasodilatation of cortical arterioles to maintain a
sufficient blood supply.9,12,13 This reserve may
become exhausted if the resistance vessels of the
brain are already maximally dilated. In this state,
the vessels are refractory to any further vasodilator
stimuli, and hypercapnia cannot increase blood
flow. This condition is critical because ischemic
brain injury would occur if perfusion pressure were
further reduced for any reason.

During changing CO2 concentrations, the relation
between blood flow velocity and volume within a
large basal artery is linear as long as CO2 does not
affect the diameter of the large proximal arterial
segments themselves. It has been shown that the
CO2 effect is restricted mainly to the peripheral
vascular bed, in particular the small cortical
vessels.14-16 This view is further supported by our
findings and those of others17,18 that MCA blood
flow velocity increases during hypercapnia and
decreases during hypocapnia. Just the opposite
would occur if the MCA diameter were enlarged
during CO2 breathing, and vice versa. Thus,
assuming that the diameter of large basal cerebral
arteries remains fairly constant, intraindividual
changes in blood flow velocity during TCD exami-
nation directly reflect changes in volume flow.17

During comparison of CO2-induced CBF changes
(xenon-133 inhalation technique) with blood flow
velocity modulation in the basal cerebral arteries,19
a close and linear correlation between these two
parameters was found.

Subjects and Methods

Methods

Blood flow velocity was measured using TCD
during CO2 activation, with each subject supine
and instructed to rest comfortably. While the subject
was breathing room air and relaxing, a mask was
placed on his face to allow acclimation to the test
situation. The TCD transducer was placed over one
temporal plane, and the MCA under study was
insonated at a depth of 50–55 mm, depending on the
optimization and stability of the signal.

The end-tidal CO2 volume percentage (CO2 vol%)
was recorded by an infrared CO2 analyzer (Cap-
nolog, Datex Instrumentarium OY, Helsinki,
Finland). Blood pressure (systolic, diastolic, and
mean) and heart rate were also monitored noninva-
sively (Dinamap ergometer, Criticon Inc., Tampa,
Florida) while the subject breathed room air (nor-
mocapnia), air with CO2 concentrations of 2%, 3%,
4%, and 5%, and during various intensities of hyper-
ventilation. When the mean MCA blood flow veloc-
ity, end-tidal CO2 vol%, arterial blood pressure, and
heart rate reached steady states, a sequence of
approximately 20 cardiac cycles was recorded on
tape for a more precise offline, computer-assisted
determination of mean MCA blood flow velocities.

Mean blood flow velocity during inhalation of
room air was considered to be 100% and was
compared with the percentage changes in mean
blood flow velocity during inhalation of various CO2
concentrations or during hyperventilation. These
relative blood flow velocities were plotted against
the corresponding end-tidal CO2 vol% (Figure 1).
Because of interindividual variation of MCA blood
flow velocities at rest and because of individual
attenuation of the blood flow echoes within the
skull, no attempt was made to convert relative
blood flow velocities to absolute values.

Plotted data were subjected to curve fitting. A
tangent–hyperbolic function gave the best fit. The
distance between the two asymptotes was consid-
ered to reflect reactivity span, that is, responsive-

FIGURE 1. Vasomotor reactivity in 40 normal individu-
als of widely varying age (20–75 years). CO2-induced
blood flow velocity changes differed for hypercapnia
(upper curve) and hypocapnia (lower curve), with changes
of 53.5% and 35.3%, respectively; average change was
87.8%. Due to greater variation during hypercapnia,
correlation coefficient of upper curve (r=0.92) was lower
than that of lower curve (r=0.95). %, relative blood
flow velocity; Vol. % CO2, end-tidal carbon dioxide
volume percentage.
TABLE 1. Clinical and Computed Tomography Findings in 40 Patients With Unilateral ICA Occlusions

<table>
<thead>
<tr>
<th>Sex</th>
<th>30 men</th>
<th>10 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side of occlusion</td>
<td>24 on right</td>
<td>16 on left</td>
</tr>
<tr>
<td>Lesions of contralateral carotid arteries</td>
<td>27 intact</td>
<td>13 with &gt;70% ICA stenoses</td>
</tr>
<tr>
<td>Lesions of other neck arteries</td>
<td>27 intact</td>
<td>7 stenoses/occlusions of ECA*</td>
</tr>
<tr>
<td>Type of stroke</td>
<td>12 asymptomatic patients†</td>
<td>12 major strokes with severe deficits</td>
</tr>
<tr>
<td>Vascular eye disease</td>
<td>3 amaurosis fugax</td>
<td>2 hypostatic TIAs</td>
</tr>
<tr>
<td>Ipsilateral hemispheric computed tomography findings</td>
<td>17 normal, 23 with infarcts</td>
<td>16 low-flow infarctions*</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; VA, vertebral artery; RIND, reversible ischemic neurologic deficit; TIA, transient ischemic attack.
*Overlapping counts; †two asymptomatic patients had visible lesions on computed tomography.

TABLE 2. Clinical and Computed Tomography Findings in 15 Patients With Bilateral Internal Carotid Artery Occlusions

<table>
<thead>
<tr>
<th>Sex</th>
<th>40 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions of other neck arteries</td>
<td>5 intact</td>
</tr>
<tr>
<td>Type of stroke</td>
<td>6 patients without stroke symptoms</td>
</tr>
<tr>
<td>Vascular eye disease</td>
<td>1 severe ischemic ophthalmopathy</td>
</tr>
<tr>
<td>Computed tomography findings</td>
<td>6 normal</td>
</tr>
</tbody>
</table>

*Overlapping counts.

the remaining six patients had either frequently recurring TIAs during orthostatic challenge or ischemic eye disease. The clinical and extracranial sonographic findings are summarized in Table 1. Fifteen patients with bilateral occlusion of the ICAs were also examined (ages ranged from 47 to 84, mean 63, years). Five patients were asymptomatic, eight had been symptom-free for at least 6 weeks after stroke, and two were experiencing either orthostatically induced TIAs or progressive ischemic ophthalmopathy. The clinical, ultrasonography, and computed tomography (CT) findings are summarized in Table 2.

All 55 patients with occlusion(s) were studied by CT imaging of the head to identify both symptomatic and silent infarctions ipsilateral to the ICA occlusion(s). Territorial infarctions were differentiated from low-flow lesions. Low-flow infarcts were located in the subcortical white matter or in the watershed areas of the cortex.

Blood flow velocity in the MCA over a range of end-tidal CO2 concentrations was determined 10 times in two volunteers to estimate the intrapatient reproducibility of the test.

Results

The mean ± SD change in blood flow velocity from hypcapnia to hypercapnia in the 40 normal individuals was 87.8 ± 16% (calculated from curve fitting in Figure 1) or 85.63 ± 15.96% (calculated from 40 individual values). The data corresponded to a biasymptotic, s-shaped curve with the upper asymptote corresponding to a relative MCA blood flow velocity of 152.5% and the lower asymptote (during hyperventilation) to 64.7% of the MCA blood flow velocity at rest (Figure 1). The algorithm for curve fitting was f(X) = k × τ(X) = k(e^x) -
FIGURE 2. Vasomotor reactivity in patient with unilateral internal carotid artery occlusion. a: Severely reduced vasomotor reactivity (30.9%) on occluded side, corresponding to ipsilateral low-flow infarction and contralateral mild hemiparesis. Other neck arteries were completely intact. b: On nonoccluded side, vasomotor reactivity was nearly normal (74.4%). v%, relative blood flow velocity; Vol. % CO₂, end-tidal carbon dioxide volume percentage.

\[ \frac{e^{-X}}{(e^{X} + e^{-X})} \text{, performed separately for each branch of the curve.} \]

\[ k \text{ is a factor necessary for data processing, which transforms each concrete mean flow velocity into a corresponding value within the -1 to 1 range of } r. \]

A sufficient adaptation of the line was achieved by weighting the \[ Y \] closest to the normocapnic value with 1, the next-closest with 2, and so forth.

In the 40 patients with unilateral ICA occlusion, vasomotor reactivity on the occluded side was significantly lower (mean 45.2%, median 50.4%) than on the nonoccluded side (mean ± SD 67.7 ± 13.3%; \( p < 0.0001 \), Wilcoxon unpaired two-sample test). On the nonoccluded side, mean ± SD vasomotor reactivity was less than that for normal individuals (\( p < 0.01 \), \( t \) test for nonequal variances). An illustrative case with severely reduced vasomotor reactivity due to unilateral ICA occlusion is shown in Figure 2. Among the 28 patients with symptomatic ICA occlusions, vasomotor reactivity was significantly lower (mean 37.6%, median 42.0%) than among the 12 asymptomatic patients (mean ± SD 62.9 ± 15.6%; \( p < 0.006 \), Wilcoxon unpaired two-sample test).

Among patients with unilateral ICA occlusion, 17 CTs were normal and 23 patients had 25 visible infarctions on CT that corresponded to the side of occlusion. The infarctions were classified as low-flow in 16 and as territorial or thromboembolic type in nine; two patients had both types of infarction. Mean ± SD vasomotor reactivity was significantly lower in patients with low-flow infarctions (36.7 ± 25%) than in patients with normal CTs (60.2 ± 16.9%; \( p = 0.008 \), \( t \) test for equal variance), whereas mean ± SD vasomotor reactivity in those with territorial infarctions (52.6 ± 27.8%) was not significantly different from those with normal CT (\( p = 0.45 \)). Mean ± SD vasomotor reactivity in 14 patients with purely territorial infarcts was not significantly different from that in 7 with pure low-flow infarctions (\( p = 0.19 \), \( t \) test), presumably due to the small number of patients.

In the 15 patients with bilateral ICA occlusions, mean ± SD vasomotor reactivity was severely reduced on both sides (right 36.6 ± 15.9%; left 44.9 ± 24.6%; \( p = 0.28 \), \( t \) test). Both values were significantly different from normal findings (\( p < 0.0001 \)). In spite of bilateral ICA occlusion, vasomotor reactivity was fairly well-preserved in two patients with values on the right or left side of 77.3% or 78.2% and 68.4% or 75.9%, respectively.

FIGURE 3. Vasomotor reactivity and blood pressure during CO₂ testing in 44-year-old patient with unilateral internal carotid artery occlusion. Despite slight increase of arterial blood pressure (BP), blood flow velocity within middle cerebral artery (MCA) decreased during 5% CO₂ inhalation (arrow), indicating some degree of intracerebral steal. Vasomotor reactivity was nearly lost. Residual vasomotor reactivity of 9.8% was mainly due to vasoconstrictor response during hypocapnia, which was less severely affected. These findings indicate severe low-flow conditions within MCA territory under study (•, mean; ▼, systolic; △, diastolic BP). Patient had repeated hypostatic transient ischemic attacks, and computed tomography demonstrated atypical low-flow infarction within centrum semiovale. v%, relative blood flow velocity; Vol. % CO₂, end-tidal carbon dioxide volume percentage.
TABLE 3. Degree of Vasomotor Reactivity Reduction Compared With Frequency of Clinical Symptoms and Computed Tomography Lesions

<table>
<thead>
<tr>
<th>Patients with unilateral ICA occlusion (n = 40)</th>
<th>Patients with bilateral ICA occlusions (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe reduction (≤33%)</td>
<td></td>
</tr>
<tr>
<td>Occluded side</td>
<td>Nonoccluded side</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Moderate reduction (34–66%)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nearly normal (≥67%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
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</tbody>
</table>

ICA, internal carotid artery; IO, ischemic ophthalmopathy; HT, hypostatic transient ischemic attack; LFI, low-flow infarction.

Vasomotor reactivity was categorized arbitrarily as severe reduction, <34% change in response to CO₂ stimulation; moderate reduction, 34–66% change; and nearly normal, >66% change. Among the 40 patients with unilateral ICA occlusion, 11, 21, and eight had severely reduced, moderately reduced, and nearly normal vasomotor reactivities, respectively. Among the 30 hemispheres in the 15 patients with bilateral ICA occlusion, the corresponding numbers were 13, 14, and three. Two cases even showed a paradoxical reaction, with a decrease in blood flow velocity during hypercapnia (Figure 3). This was interpreted as an intracerebral transfer of blood from the affected to the less affected or unaffected surrounding brain tissue or contralateral hemisphere. A striking association of low-blood-flow–induced infarctions of the corresponding hemisphere (n = 3), ischemic ophthalmopathy (n = 2) and/or repeated hypostatic TIA (n = 2) with severely reduced vasomotor reactivity was noted. This was true for both unilateral and bilateral ICA occlusions (Table 3). The low-flow infarctions of these patients within the terminal supply and watershed areas were small in two and large in one but had a good clinical prognosis in all three cases.

The intraindividual reproducibility of vasomotor reactivity measurements within the MCA territory was high (Figure 4). The mean ± SD, range in the two volunteers were 97.5 ± 5.6%, 19% (average 98.1%) and 80.5 ± 7.0%, 19.2% (average 79.2%), respectively.

Discussion

In our study, blood flow velocity within the normal MCA under various capnic conditions was increased 52.5% during hypercapnia and decreased 35.3% during hypocapnia. These findings agree precisely with those of Harper and Glass in animals and of previous workers in humans using continuous-wave Doppler ultrasonography of the extracranial cerebral arteries or rCBF measurements under CO₂ stimulation. Kindt et al found a relative increase of 48% in blood flow velocity within the common carotid artery of individuals breathing 5% or 6.8% CO₂, and Breslau et al demonstrated a 47% increase within the ICA. Kety and Schmidt measured a CBF increase of 43% in five subjects and of 124% in one young healthy adult during administration of 5% CO₂. Yamaguchi et al found a 35.5–44% decrease of the fast-compartment CBF during hyperventilation (our calculations from the original data of Yamaguchi et al). Yonas et al reviewed the rCBF literature and reported a 3–5% change in CBF per unit change in Paco₂. From the CO₂-reactivity curve in Figure 1, an 80% change of the MCA blood flow velocity can be estimated during the steepest part of the curve, that is, from 3.5 to 5.5 CO₂ vol%. After transforming this CO₂ vol% data to Paco₂ values, this change would correspond to a 16 mm Hg change, thus a 5% blood flow velocity change per mm Hg CO₂. The above-described TCD technique is more informative than the two-point measurement used by others, which does not consider the vasoconstrictor effects of hypocarbia.

Similar to other rCBF methods, a principal limitation must be kept in mind when clinical conclusions are drawn from the measurements. Cerebral autoregulation in a strict sense is defined as the vasomotor ability to maintain constant CBF in spite of changing perfusion pressure. Cerebrovascular reactivity to CO₂ is a partially independent mechanism, although its loss is always associ-
ated with lack of dilatatory arterial reactions to diminishing perfusion pressure. The opposite, however, need not be invariably true. CO₂ reactivity has been clearly shown to be retained in certain circumstances in which autoregulation has been abolished.¹⁴ States of preserved CO₂ reactivity but impaired autoregulation have been termed dissociated vasoparalysis and have been proven to occur during postischemic hyperperfusion.³⁰ Even more complicated, the vasoconstrictor reaction to increased blood pressure may be preserved, whereas the vasodilatation to meet a perfusion pressure reduction might be exhausted.³¹

The intact circle of Willis with its immense collateralizing capacity via the posterior and/or anterior communicating arteries is usually capable of fully compensating for blood flow reductions due to unilateral ICA occlusion.³ In individual cases, this may be true even if additional contralateral ICA or vertebral artery disease is present. Obviously, the severity of the extracranial obstructions per se is less relevant for the final brain perfusion than the configuration of the circle of Willis.

From our experience with these patients, low-blood-flow–induced TIAs occur if the compensatory mechanisms of the brain to preserve adequate hemispheric perfusion are exhausted. This may be the case if 1) the circle of Willis is incompetent, 2) the cerebral vasodilatation within the depleted brain territory has already been maximized, 3) the oxygen extraction rate cannot be further augmented, and/or 4) if additional factors such as hypotension, hypoxia, anemia, etc stress the cerebral circulation. The mildness of these strokes does not contradict structural damage of the brain, which most often has the typical features of a low-flow infarction. In most cases, low-flow infarctions are solitary lesions within the subcortical white matter. They are larger as well as less sharply demarcated than lacunes and are associated with a relatively benign prognosis.²⁰

In patients with severe ICA disease in whom no regular collateral channel of the circle of Willis is present or sufficiently working, perfusion of the depleted hemisphere must rely solely on retrograde influx via the ophthalmic artery. This was angiographically confirmed in our patients with both frequently recurring hemispheric TIA, chronic ischemic eye disease, and low-flow infarction on CT scan. The ophthalmic artery, however, is only a minor pathway with very limited channeling capacities. In these patients, blood supply to the eye may also be compromised by a siphoning effect of the distal carotid artery on the ocular circulation, resulting in recurring ischemic attacks of the marginally supplied brain, as well as chronic, progressive, ischemic disease of the eye. In patients with evidence of low-blood-flow–induced TIAs, a thorough examination of the fundus oculi is necessary to detect the early stages of ischemic eye disease and to prevent complete loss of vision.³²,³³

A relatively normal CO₂ response in the presence of (an) occluded ICA(s) indicates satisfactory collateral blood supply, as is often the case. Only moderately reduced or nearly normal vasomotor reactivities were found ipsilaterally in 73% of the patients with unilateral ICA occlusion and in 57% of the hemispheres from patients with bilateral ICA occlusions. Five of 11 patients in the unilaterally occluded group with <34% values were symptomatic, with ischemic ophthalmopathy, low-flow brain infarctions, or hypostatic TIAs. This was also true in four of 13 hemispheres in the patients with bilaterally occluded ICAs. In contrast, no ischemic symptoms occurred at all if vasomotor reactivity was >65%. This was the case in 20% of the patients with unilateral and in 10% of the hemispheres from patients with bilateral ICA occlusion(s). From our experience, patients with convincing signs of carotid distribution "insufficiency" in the hemodynamic sense are rare, and they account for only approximately 1–2% of our stroke cases. With increasing experience, the vasomotor reactivity threshold for the identification of patients who are at risk for hemodynamically caused stroke symptoms will be better defined and will help to guide recanalizing procedures.

A few patients who demonstrated low-flow infarctions on CT revealed normal or only moderately reduced vasomotor reactivities on the corresponding side. They all had suffered a stroke many months or even years before. This suggests that a gradual restitution of CBF had occurred over a period of time following the decompensation during the acute phase. This view is supported by our findings in two patients during follow-up studies who demonstrated a spontaneous improvement of a formerly severely reduced vasomotor reactivity. Conversely, patients with severely reduced vasomotor reactivity who remain asymptomatic may in fact be stroke-prone but may not have experienced critical challenges of their marginal cerebral blood supply yet. Long-term follow-up of vasomotor reactivity and clinical reexaminations are necessary to further support our assumptions.

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References


Key WORDS • blood flow velocity • cerebral blood flow • carotid artery diseases • ultrasonics
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http://stroke.ahajournals.org/content/19/8/963