Course of Carotid Artery Occlusions With Impaired Cerebrovascular Reactivity

Bernhard Kleiser, MD, and Bernhard Widder, MD, PhD

Background and Purpose: Retrospective studies have found a close correlation between an impaired cerebrovascular reserve capacity and the incidence of hemodynamic stroke. The present study evaluates this relation prospectively.

Methods: We measured the CO₂ reactivity in 85 patients with internal carotid artery occlusions by transcranial Doppler sonography (Doppler CO₂ test). All patients were prospectively followed for 38±15 (mean±SD) months.

Results: In the group with sufficient CO₂ reactivity, four of 48 (8%) developed ipsilateral transient symptoms, none a stroke. In cases with diminished or exhausted cerebrovascular reserve capacity, 12 of 37 (32%) suffered an ipsilateral event (four transient ischemic attacks, eight strokes) \((p<0.01)\).

Conclusions: The Doppler CO₂ test seems to be a valuable method of estimating the risk of stroke in patients with carotid artery occlusions. (Stroke 1992;23:171-174)
BHBH, HHKS, 92.11.38 11.81.91 LI C02 5 : 16 Din

N/l  2 3 4 5 6 7
HCA 866 867 857  B68 866 856
C02 6.4 7.5 5.2 5.6 7.2 5.2

**FIGURE 1.** Mean values of middle cerebral artery (MCA) blood flow velocity in centimeters per second and end-tidal PCO2 values in percent during steady states of normocapnia, hypercapnia, and hypocapnia. Right lower graph shows relation between PCO2 (abscissa) and MCA blood flow velocity (ordinate).

an infrared CO2 analyzer (Capnolog, Datex Instrumentarium OY, Helsinki, Finland).

The method of calculating CO2 reactivity has already been described in detail.13 Briefly, the relation of the cerebral blood flow velocity to the concentration of CO2 in the blood normally shows a sigmoid curve with a linear relation in the physiological range of 30–50 mm Hg Pco2.14 In pathological cases the curve is shifted to the left, resulting in a decreased flow during hypercapnia or even no response to hypercapnia as well as to hypocapnia.

Since previous studies showed that only markedly diminished or exhausted CO2 reactivities correlated with an increased rate of ipsilateral ischemic events,13 we distinguished between three categories of sufficient, diminished, and exhausted cerebrovascular capacity (Table I).15 In the case of a sufficient CO2 reactivity, the MCA blood flow velocity increased at least 10% during hypercapnia of 1 vol% CO2 enhancement and decreased at least 10% during hypocapnia of 1 vol% CO2 diminution in the physiological range. A diminished cerebrovascular reactivity was characterized by a marked decrease or lack of increase in flow during hypercapnia. A marked decrease or lack of change in blood flow during hypercapnia as well as hypocapnia revealed an exhausted CO2 reactivity.

**Results**

The 85 patients were observed for 38±15 (mean±SD) months without respect to ischemic events. All subjects who did not reach the end point were observed for at least 24 months; dropouts did not occur. A total of 16 patients suffered an ipsilateral ischemic deficit during the follow-up period (eight strokes, eight TIA or prolonged reversible deficits). Five developed a contralateral ischemic deficit (four strokes, one TIA), which was combined with a progression of an ICA stenosis on the same side in three cases. This resulted in an annual stroke rate of 3% ipsilateral to the occluded artery and of 1.5% on the contralateral side without respect to death or survival. Ten patients died of noncerebral causes.

In the group with sufficient cerebrovascular reserve, four of 48 (8%) developed an ipsilateral TIA or prolonged reversible deficit, none a stroke (Figure 2). Five patients died of other causes. The mean follow-up time was 42±14 months.

In the group with diminished CO2 reactivity, six of 26 (23%) suffered an ipsilateral ischemic event (three strokes, three TIA) (Figure 2), and three a contralateral deficit (two strokes, one TIA). Four patients died of other causes. The mean follow-up time was 34±13 months, and the annual rate for ipsilateral strokes was 4%.

Of the cases with exhausted cerebrovascular capacity, six of 11 (55%) developed an ipsilateral neurological deficit (five strokes, one TIA). Four events occurred during the first 3 months after entering the study (Figure 2). In two of these cases, the cerebral ischemia was due to a drop in blood pressure during abdominal surgery. One other patient developed symptoms during antihypertensive treatment. Two patients suffered a stroke of the contralateral hemisphere, and one subject died of a noncerebral cause. The mean follow-up time was 32±18 months, and the annual rate for ipsilateral strokes was 17%. A significant correlation between ipsilateral ischemic events and a diminished or exhausted CO2 reactivity was found ($\chi^2$ test, $p<0.01$).

Concerning the clinical course, there was no significant relation between patients with and without history of neurological symptoms such as TIA or stroke ($\chi^2$ test, $p>0.05$). Moreover, no significant influence of the patency of the contralateral carotid artery could be established.

**Discussion**

The overall annual rate of 3% for ipsilateral strokes in our study is comparable to the results of other investigations (Table 2). In a similar group of mixed asymptomatic and symptomatic patients with ICA occlusions, Furlan et al1 found an ipsilateral stroke rate of 2% per year, and Hennerici et al2 described 4% in asymptomatic cases. In symptomatic

<table>
<thead>
<tr>
<th>CO2 reactivity</th>
<th>Increase during hypercapnia of +1 vol% CO2 (%)</th>
<th>Decrease during hypocapnia of -1 vol% CO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>$\geq 10$</td>
<td>$\geq 10$</td>
</tr>
<tr>
<td>Diminished</td>
<td>$&lt; 10$</td>
<td>$\geq 10$</td>
</tr>
<tr>
<td>Exhausted</td>
<td>$&lt; 5$</td>
<td>$&lt; 10$</td>
</tr>
</tbody>
</table>

Values reflect change in middle cerebral artery velocity compared with physiological baseline values.
patients the annual stroke rates were slightly higher: Cote et al\textsuperscript{3} reported 5\%, and the EC/IC Bypass Study Group\textsuperscript{4} reported a rate of 6\% among nonoperated patients. In all these investigations, however, the quality of the intracranial collateralization was not assessed.

In our study the classification into three groups with sufficient, diminished, and exhausted CO\textsubscript{2} reactivity revealed considerable differences concerning the prognosis. Compared with the cases with sufficient cerebrovascular reserve and compared with the long-term follow-up studies in the literature, the patients with diminished and exhausted CO\textsubscript{2} reactivity suffered an ipsilateral stroke significantly more often. The stroke rate was as high as 20\% during the first year of follow-up.

In cases with exhausted CO\textsubscript{2} reactivity, neurological events occurred remarkably more frequently during the first months than in the later period. This could be explained by the fact that an initially insufficient collateralization may improve because of a delayed formation of preformed collaterals.\textsuperscript{16} About one third of another group of patients with ICA occlusions and originally diminished or exhausted cerebrovascular capacity showed an increase of CO\textsubscript{2} reactivity during the first year (B. Kleiser and B. Widder, unpublished observations).

Unexpectedly, stenoses of the contralateral ICA influenced neither the cerebrovascular reactivity nor the clinical course in our study. This may be explained by the fact that the patency of the intracranial anastomoses (circle of Willis, leptomeningeal anastomoses) plays a more important role for cerebral hemodynamics than the extracranial vessels.

A comparable investigation has been published by Durham et al\textsuperscript{17} using xenon computed tomography with acetazolamide challenge for evaluating cerebral hemodynamics. During a mean follow-up time of 18 months, nine of 33 (27\%) of their patients with compromised vasoreactivity and one of 33 (3\%) with normal hemodynamics suffered a stroke.

Powers et al\textsuperscript{18} examined 23 patients with ICA occlusions by PET scanning and followed them for about 1 year. The only ischemic stroke occurred in the five patients with increased oxygen extraction rate 15 months after admission. Such an increased oxygen extraction rate indicates that the arterioles are already maximally dilated and the cerebral me-

### Table 2. Spontaneous Course of Internal Carotid Artery Occlusions

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Date</th>
<th>n</th>
<th>Status before follow-up</th>
<th>Follow-up time (mo)</th>
<th>Annual rate of ipsilateral Stroke (%)</th>
<th>TIA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bornstein and Norris\textsuperscript{6}</td>
<td>1989</td>
<td>19</td>
<td>Asymptomatic</td>
<td>48</td>
<td>0</td>
<td>4.0</td>
</tr>
<tr>
<td>Cote et al\textsuperscript{3}</td>
<td>1983</td>
<td>47</td>
<td>Symptomatic</td>
<td>34</td>
<td>5.2</td>
<td>...</td>
</tr>
<tr>
<td>Eriksson\textsuperscript{3}</td>
<td>1986</td>
<td>43</td>
<td>Asymptomatic</td>
<td>47</td>
<td>5.0</td>
<td>...</td>
</tr>
<tr>
<td>Furlan et al\textsuperscript{3}</td>
<td>1980</td>
<td>138</td>
<td>Asymptomatic/symptomatic</td>
<td>60</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Hennerici et al\textsuperscript{3}</td>
<td>1986</td>
<td>49</td>
<td>Asymptomatic</td>
<td>31</td>
<td>3.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Nicholls et al\textsuperscript{3}</td>
<td>1989</td>
<td>24</td>
<td>Asymptomatic/symptomatic</td>
<td>39</td>
<td>2.5</td>
<td>3.8</td>
</tr>
<tr>
<td>EC/IC Bypass Study Group\textsuperscript{4}</td>
<td>1985</td>
<td>423</td>
<td>Symptomatic</td>
<td>56</td>
<td>6.2</td>
<td>...</td>
</tr>
<tr>
<td>Own investigations</td>
<td>1985</td>
<td>423</td>
<td>Symptomatic</td>
<td>38</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack; EC/IC, extracranial/intracranial.
tabolism can only be maintained by an enlarged extraction of oxygen from the blood. Although this result seems to support our own findings, the number of patients studied is too small for a definite analysis. Moreover, most PET investigations were performed within 30 days after the onset of the (last) neurological symptoms. During the first weeks after a stroke, however, cerebral hemodynamics may be disturbed, and the intracranial collaterals may not be fully developed.  

In conclusion, our results support the hypothesis that the Doppler CO$_2$ test may be a suitable method for evaluating the risk of hemodynamically induced stroke in patients with ICA occlusions. Compared with other available methods such as PET and single photon emission computerized tomography, the transcranial Doppler CO$_2$ test is much less expensive. Additionally, compared with the competitive method of achieving vasodilation by intravenous acetazolamide (Diamox) administration, carbogene ventilation has several advantages: the method is noninvasive, consumes less time, and in more than 1,000 investigations we could observe no side effects. During the 1–2 minutes of carbogene administration we never found relevant changes in blood pressure. On the other hand, two limitations of transcranial Doppler sonography have to be considered: Doppler recordings from the MCA are inadequate or even absent in about 5–10% of all patients because of insufficient ultrasound transmission through the skull, and cardiac arrhythmia can cause unreliable flow velocity measurements.

The occurrence of ischemic deficits in three patients during surgery and antihypertensive treatment indicates the important role of the systemic blood pressure in hemodynamically impaired cases. Therefore, lowering of blood pressure should be avoided in patients with ICA occlusions until there is evidence of a sufficient collateralization. Moreover, the small subgroup of patients with markedly diminished cerebrovascular reserve capacity could benefit from extracranial–intracranial bypass surgery, if the surgical procedure is able to significantly improve the hemispheric blood supply.

References


Key Words: • carotid artery diseases • hemodynamics • ultrasonics
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