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)

The natural history of internal carotid artery (ICA) occlusions is well known. In these studies, however, the patency of intracranial collateralization was not considered. Pathophysiological considerations suggest that an insufficient collateralization may cause a critical reduction of cerebral blood flow and an increased risk of hemodynamically induced stroke.

Investigation of the cerebrovascular reserve capacity by regional cerebral blood flow measurement and positron emission tomography (PET) scanning have been considered suitable methods of evaluating the efficiency of the collaterals. Another simple and noninvasive technique is the Doppler CO₂ test. It is based on transcranial Doppler sonography that gives information about changes of blood flow velocity in the basal cerebral arteries.

Previous retrospective results found a close correlation between an impaired CO₂ reactivity measured by Doppler CO₂ testing and the incidence of ipsilateral ischemic stroke. Moreover, a comparison between the patterns of infarction in cranial computerized tomography and the cerebrovascular reserve capacity showed a significant relation between hemodynamic infarctions and an exhausted CO₂ reactivity. The present study reports the results of a prospective 3-year follow-up study of patients with ICA occlusions based on Doppler CO₂ testing.

Subjects and Methods

Eighty-five patients with 81 angiographically proven unilateral and four bilateral ICA occlusions entered the study. Seventy-seven were men and eight women, aged 43–81 years. Forty-six patients were ipsilaterally asymptomatic, 13 had suffered reversible symptoms, and 26 had had a minor stroke. On the contralateral side, two patients had developed a transient ischemic attack (TIA) and eight a stroke before admission to the study. Patients were reinvestigated clinically every year; end points were defined as ipsilateral stroke and death. In those cases, the relatives or physicians last involved with the patients were asked for the cause.

The cerebrovascular reserve capacity was evaluated in all patients by Doppler CO₂ testing at the beginning of the observation period. Middle cerebral artery (MCA) blood flow velocity and end-tidal Pco₂ were monitored during steady states of normocapnia, hypercapnia induced by breathing a fixed mixture of 5% CO₂ in 95% O₂ (carbogene), and hypocapnia caused by voluntary hyperventilation (Figure 1). Steady states were always reached within 1–2 minutes of constant breathing. The complete test usually took about 5 minutes for each hemisphere.

The transcranial Doppler sonography was performed by an EME TC-2 64 instrument (Eden Medizinische Elektronik, Überlingen/Bodensee, FRG), and the end-expiratory Pco₂ was measured by...
an infrared CO₂ analyzer (Capnolog, Datex Instrumentarium OY, Helsinki, Finland).

The method of calculating CO₂ reactivity has already been described in detail. 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. 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, we distinguished between three categories of sufficient, diminished, and exhausted cerebrovascular capacity (Table I). 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 al found an ipsilateral stroke rate of 2% per year, and Hennerici et al described 4% in asymptomatic cases. In symptomatic

**Table I. Classification of CO₂ Reactivity**

<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>≥10</td>
<td>≥10</td>
</tr>
<tr>
<td>Diminished</td>
<td>&lt;10</td>
<td>≥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.
In our study the classification into three groups with sufficient, diminished, and exhausted CO₂ 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 CO₂ 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 CO₂ 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.16 About one third of another group of patients with ICA occlusions and originally diminished or exhausted cerebrovascular capacity showed an increase of CO₂ 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 al17 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 al18 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>
<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 Norris6</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 al1</td>
<td>1983</td>
<td>47</td>
<td>Symptomatic</td>
<td>34</td>
<td>5.2</td>
<td>...</td>
</tr>
<tr>
<td>Eriksson5</td>
<td>1986</td>
<td>43</td>
<td>...</td>
<td>47</td>
<td>5.0</td>
<td>...</td>
</tr>
<tr>
<td>Furlan et al1</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 al2</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 al7</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 Group4</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>85</td>
<td></td>
<td>Asymptomatic/symptomatic</td>
<td>38</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack; EC/IC, extracranial/intracranial.

FIGURE 2. Graphs showing probability of ipsilateral ischemic events (left panel) and stroke (right panel) in 85 patients with internal carotid artery occlusion. Patients are divided into three groups with sufficient (n=48), diminished (n=26), and exhausted (n=11) CO₂ reactivity.
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.16

In conclusion, our results support the hypothesis that the Doppler CO2 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 CO2 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 cerebral vascular 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
Course of carotid artery occlusions with impaired cerebrovascular reactivity.
B Kleiser and B Widder

Stroke. 1992;23:171-174
doi: 10.1161/01.STR.23.2.171

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/23/2/171

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/