Course of Cerebrovascular Reactivity in Patients With Carotid Artery Occlusions

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Background and Purpose Patients with internal carotid artery occlusions and highly impaired cerebrovascular reactivity have been identified as having an increased risk of stroke. It is still unclear, however, whether cerebral hemodynamics may be restored in the course of time by the development of collaterals.

Methods During a 5-year period we assessed cerebrovascular reactivity in 452 carotid occlusions by transcranial Doppler CO2 testing. Ninety-eight patients could be reinvestigated at least once after 2 to 58 months (mean follow-up time, 26 months).

Results On admission, patients with recent transient ischemic attack or stroke (≤3 months) as well as patients with contralateral carotid stenoses of 80% diameter reduction or greater and occlusions revealed a significantly higher incidence of impaired CO2 reactivity (P<.0001 and P<.01, respectively). During follow-up, 64% of the patients with no or minor contralateral carotid stenoses, but only 22% of the patients with bilateral carotid occlusions, showed a spontaneous improvement in cerebrovascular reactivity (P<.001), mainly during the first few months. In six of eight patients cerebral hemodynamics on the occluded side improved after endarterectomy of a contralateral high-grade carotid stenosis. Five of the patients who did not undergo surgery developed a stroke during follow-up, with three of them occurring in patients with permanently exhausted cerebrovascular reactivity.

Conclusions In the majority of patients with carotid occlusions an initially impaired cerebrovascular reactivity improves spontaneously with time. This could influence therapeutic decisions: During the first few months antihypertensive treatment may be avoided in such cases until a reestablished reactivity can be demonstrated. If cerebral hemodynamics remain depleted, extracranial-intracranial bypass surgery or endarterectomy of an asymptomatic contralateral high-grade carotid stenosis could be helpful.

Key Words • carotid artery diseases • hemodynamics • carotid endarterectomy • ultrasounds

Although extracranial-intracranial bypass surgery has failed to show a benefit in the majority of internal carotid artery (ICA) occlusions,1 it is still a matter of discussion whether this technique could be helpful in a selected group of patients with insufficient cerebral collateralization. Such cases may be detected by assessing the cerebrovascular reactivity (CVR), which provides information as to whether the intracerebral arterioles are already maximally dilated and whether they can react to drops in blood pressure with further dilation.2

During the past few years numerous methods for assessing CVR have been published. These include positron emission tomography,3-4 single-photon emission computed tomography,5-8 xenon computed tomography,9,10 and transcranial Doppler sonography.11-15 Most techniques require stimulation of the intracerebral arterioles to cause them to dilate. This can be achieved either by increasing the arterial PCO2 (CO2 test) or by intravenous administration of acetazolamide (Diamox test).16

Recent studies have shown that patients with a highly impaired CVR have an increased risk of developing a stroke during the follow-up period.6,10,17,18 On the other hand, experimental findings in animals demonstrated that the intracranial collaterals need a certain amount of time to become fully established.19,20 If this is also true for humans, there will be important consequences for the treatment of patients with impaired cerebral hemodynamics. The present study reports the results of serial CVR measurements in patients with ICA occlusions.

Subjects and Methods

Between 1988 and 1993 a total of 458 patients with 422 unilateral and 36 bilateral ICA occlusions were identified by Doppler and duplex sonography. During the first 3 years the findings were routinely confirmed by digital subtraction angiography. After the positive results of a study dealing with the accuracy of color duplex scanning in differentiating ICA occlusions from subtotal stenoses,21 the diagnosis is now mainly based on ultrasound investigation.

In 452 of the 494 ICA occlusions (91%), CVR was investigated at least once by transcranial Doppler sonography of the middle cerebral artery (MCA) using different states of normocapnia, hypercapnia, and hypocapnia. Thirty-eight (8%) could not be tested because of inadequate ultrasound transmission through the temporal bone. In 4 additional patients CVR was not assessed for various reasons (eg, lack of time, defective Doppler device).

Details of the technique used have already been published.2,12,12 For a first rapid orientation, patients were asked to hold their breath as long as possible and then to hyperventilate moderately (apnea-hyperventilation test). If the relative increase during hypercapnia and/or the relative decrease during hypocapnia in MCA blood flow velocity reached at least 15% compared with normocapnia, a relevant reduction in CVR was excluded. All other patients underwent an additional, more sophisticated investigation including continuous monitoring of end-expiratory CO2 and the use of carbogene
lateral cerebral ischemic events with respect to cerebrovascular reactivity. TIA indicates transient ischemic attack.

**FIG 2.** Bar graph shows frequency of recent and remote ipsilateral cerebral ischemic events with respect to cerebrovascular reactivity. TIA indicates transient ischemic attack.

For evaluating the course of CVR statistically we used $U$ testing. In addition, the Mann-Whitney $U$ test was used to assess the different follow-up times and the age dependency of CVR restitution. Values of $P<.05$ were considered statistically significant.

**Results**

Of the total 452 ICA occlusions, 52 (12%) initially showed an exhausted ipsilateral CO$_2$ reactivity; in 132 cases (29%) the CVR was diminished. Two hundred thirty-eight occlusions (53%) were ipsilaterally asymptomatic; in 205 cases the patients had suffered at least one transient or persistent neurological deficit on the side of the occlusion. Nine patients revealed indefinite neurological symptoms that could not be related to a hemisphere. Comparing the initial symptoms with the ipsilateral CVR, we found that a highly significant ($P<.0001$) number of patients with recent ipsilateral ischemic events (≤3 months) showed an exhausted CO$_2$ reactivity on the ipsilateral side (Fig 2).

Relevant stenoses with greater than 50% diameter reduction of the contralateral carotid arteries could be found in 188 patients (42%). However, a significantly increased number of cases of ipsilaterally impaired CVR were present only in the case of contralateral diameter reductions of 80% or more (Fig 3). Approximately one third of the patients with bilateral ICA occlusion revealed an exhausted CVR on at least one side.

The influence of the vertebral arteries seemed to be less evident: Only in the case of a concomitant occlusion of one vertebral artery (bilateral vertebral artery occlusions could not be found) was the CO$_2$ reactivity measured in the MCA ipsilateral to an ICA occlusion significantly reduced ($P<.05$) (Fig 4).

Ninety-eight of the patients could be reinvestigated at least once after 2 to 58 months (mean follow-up time, 26.0 months). At admission, 85 of those patients had unilateral and 13 bilateral ICA occlusions. Approximately half of the patients (n=51) had two or more transcranial Doppler CO$_2$ tests during the follow-up.

Twenty-eight of the 55 non-surgically treated patients (51%) with an initially exhausted or diminished CVR revealed spontaneous improvement in CVR during the follow-up (Table 1). In patients with normal or only moderately stenosed contralateral carotid arteries, the percentage of improving CO$_2$ reactivities actually reached 64%. The improvement did not depend on age ($P=.12$), which, however, was rather similar in most patients (mean±SD age, 62.5±7.9 years).

In 2 patients an initially sufficient CO$_2$ reactivity diminished during the follow-up. One had developed a contralateral ICA occlusion; another showed progression of a minimal contralateral ICA stenosis to a subtotal diameter reduction. In 2 other patients, 1 with contralateral progression to a high-grade stenosis and 1 with contralateral progression to an occlusion, the ipsilateral CO$_2$ reactivity remained unchanged.

In contrast, an initially exhausted or diminished CO$_2$ reactivity remained unchanged in 14 of 18 patients (78%) with bilateral ICA occlusions ($P<.001$). One additional patient with an initially bilateral ICA occlusion showed a spontaneous recanalization of one carotid artery 8 months after the first investigation, with a
and +, sufficient CO₂ reactivity. None of these patients developed (new) symptoms during follow-up.

- indicates exhausted; (-), diminished; their first reinvestigation was within the initial 6 months after admission.  

FIG 5. Graph shows course of CO₂ reactivity in 10 patients who underwent surgery on the stenosed side. Six of the 8 patients with an initially impaired CVR (75%) showed improvement in CO₂ reactivity during the postoperative course (Table 2).

Fourteen of the 86 patients in the nonsurgical group and none of the patients in the surgical group who were reinvestigated developed new ischemic cerebral events during the follow-up; most of them were transient ischemic attacks (Table 3). A stroke ipsilateral to an occluded ICA occurred in 3 of the 26 hemispheres with an exhausted CVR, corresponding to an annual stroke rate of 8% (mean follow-up time, 19 months). Of the 37 hemispheres with diminished CO₂ reactivity and the 48 with sufficient CO₂ reactivity, only 1 of every group developed a persistent ipsilateral ischemia, although the follow-up time was significantly longer (P<.01) (mean follow-up time, 31.7 months). Three additional patients suffered a stroke contralateral to the occluded carotid artery; two of the strokes were related to progression of an initially middle-grade ICA stenosis.

Discussion

Our results demonstrate that CVR is not an invariable quantity but may change with time because of the development of intracranial collateralization across the circle of Willis and leptomeningeal anastomoses. Although only some of the patients could be reinvestigated during the first months after admission, our data suggest that the improvement in cerebral hemodynamics occurs mainly during the first few months after ICA occlusion. Moreover, as could be expected from pathophysiological considerations, hemodynamics seemed to recover faster in patients with exhausted CVR than in those with only diminished CVR.

In humans, changes in cerebral hemodynamics have recently been reported by Ringelstein and Otis, who found an improvement in 5 of 7 patients with ICA occlusions and highly impaired CVR at admission. In contrast, Hasegawa et al reported a normalization in only 3 of 20 patients. The development of intracranial collateralization in the course of time has been also demonstrated experimentally. In rats, De Ley et al reported a spontaneous improvement in CO₂ reactivity within 1 month. Concerning the cause of this effect, Coyle and Panzenbeck found a significant increase in the diameter of the anterior communicating artery during the first 6 weeks after unilateral carotid artery ligation.

The assumption of an improvement with time is also supported by our retrospective findings within the whole group of patients with ICA occlusions: Patients with

--Table 1. Course of Cerebrovascular Reactivity in 99 Internal Carotid Artery Occlusions With Respect to the Diameter Reduction of the Contralateral Internal Carotid Artery--

<table>
<thead>
<tr>
<th>Initial CVR</th>
<th>Exhausted</th>
<th>Diminished</th>
<th>Sufficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter reduction of contralateral ICA &lt;80% (n=74)</td>
<td>4(5)*</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Exhausted</td>
<td>...</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Diminished</td>
<td>...</td>
<td>2+</td>
<td>36</td>
</tr>
<tr>
<td>Sufficient</td>
<td>...</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Occlusion of contralateral ICA (n=25)</td>
<td>...</td>
<td>...</td>
<td>6</td>
</tr>
</tbody>
</table>

CVR indicates cerebrovascular reactivity.

*Spontaneous recanalization of contralateral ICA occlusion during follow-up in 1 patient.

†Progression of minor contralateral ICA stenoses to high-grade stenosis or occlusion.

‡Spontaneous recanalization of ipsilateral ICA occlusion during follow-up in 1 patient.

fairly normal extracranial blood flow volume through the recanalized vessel. Spontaneously improved CO₂ reactivity could be found ipsilateral to the recanalization. CVR on the contralateral side with a still-occluded ICA occlusion, however, remained unchanged.

The improvement in cerebral hemodynamics seemed to occur mainly during the first months after the occlusion. Thirteen of the 17 non-surgically treated patients with improving CO₂ reactivity, who had their first reinvestigation within the initial 6 months after admission, developed an at least partially restored CVR during this period. When we analyzed the subgroup with multiple CO₂ tests in the initial phase, 4 of 5 patients with exhausted CVR revealed an improvement during the first 4 months, whereas this was the case in only 2 of the 5 patients with diminished CO₂ reactivity at admission (Fig 5).

All 12 patients with an ipsilateral ICA occlusion and a high-grade contralateral ICA stenosis at admission underwent surgery on the stenosed side. Six of the 8 patients with an initially impaired CVR (75%) showed improvement in CO₂ reactivity during the postoperative course (Table 2).

Fourteen of the 86 patients in the nonsurgical group and none of the patients in the surgical group who were reinvestigated developed new ischemic cerebral events during the follow-up; most of them were transient ischemic attacks (Table 3). A stroke ipsilateral to an occluded ICA occurred in 3 of the 26 hemispheres with an exhausted CVR, corresponding to an annual stroke rate of 8% (mean follow-up time, 19 months). Of the 37 hemispheres with diminished CO₂ reactivity and the 48 with sufficient CO₂ reactivity, only 1 of every group developed a persistent ipsilateral ischemia, although the follow-up time was significantly longer (P<.01) (mean follow-up time, 31.7 months). Three additional patients suffered a stroke contralateral to the occluded carotid artery; two of the strokes were related to progression of an initially middle-grade ICA stenosis.

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The assumption of an improvement with time is also supported by our retrospective findings within the whole group of patients with ICA occlusions: Patients with
recent ischemic events revealed an exhausted CO₂ reactivity significantly more often than those with the (last) ischemic event more than 3 months previously. Although periocclusive embolism is unquestionably by far the most frequent source of stroke in these patients, this number seems to be superposed by hemodynamic infarctions shortly after the occlusion. The study of Yonas et al,10 as well as our previous investigation in another series of patients,18 confirms that strokes in hemodynamically compromised hemispheres occur mainly during the first 6 months.

Our results emphasize the important role of the contralateral carotid artery not only in relation to the presence of impaired cerebral hemodynamics but also in relation to prognosis. Whereas an exhausted CO₂ reactivity could only be found in 9% of the patients with unilateral occlusion and no or moderate contralateral ICA stenosis, this was the case in 27% of those with bilateral occlusions. Moreover, whereas approximately two thirds of the patients with unilateral ICA occlusions and initially impaired cerebral hemodynamics showed an improvement in CO₂ reactivity, this was the case in less than one fourth of those with bilateral occlusions.

Although the absolute number is small, our study supports the hypothesis that endarterectomy of a contralateral high-grade ICA stenosis may improve hemodynamics on the ipsilateral occluded side. Similar results have been published by Cikrit et al,9 who found an increased vasoreactivity as well as perfusion on the occluded side contralateral to a surgically corrected high-grade stenosis in 2 of 3 patients. Recently Markus et al24 reported an improvement in cerebral hemodynamics in 3 of 4 patients on the nonoperated side with subtotal ICA stenosis or occlusion.

Despite the significantly shorter mean follow-up time, at least 3 of 26 patients with exhausted CVR developed an ipsilateral stroke, whereas this was the case in only 1 of 37 patients with diminished CO₂ reactivity and 1 of 48 patients with sufficient CO₂ reactivity. This trend is in agreement with the findings in prospective clinical studies of ICA occlusions with respect to the CVR.8,10,17,18

On the other hand, the annual stroke rate in patients with exhausted CO₂ reactivity was considerably lower in the present investigation than in our previous study. Although still unproved, this could be interpreted as a positive effect of our policy for treating patients with impaired CVR. After having observed several iatrogenic strokes due to drug-induced decreases in blood pressure during the initial phase of measuring CO₂ reactivity since 1985,18 we now strictly recommend avoiding antihypertensive treatment other than dietary measures25 in patients with highly impaired CVR at least during the first 2 to 3 months, except in patients with excessive systolic blood pressure values of more than 220 mm Hg.

In conclusion, the present findings may have several clinical implications. First, due to the variable cerebral collateralization, we would discuss extracranial-intracranial bypass surgery only in the relatively rare case of CVR remaining depleted for a period of approximately 3 months after the occlusion occurred.26 At first this seems contradictory because hemodynamic strokes usually occur during these first few months. On the other hand, the extracranial-intracranial bypass also requires

### Table 3. Patients With Internal Carotid Artery Occlusions Developing (New) Cerebral Symptoms During Follow-up

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age, y/Sex</th>
<th>Follow-up, mo</th>
<th>Ipsilateral CO₂ Reactivity</th>
<th>Contralateral ICA</th>
<th>Neurological Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial Follow-up</td>
<td>Initial</td>
<td>Follow-up</td>
</tr>
<tr>
<td>1</td>
<td>61/F</td>
<td>10</td>
<td>Exhausted Exhausted</td>
<td>Occlusion</td>
<td>Ipsilat TIA</td>
</tr>
<tr>
<td>2</td>
<td>67/M</td>
<td>32</td>
<td>Exhausted Exhausted</td>
<td>60% stenosis</td>
<td>Asympt</td>
</tr>
<tr>
<td>3</td>
<td>68/M</td>
<td>44</td>
<td>Exhausted Exhausted</td>
<td>Occlusion</td>
<td>Asympt</td>
</tr>
<tr>
<td>4</td>
<td>71/F</td>
<td>40</td>
<td>Exhausted Diminished</td>
<td>50% stenosis</td>
<td>Asympt</td>
</tr>
<tr>
<td>5</td>
<td>60/M</td>
<td>15</td>
<td>Exhausted Diminished</td>
<td>40% stenosis</td>
<td>Ipsilat TIA</td>
</tr>
<tr>
<td>6</td>
<td>63/M</td>
<td>30</td>
<td>Diminished Diminished</td>
<td>Occlusion</td>
<td>Asympt</td>
</tr>
<tr>
<td>7</td>
<td>56/F</td>
<td>23</td>
<td>Diminished Sufficient</td>
<td>Unstenosed</td>
<td>Ipsilat</td>
</tr>
<tr>
<td>8</td>
<td>63/M</td>
<td>20</td>
<td>Diminished Sufficient</td>
<td>Unstenosed</td>
<td>Asympt</td>
</tr>
<tr>
<td>9</td>
<td>60/M</td>
<td>10</td>
<td>Sufficient Sufficient</td>
<td>Unstenosed</td>
<td>Asympt</td>
</tr>
<tr>
<td>10</td>
<td>80/F</td>
<td>23</td>
<td>Sufficient Sufficient</td>
<td>Unstenosed</td>
<td>Ipsilat TIA</td>
</tr>
<tr>
<td>11</td>
<td>46/M</td>
<td>39</td>
<td>Sufficient Sufficient</td>
<td>60% stenosis</td>
<td>Ipsilat TIA</td>
</tr>
<tr>
<td>12</td>
<td>64/M</td>
<td>58</td>
<td>Sufficient Sufficient</td>
<td>50% stenosis</td>
<td>Asympt</td>
</tr>
<tr>
<td>13</td>
<td>76/M</td>
<td>30</td>
<td>Sufficient Sufficient</td>
<td>70% stenosis</td>
<td>Asympt</td>
</tr>
<tr>
<td>14</td>
<td>61/M</td>
<td>50</td>
<td>Sufficient Diminished</td>
<td>50% stenosis</td>
<td>Asympt</td>
</tr>
</tbody>
</table>

Pt indicates patient; ICA, internal carotid artery; ipsilat, ipsilateral; TIA, transient ischemic attack; asympt, asymptomatic; contralat, contralateral; and BP, blood pressure.
some time to become functionally established.27 Also, it should not be forgotten that the operation itself contains a certain risk of causing a stroke.1 Therefore, we believe that a circumscribed waiting period while avoiding any antihypertensive treatment may be justified. Only in bilateral occlusions should the time of observation be shortened, because in these cases the probability of a spontaneous improvement in cerebral hemodynamics is rather low.

Second, in patients with an insufficiently collateralized ICA occlusion and a contralateral high-grade ICA stenosis, the surgical removal of the stenosis seems to be the method of choice for restoring cerebral hemodynamics. Although the absolute number of patients is small, this may be of special interest in asymptomatic patients in whom the optimal treatment has not yet been established.

Third, as already mentioned in our previous study,18 we believe that decreases in blood pressure should be avoided in patients with ICA occlusions and highly impaired CVR. The present data, however, indicate that, in most cases, such precautions may only be necessary during the first few months after the occlusion occurred. The exclusion of a highly impaired CVR does not require sophisticated techniques and can be readily achieved by transcranial Doppler sonography and the aforementioned apnea-hyperventilation test.15,22

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