Effect of Carotid Endarterectomy on Patterns of Cerebrovascular Reactivity in Patients With Unilateral Carotid Artery Stenosis

Wolfgang H. Hartl, MD; Ingrid Janssen, BS; Heinrich Fürst, MD

Background and Purpose  Patients with unilateral significant carotid artery stenosis present with a variable intracranial hemodynamic status. In the majority of patients, hemodynamics are normal because of sufficient collateral flow. One subgroup shows poor ipsilateral hemodynamics because of a severely reduced blood supply, whereas in another subgroup of patients a steal phenomenon from the contralateral to the ipsilateral hemisphere can be observed during pharmacological provocation. The present study examined the effect of carotid endarterectomy (CEA) on these patterns of cerebrovascular hemodynamics in patients with carotid artery stenosis.

Methods  The CO$_2$ reactivity of the cerebral resistance index (CR) was determined with transcranial Doppler sonography in 63 patients with unilateral high-grade to threadlike carotid artery stenosis before and 3 months after CEA and in 37 control subjects. The interhemispheric asymmetry of CR, reactivity of the control group was used to differentiate between normal and abnormal findings.

Results  In patients with normal CR, asymmetry (comparable CR, reactivities at both hemispheres, n=41), CEA did not change hemispheric CR, reactivity. In patients in whom CR, reactivity was absent at the contralateral hemisphere (intracerebral steal during hypercapnia, n=12), CEA abolished the steal phenomenon by significantly increasing CR, reactivity at the contralateral hemisphere (preoperative, -1.0±2.1 %CR,/vol%CO$_2$; postoperative, 5.2±0.7 %CR,/vol%CO$_2$; P<.01). Patients who showed severely diminished ipsilateral CR, reactivity, compatible with a significantly reduced perfusion pressure at the poststenotic hemisphere (n=10), demonstrated an improvement of ipsilateral CR, reactivity after surgery (preoperative, 0.6±0.8 %CR,/vol%CO$_2$; postoperative, 3.7±1.1 %CR,/vol%CO$_2$; P<.01).

Conclusions  Most patients do not respond significantly to CEA. One small subgroup of patients who presented with severely disturbed ipsilateral hemodynamics demonstrated postoperative improvement at the poststenotic hemisphere, whereas in another small subgroup, who showed a steal phenomenon at the contralateral hemisphere, CEA improved contralateral hemodynamics. Determination of preoperative CR, reactivity allowed precise prediction of the effect of CEA on intracerebral hemodynamics. (Stroke. 1994;25:1952-1957.)

Key Words  • carotid endarterectomy • carotid stenosis • hemodynamics • ultrasonics
side asymmetry), it is possible to eliminate interindividual variability caused by age as well as by differences in CO₂-induced systemic hemodynamic changes, blood viscosity, myocardial contractility, or preexisting extent of arteriosclerosis.7

Subjects and Methods

Subjects

Studies were performed in 63 subjects seeking treatment in our hospital. Carotid artery disease was diagnosed during clinical evaluation or during routine examination in vascular high-risk patients. Thirty-six patients had symptomatic unilateral high-grade to threadlike stenosis of the ICA (age, 65.6±1.0 years; 20 men, 16 women). These patients demonstrated either transient reversible neurological deficits or minor strokes that had occurred at least 12 weeks before the study. None of these patients was suffering from a major stroke. Twenty-seven patients were completely asymptomatic but had a unilateral threadlike ICA stenosis (age, 66.8±1.1 years; 12 men, 15 women). According to previous randomized trials,8,9 it is the current policy in our department to perform CEA in symptomatic and asymptomatic patients who have the respective lesions at the ICA as described above. High-grade stenosis corresponds to a maximum percentage reduction in the angiographic diameter of the relevant carotid artery of 80% or more. A threadlike stenosis corresponds to a 99% diameter reduction. All patients underwent careful neurological examinations. Extracranial and intracranial supra-aortic vessels were screened by TCD sonography, duplex sonography, color-flow Doppler imaging, and continuous-wave Doppler sonography. Color-flow Doppler imaging and continuous-wave Doppler sonography have recently been shown to be more than 90% accurate in identifying carotid artery stenosis with a lumen diameter reduction from 80% to 99%.10

All patients had a preoperative cranial computed tomography. In 9 of these patients, small lacunar infarctions were found at the poststenotic hemisphere. However, cerebral lesions should not have affected the results of our study. An abnormal cerebrovascular reactivity is seen mainly in the acute phase after major stroke.11,12 In patients with minor stroke, a normal CO₂ response was found in the chronic phase.13 In more recent studies, poor cerebrovascular reactivity did not correlate with the presence of ipsilateral infarction.14,15

Exclusion criteria included lumen diameter reduction of less than 80% at the extracranial ipsilateral ICA, lumen diameter reduction of more than 50% at the contralateral ICA, tandem lesions of the ICA/MCA, subclavian steal syndrome, vertebral artery occlusion or stenosis, lumen diameter reduction of more than 50% at the common carotid artery, previous ipsilateral or contralateral carotid endarterectomy or extracranial/intracranial bypass, and uncontrolled atrial fibrillation (absolute arrhythmia).

Measurements

Systolic and diastolic blood flow velocity of the MCA in both hemispheres was measured by TCD before surgery and 3 months after surgery as described previously.7 In brief, a 2-MHz TCD sonography transducer (VingMed SD 50, Sonotron) was placed on the “skull window” above the sylvian arch, and the MCA was studied at the depth of 50 to 60 mm. Average blood flow velocity at peak systole and diastole was transferred to a personal computer (Macintosh II CI, Apple) for further off-line data processing. To evaluate the complete reactivity of blood flow velocity to changes in CO₂ concentrations, the arterial CO₂ content was changed from normocapnia (CO₂ concentration at rest) to hypercapnia and hypocapnia. To produce hypercapnia the subjects were connected through a mouthpiece with a nonreturn valve to a tank containing 5% CO₂. Hypocapnia was achieved by having the patient hyperventilate. During the CO₂ manipulation, the end-expiratory CO₂ content (vol%) was recorded continuously by an infrared CO₂ analyzer (Engstrom Eliza, CO₂ Analyzer). Mean end-tidal values were used to estimate the arterial CO₂ content. Flow velocity in the MCA was recorded when a steady state was reached in end-tidal CO₂ and in flow velocity.

Calculations

Each examination yielded values of minimal diastolic and maximal systolic flow velocity (Vₘₐᵢₐᵢ and Vₘᵢₜ, respectively) in the MCA in both hemispheres during normocapnia, hypercapnia, and hypocapnia. Flow velocities were used to calculate the relative peak-to-peak velocity (referred to Vₘₐᵢₐ) of the flow velocity wave: (Vₘₜ−Vₘᵢₐ)/Vₘᵢₐ. The relative peak-to-peak velocity represents a measure of cerebral resistance during pulsatile flow and is named cerebral resistance index (CRᵢ), which corresponds to Pourcelot's index. Subsequently, we calculated the relative reactivity of CRᵢ to changes in the arterial CO₂ content. Total CRᵢ, reactivity (%CRᵢ/vol%CO₂) was quantified as

\[
\text{CRᵢ at hypocapnia} - \text{CRᵢ at hypercapnia} \times \left(\frac{\text{CO₂ concentration at hypercapnia}}{\text{CO₂ concentration at hypocapnia}}\right)
\]

The rationale behind the above formula is described in detail in previous publications6,7 and is based on aspects of interindividual comparison and on the particular interactions between the shape of the flow velocity curve and changes of vascular impedance.

To define normal values, a control group of elderly subjects (n=37 [18 men, 19 women]; age, 65±3.5 years) was studied. Details of this group were published recently.7 To determine the normal absolute side-to-side asymmetry, we subtracted arbitrarily right CRᵢ, reactivity from left CRᵢ, reactivity in control subjects and ignored the signs. Normal absolute side-to-side asymmetry amounted to 1.6±0.2 [1.2] %CRᵢ/vol%CO₂ (mean±SEM [SD]). The normal range of absolute side-to-side asymmetry was defined as mean±2 SD, and correspondingly, we obtained a normal span for absolute side-to-side asymmetry ranging from 0 to 4.0 %CRᵢ/vol%CO₂. Then, we determined in all patients the side-to-side asymmetry of total CRᵢ, reactivity and differentiated between normal, abnormal positive, and abnormal negative asymmetry of CRᵢ, reactivity. Patients with an absolute side-to-side asymmetry of more than 4.0 %CRᵢ/vol%CO₂ and with a greater CRᵢ, reactivity of the affected hemisphere than of the contralateral hemisphere were classified as having an abnormal positive side-to-side asymmetry. Correspondingly, patients with an absolute side-to-side asymmetry of more than 4.0 %CRᵢ/vol%CO₂ and with lesser CRᵢ, reactivity of the affected hemisphere than of the contralateral hemisphere were placed into an abnormal negative side-to-side asymmetry category. All patients with an absolute side-to-side asymmetry of less than 4.0 %CRᵢ/vol%CO₂ were classified as normal.

Statistics

The differences between means of the two hemispheres and between preoperative and postoperative values were compared with the paired t test. Because means of several variables were compared, the Bonferroni method was applied, taking into account the multiplicity of comparisons. For convenience, a significance level of P=0.01 was used throughout the study.

Results

Preoperative Findings

Normal side-to-side asymmetry of CRᵢ, reactivity (<4.0 %CRᵢ/vol%CO₂), which had been derived from
Effect of Hypocapnia and Hypercapnia on Hemispheric Peak Systolic Flow Velocity and on Peak Diastolic Flow Velocity at the Middle Cerebral Artery in Patients With Unilateral Carotid Artery Stenosis Who Presented With Normal, Abnormal Negative, or Abnormal Positive Side-to-Side Asymmetry in Cerebral Resistance Index Reactivity

<table>
<thead>
<tr>
<th>Side-to-Side Asymmetry</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Negative</td>
<td>Ipsi</td>
<td>Contra</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>V&lt;sub&gt;syst&lt;/sub&gt;, m/s</td>
<td>0.80±0.10</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dia&lt;/sub&gt;, m/s</td>
<td>0.35±0.04</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>V&lt;sub&gt;syst&lt;/sub&gt;, m/s</td>
<td>0.51±0.08</td>
</tr>
<tr>
<td></td>
<td>V&lt;sub&gt;dia&lt;/sub&gt;, m/s</td>
<td>0.22±0.03</td>
</tr>
</tbody>
</table>

V<sub>syst</sub> indicates systolic flow velocity; V<sub>dia</sub>, diastolic flow velocity. Velocities were determined at the hemisphere ipsilateral (Ipsi) and contralateral (Contra) to carotid artery stenosis before carotid endarterectomy and 3 months thereafter. Patients whose ipsilateral CR, reactivity was abnormally low compared with the contralateral CR, reactivity were classified as having an abnormal negative side-to-side asymmetry. Positive side-to-side asymmetry refers to patients in whom the ipsilateral CR, reactivity was abnormally high compared with the contralateral CR, reactivity. Normality was based on the side-to-side asymmetry in 37 age-matched, healthy control subjects. Values are mean±SEM.

The remaining patients had an abnormal side-to-side asymmetry (>4.0 %CRi/vol%CO<sub>2</sub>) and could be separated into two subgroups: (1) patients in whom CRi reactivity of the affected hemisphere was smaller than that of the opposite hemisphere (group 2, n=10; absolute side-to-side asymmetry=7.1±0.7 %CRi/vol%CO<sub>2</sub>; Fig 1) and (2) patients in whom CRi of the affected hemisphere was larger than that of the opposite hemisphere (group 3, n=12; absolute side-to-side asymmetry=8.0±1.4 %CRi/vol%CO<sub>2</sub>; Fig 1). In the latter group, corresponding hemispheric CRi reactivities were as follows: ipsilateral, 7.1±1.1 %CRi/vol%CO<sub>2</sub>; contralateral, -1.0±2.1 (Figs 2 and 3).

Patients in group 2 (abnormal negative side-to-side asymmetry, ipsilateral CRi reactivity less than contralateral CRi reactivity) demonstrated the opposite situation. CRi reactivities were as follows: ipsilateral, 0.6±0.8 %CRi/vol%CO<sub>2</sub>; contralateral, 7.6±0.9 %CRi/vol%CO<sub>2</sub> (Figs 2 and 3).

Effect of Endarterectomy

CEA was performed without perioperative morbidity and mortality. When data of all 63 patients were combined, total CRi reactivity was not significantly affected by endarterectomy (hemisphere of ICA stenosis: preoperative value, 4.1±0.5 %CRi/vol%CO<sub>2</sub> and postoperative value, 4.3±0.5 %CRi/vol%CO<sub>2</sub>; contralateral hemisphere: preoperative value, 4.2±0.4 %CRi/vol%CO<sub>2</sub> and postoperative value, 4.5±0.4 %CRi/vol%CO<sub>2</sub>). However, a significant effect of the surgical procedure was found when changes in CRi reactivity were analyzed depending on the preoperative side-to-side asymmetry. Thus, all patients with an abnormal
absolute side-to-side asymmetry responded to the surgical procedure significantly. In patients in whom ipsilateral CR, reactivity was lower than contralateral CR, reactivity (group 2), ipsilateral CR, reactivity rose significantly after surgery in all patients (preoperative value, 0.6±0.8 %CR/vol%CO₂; postoperative value, 3.7±1.1; P<.01; Fig 2). CEA did not alter contralateral CR, reactivity. In patients in whom ipsilateral CR, reactivity was higher than contralateral CR, reactivity (group 3), contralateral CR, reactivity rose significantly after surgery (preoperative value, -1.0±1.2 %CR/vol%CO₂; postoperative value, 5.2±1.7; P<.01; Fig 3). Postoperative ipsilateral CR, reactivity in group 3 showed a tendency toward lower values but was not significantly different from preoperative findings (preoperative value, 7.1±2.1 %CR/vol%CO₂; postoperative value, 3.9±1.1; P=.04; Fig 3). Ipsilateral and contralateral CR, reactivity remained unchanged in group 1 (patients with normal absolute side-to-side asymmetry, Figs 2 and 3). CEA normalized the pathological absolute side-to-side asymmetry in group 2 (preoperative value, 7.1±0.7 %CR/vol%CO₂; postoperative value, 1.3±1.4; P<.01; Fig 1) and in group 3 (preoperative value, 8.0±1.4 %CR/vol%CO₂; postoperative value, 1.2±1.4; P<.01; Fig 1). Side-to-side asymmetry in patients of group 1 (normal side-to-side asymmetry) did not change after surgery.

Discussion

The present study confirms results of a previous study in completely asymptomatic patients with unilateral high-grade to threadlike ICA stenosis. Corresponding to the latter study, we could identify three different patterns of hemispheric CR, reactivity as well as side-to-side asymmetry in patients with symptomatic ICA stenosis. Because relative frequency of the hemody-
The hemodynamic effect of CEA varies and depends on the preexisting hemodynamic status. When data from all patients are combined, a significant hemodynamic effect of CEA is not evident. Also, the majority of patients (group 1, normal side-to-side asymmetry) did not respond to CEA either at the poststenotic or at the contralateral hemisphere (Figs 2 and 3). Correspondingly, side-to-side asymmetry remained unchanged (Fig 1). A clear effect of the surgical procedure could be identified when patients were analyzed according to their preoperative side-to-side asymmetry. Thus, all those patients who had an abnormal side-to-side asymmetry with the ipsilateral CR, reactivity ipsilateral to ICA occlusion or stenosis and the change in reactivity after surgery. The abnormal side-to-side asymmetry returned to the normal range (Fig 1).

Similar observations have been made by others using the acetazolamide test to evaluate cerebral blood flow (CBF) reactivity in patients with unilateral ICA stenosis. They found that surgery improved intracerebral hemodynamics ipsilateral to ICA stenosis only in patients who preoperatively had a reduced cerebral perfusion pressure at the side of ICA stenosis of at least 20% (indicating inadequate intracerebral collateralization) compared with the pressure in the common carotid artery. Halsey et al., Widder et al.,28 and our group29 reported a significant inverse correlation between the preoperative CBF reactivity, flow velocity reactivity, or CR, reactivity ipsilateral to ICA occlusion or stenosis and the change in reactivity after surgery. Correspondingly, Vorstrup et al., Russel et al.,28 and Karnik et al.29 found that surgery significantly improved CBF or flow velocity reactivity (as evaluated by the acetazolamide test) only in patients who had an abnormal side-to-side asymmetry in reactivity before surgery.

However, in contrast to previous studies, measurement of CR, reactivity allows identification of a select group of patients in whom CEA may especially affect hemodynamics of the contralateral hemisphere. This phenomenon was exclusively observed in patients who had a pathological side-to-side asymmetry and whose contralateral CR, reactivity was poor and lower than the ipsilateral CR, reactivity before surgery (group 3). In those patients CEA apparently removed the hypercapnic steal phenomenon, thereby normalizing not only...
contralateral CR, reactivity but also the pathological side-to-side asymmetry (Figs 1 and 3). Ipsilateral CR, reactivity of these patients was reduced after surgery. However, this effect was not significant, presumably because the number of subjects studied was small.

Postoperative disappearance of hypercapnic steal cannot be explained by equilibration of perfusion pressure, since such an equilibration already existed before surgery in this group.6 A postoperative attenuation of the exaggerated ipsilateral CR, reactivity may have contributed to the observed normalization of side-to-side asymmetry. Apparently, the poststenotic hemisphere "noticed" the improved inflow capacity after CEA. Such a situation could have occurred under conditions in which systemic blood pressure dropped and in which, without CEA, ipsilateral perfusion pressure would have otherwise fallen to critical values.

In conclusion, determination of CR, reactivity and its side-to-side asymmetry by TCD sonography can identify patients with inadequate intracerebral collateralization and with interhemispheric steal in association with significant carotid artery disease. Determination of preoperative CR, reactivity allows precise prediction of the effect of CEA on intracerebral hemodynamics. Our study does not address the clinical outcome of the patients. However, identification of abnormal hemodynamics may help to find the appropriate therapy for patients in which indication for operative or conserva-

tive therapy is still controversial (eg, patients with significant carotid artery disease). Future prospective studies will have to show whether CEA is of benefit in patients with poor cerebrovascular reactivity or with interhemispheric steal.

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