Evaluation of Vasomotor Reactivity by Transcranial Doppler and Acetazolamide Test Before and After Extracranial–Intracranial Bypass in Patients With Internal Carotid Artery Occlusion

Ronald Karnik, MD; Andreas Valentin, MD; Hans-Peter Ammerer, MD; Peter Donath, MD; and Jörg Slany, MD

Background and Purpose: The aim of this trial was to evaluate the effectiveness of extracranial–intracranial bypass with respect to vasomotor reactivity in patients with internal carotid artery occlusions and absent vasomotor reactivity, comparing them with a control group treated conservatively.

Methods: To test vasomotor reactivity in 104 patients with unilateral occlusion of the internal carotid artery, we measured blood flow velocity in the middle cerebral artery by transcranial Doppler sonography both at rest and after injection of acetazolamide. Among the 39 patients who failed to show increased mean blood flow velocity after the acetazolamide test distal to an occluded internal carotid artery by ≥10%, 14 subjects subsequently underwent extracranial-intracranial bypass surgery (group A) and 14 age- and sex-matched subjects in whom no such procedure was done composed the control group (group B). Follow-up examinations were performed 3–6 months postoperatively and in the control group 3–6 months after initial examination.

Results: Baseline values of the mean blood flow velocity at rest on the affected side were reduced in both groups compared with the contralateral healthy side (group A, 46.0±15.1 cm/sec; group B, 48.1±16.7 cm/sec) and revealed only a marginal increase after acetazolamide. The contralateral side showed a normal blood flow velocity at rest and an adequate response to acetazolamide in both groups. On the follow-up examination group A demonstrated a normalized vasodilatory capacity. Blood flow velocity increased significantly after acetazolamide from 41.9±13.1 cm/sec to 53.5±16.0 cm/sec (p<0.002). In group B, the compromised vasomotor reactivity remained unchanged.

Conclusions: Our results demonstrate that transcranial Doppler sonography together with the acetazolamide test can identify subjects with reduced vasomotor reactivity distal to an occluded internal carotid artery, who may improve hemodynamically by an extracranial–intracranial bypass. (Stroke 1992;23:812–817)

KEY WORDS • acetazolamide • cerebral revascularization • ultrasonics

Since publication of the results of the International Extracranial–Intracranial (EC–IC) Arterial Bypass Study demonstrated a failure to reduce the risk of ischemic stroke, the number of such procedures has dropped dramatically worldwide. Although this study could not identify any subgroup in which bypass surgery was superior to conventional treatment, the discussion of whether EC–IC bypass surgery should be performed in certain subgroups of ischemic stroke patients or eliminated completely continues. In half of the patients with internal carotid artery (ICA) occlusion, only transient or mild focal neurological disorders are present, if at all. In such patients, who seem to be ideal candidates for EC–IC bypass, a yearly stroke incidence of 2–6% is reported in the literature. In many cases, strokes distal to an occluded ICA are thromboembolic and therefore cannot be prevented by an additional collateral pathway. However, in a subgroup of patients with ICA occlusions and an impaired reserve capacity due to insufficient collaterals, critically reduced cerebral perfusion might lead to neurological symptoms.

Vasomotor reactivity can easily be tested clinically by the acetazolamide test. Acetazolamide inhibits carbonic anhydrase, an enzyme that catalyzes either the dissociation or the formation of carbonic acid, thus causing a marked cerebral acidosis. This effect develops rather slowly, peaking after 10 minutes, and is a very strong vasodilatory stimulus. Acetazolamide increases cerebral blood flow (CBF) usually to a greater extent than that induced by 5 minutes of 5% CO₂ inhalation. Vorstrup et al reported an increase in the regional
vascular capacity in 16 of 18 cases when measuring CBF by xenon-133-inhalation tomography and the acetazolamide test in patients with ICA occlusions before and after EC-IC bypass surgery. However, 50% of the subjects in this study had already shown a positive response to acetazolamide preoperatively.

Accordingly, in our study, we selected patients with ICA occlusions for EC-IC bypass surgery using hemodynamic criteria, together with clinical and angiographic standards. Blood flow velocity of the basal cerebral arteries was measured by transcranial Doppler sonography (TCD). The vasodilatory capacity of acetazolamide was used to test vasomotor reactivity. The aim of our trial was to evaluate the effectiveness of EC-IC bypass with respect to vasomotor reactivity, comparing the EC-IC bypass group with a control group treated conservatively.

**Subjects and Methods**

The admission criteria included the clinical and angiographic standards applied in the EC-IC bypass study, together with the following standard: subjects were eligible for the trial if the mean blood flow velocity in the middle cerebral artery (MCA) on the affected side showed an increase of <10% after the acetazolamide test. The cutoff point of 10% was chosen because in our normal control subjects we found an average increase in mean blood flow velocity after acetazolamide of 40±20.6% (minimum increase, 11.9%). These normal values were established by measuring mean blood flow velocity at rest and after acetazolamide in our cardiovascular outpatient clinic in 100 patients who were clinically and sonographically free of cerebrovascular diseases. The control group comprised 81 men and 19 women with an average age of 63.5±11 years. Thirty-eight patients had well-controlled mild to moderate hypertension, 21 had diabetes mellitus, and 34 were cigarette smokers. Hyperlipemia was present in 45 patients, and 36 had coronary heart disease. Congestive heart failure of New York Heart Association classes I and II was present in 27 patients. Subjects with congestive heart failure of NYHA classes III and IV were not admitted to the study.

Among 104 patients with unilateral ICA occlusions who were examined at our laboratory by TCD and the acetazolamide test between January 1987 and July 1990, 39 subjects showed impaired vasomotor reactivity after the acetazolamide test. In these patients EC-IC bypass was considered and discussed with the physician-in-charge and the family doctor. All patients were informed of the questionable outcome of the procedure, as presented by the EC-IC bypass study. Finally an EC-IC bypass was performed in 14 patients (nine men and five women) with a mean age of 64.7±12 years (age range, 32–77 years). Fourteen sex- and age-matched subjects formed the control group. These 11 men and three women with a mean age of 64.1±7 years (age range, 54–78 years) also met all criteria for the EC-IC surgery, but the operation was refused either by the patients themselves or by the attending doctors. The clinical characteristics of both patient groups are depicted in Table 1.

All patients were examined by TCD and the acetazolamide test within 6 weeks after the acute onset of symptoms or after the first diagnosis of an ICA occlusion. Subjects with hemodynamically relevant stenosis of the contralateral side (degree of stenosis >75%) were admitted to the study only after successful endarterectomy and were examined 2–6 weeks after this operation.

A three-dimensional transcranial Doppler scanner (Trans-Scan, EME, Ueberlingen, FRG) as described by Aaslid and was used for the TCD examination. A 2-MHz probe is connected by ball joints and rods to scanning arms in the horizontal and coronal planes. The probe position on the surface is detected by potentiometers. By computer readout of different angles and the sonation depth, the orthogonal coordinates of the sample volume can be calculated. The scanning arms are fastened on curved pads that fit over the forehead and the dome of the cranium. The position of the probe can be locked when performing a scan, so that repeated recordings of the Doppler spectra from the same spots are possible. The recorded color-coded frequency spectra were drawn by the computer in three projections. Spectral information was displayed as velocity in centimeters per second. Calculation of the CBF velocity from Doppler shift frequency assumed an angle of 0° between the probe and blood vessel.

The patients were studied in the supine, resting state with the eyes closed. The probe of the Trans-Scan was placed against the side of the skull just above the zygomatic arch. The MCA on both sides was insonated at a depth of 45–60 mm. The position of the probe was slightly corrected until an optimal signal of the MCA was obtained. The probe was fixed in this position and the spots marked for further evaluation. Systolic, diastolic, and mean blood flow velocities were recorded.

**Table 1. Basic Clinical Characteristics of Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Age (yr) (mean)</td>
<td>32–77 (64.7)</td>
<td>54–78 (64.1)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<td>11/3</td>
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<tr>
<td>Risk factors</td>
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<td></td>
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<td>Cigarette smoking</td>
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<td>5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>2</td>
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<tr>
<td>Hypertension</td>
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<td>3</td>
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<tr>
<td>Hyperlipemia*</td>
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<td>5</td>
</tr>
<tr>
<td>Medication at entry</td>
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</tr>
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<td>Platelet antiagregants</td>
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<td>11</td>
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<td>Anticoagulants</td>
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</tr>
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<td>Clinical symptoms</td>
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<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
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<td>4</td>
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<tr>
<td>Minor stroke</td>
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<td>10</td>
</tr>
<tr>
<td>Site of occlusion</td>
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<tr>
<td>R ICA</td>
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<td>6</td>
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<tr>
<td>L ICA</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Contralateral stenosis</td>
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<td>&lt;50%</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>50–75%</td>
<td>…</td>
<td>3</td>
</tr>
<tr>
<td>Contralateral endarterectomy</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*Cholesterol >200 mg/dl, triglycerides >150 mg/dl.
TABLE 2. Blood Flow Velocity at Rest and After Acetazolamide at Baseline

<table>
<thead>
<tr>
<th>Side</th>
<th>Group A</th>
<th>Group B</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>46.0±15.1</td>
<td>48.2±16.7</td>
<td>46.7±16.3</td>
<td>49.2±18.9</td>
</tr>
<tr>
<td>Contralateral</td>
<td>62.0±18.5</td>
<td>61.3±10.1</td>
<td>75.0±23.5</td>
<td>80.1±16.3</td>
</tr>
<tr>
<td>p*</td>
<td>&lt;0.006</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD cm/sec. Group A, extracranial-intracranial bypass group; Group B, control group.

*Affected vs. contralateral side.

After recording the initial blood flow velocities the patients received 1 g acetazolamide intravenously, and 15–20 minutes later the measurements were repeated.

Follow-up studies identical to the initial testing were performed 3–6 months postoperatively or in group B after the same time interval after initial examination. The temporal artery of the side in question was examined by a 4-MHz pulsed Doppler probe to evaluate patency of the EC–IC bypass and to test vasomotor reactivity of the bypass after the acetazolamide test. In six patients the anastomosis was directly insonated by TCD in a depth of 25–30 mm.

The statistical analysis was performed by an IBM mainframe 3090-400E/2VF with vector facilities installed at the University of Vienna. The statistical software used was SAS (Statistical Analysis System) and SPS (Statistical Package for the Social Sciences). The data are expressed as mean±SD. We accomplished a multivariate analysis of the mean blood flow velocities of the MCA of the affected and contralateral sides at rest and after the acetazolamide test in both groups. Friedman's two-way analysis of variance, which does not require normal distribution of the data, was used as the principal test. Pillai's, Hotelling's, Wilks', and Roy's multivariate tests of significance were used as check tests. The Wilcoxon matched-pairs signed rank test was used to analyze differences between the affected and nonaffected sides and between the values at rest and after the acetazolamide test. Differences between baseline and follow-up values between groups were analyzed by Kruskal-Wallis one-way analysis of variance. We assumed statistical significance when p<0.05.

**Results**

A total of 14 anastomoses were performed. No complications attributable to the bypass procedure occurred in any of the operated patients. In all patients, patency of the anastomosis was confirmed by sonographic examination of the temporal artery in question and/or by direct insonation of the anastomosis by TCD. Platelet antiaggregant and anticoagulant medication remained unchanged postoperatively. One patient in group A experienced recurrent transient ischemic attacks corresponding to the hemisphere of interest. One subject of this group had sudden cardiac death 2 months after the shunting. The patient had a history of ventricular arrhythmias of Lown class IV and had received antiarrhythmic therapy. One patient in the control group developed a reversible ischemic neurological deficit with a slight hemiparesis related to the occluded side.

Friedman's two-way analysis of variance rejected the H₀ hypothesis with a probability of error of p<0.001.

Table 2 summarizes the baseline values of mean blood flow velocities at rest and after acetazolamide in both groups. Figure 1 presents the statistical differences between blood flow velocity at rest and after the acetazolamide test.

In both groups, as shown in Figure 1, mean blood flow velocity on the affected side showed only a slight statistically nonsignificant increase after acetazolamide (group A, +1.2±7.6%; group B, +1.8±5.6%). On the contralateral side blood flow velocity increased significantly after the acetazolamide test (group A, +20.5±10.2%; group B, +31.5±21.9%).
TABLE 3. Blood Flow Velocity at Rest and After Acetazolamide at Follow-up Examination

<table>
<thead>
<tr>
<th>Side</th>
<th>Group A</th>
<th>Group B</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>After acetazolamide</td>
<td>At rest</td>
<td>After acetazolamide</td>
</tr>
<tr>
<td>Affecte</td>
<td>41.9±13.1</td>
<td>53.5±16.0</td>
<td>42.6±8.2</td>
<td>43.5±8.8</td>
</tr>
<tr>
<td>Contralateral</td>
<td>60.2±17.8</td>
<td>74.8±14.2</td>
<td>65.8±13.3</td>
<td>86.3±15.2</td>
</tr>
<tr>
<td>P*</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.004</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD cm/sec. Group A, extracranial-intracranial bypass group; Group B, control group.

•Affecte vs. contralateral side.

The differences between baseline values at rest and after the acetazolamide test of the affected and the contralateral sides between groups A and B were statistically nonsignificant.

The results of follow-up examinations are depicted in Table 3. Bar graphs in Figure 2 demonstrate statistical significance of mean blood flow velocity changes at rest and after acetazolamide in both groups. Follow-up studies were performed in group A 3–6 months after EC–IC bypass in 13 patients. One patient succumbed to sudden death before the control examination. The mean blood flow velocity in the MCA of the affected side increased significantly after acetazolamide by 29.4±18.3% (p<0.002). On the contralateral side velocity showed an increase of 24.1±12.1% after acetazolamide.

In group B follow-up examinations were performed 3–6 months after initial testing in all 14 patients. Mean blood flow velocity on the affected side after the acetazolamide test increased only marginally by 1.9±8.3%. On the contralateral side blood flow velocity increased significantly by 32.9±21.7%.

The differences between the values at follow-up examinations at rest and after the acetazolamide test of the affected and the contralateral sides between groups A and B were statistically nonsignificant.

In all 14 operated patients, the temporal artery on the side in question showed a markedly increased blood flow velocity after the acetazolamide test. We avoided expressing the blood flow velocity in centimeters per second because of the uncertain insonation angle.

Detailed analysis of the data of group A showed a positive response to EC–IC bypass in 10 of 13 subjects examined. These 10 patients had a restored vasomotor reactivity with an increase of mean blood flow velocity on the affected side of >10%. One patient showed unchanged vasomotor reactivity: at initial testing he had an increase of mean blood flow velocity on the affected side of 3.4% and at the follow-up study of 5.7%. Two other patients, both showing no changes of blood flow velocity before shunting (increase, 0.0%), had an improved reactivity (increase, 4.3% and 8.6%) but did not reach the defined cutoff point.

In group B, 11 of 14 patients had unchanged compromised vasomotor reactivity. In three subjects, restoration of vasoconstrictor capacity was found. One patient, who showed no increase at initial testing, had a normalized reactivity with an increase of 16.6%. Two other subjects just reached the cutoff point with increases of 10.2% and 11.1%. At the initial testing they had increases on the affected side of 2.3% and 5.2%, respectively.

**Discussion**

In this study we selected patients with ICA occlusions for EC–IC bypass surgery using hemodynamic criteria based on TCD evaluation of vasomotor reactivity after acetazolamide administration. Transcranial Doppler sonography is a noninvasive method that has proven its reliability in the measurement of blood flow velocity of the basal intracerebral arteries in several studies. Bishop et al20 found decreased mean values at rest in patients with ICA occlusions. Schneider et al21 reported...
a decreased mean blood flow velocity and pulsatility index associated with an ICA occlusion when comparing both the contralateral patent carotid arteries in the same patients and in control subjects. Our own experiences (unpublished data) with 104 consecutive patients with unilateral ICA occlusions showed a significantly lower mean blood flow velocity on the affected side compared with the contralateral side: 45.2±14.8 cm/sec and 60.0±14.3 cm/sec, respectively (p<0.001).

In most studies,5-8 measuring CBF by either 133Xe-inhalation technique, positron emission tomography (PET), or TCD, CO2 was used to assess vasomotor reactivity. Ringelstein et al,8 in a TCD study, found a significantly decreased CO2-induced vasomotor response on both the occluded (mean, 45.2%; p<0.0001) and the contralateral sides (mean, 67.1%; p<0.01). Analyzing subgroups, he reported significantly lower vasomotor reactivity among patients with symptomatic ICA occlusions than in asymptomatic subjects. However, CO2 is inconvenient to administer and causes respiratory discomfort, which limits its routine application. Ehrenreich,12 studying 10 patients with various cerebrovascular disorders, described a more marked increase in CBF by acetazolamide than that induced by 5 minutes of 5% CO2 inhalation. Piepgras and coworkers22 studied 21 patients with obstructive carotid artery disease and symptoms of ischemia using TCD and 133Xe dynamic single-photon emission computed tomography after acetazolamide stimulation. Increases in blood flow velocity and in CBF correlated significantly in both hemispheres.

In our own investigations of 100 normal control subjects examined by TCD, the mean blood flow velocity increased by 40.1±20.6% after acetazolamide. This is in accordance with the findings of Vorstrup,8 who reported an increase in mean CBF after acetazolamide of 13-46%. We therefore defined an increase in mean blood flow velocity on the affected side of ≥10% as normal vasomotor reactivity. In our normal control subjects as well as in all patients with ICA occlusion the time course of the acetazolamide response was similar, peaking within a few minutes and lasting for about 30 minutes. We studied all patients 15-20 minutes after acetazolamide injection to record the peak value of the blood flow velocity with certainty.

Our results demonstrate the restoration of vasomotor reactivity distal to an occluded ICA in the majority of patients after EC-IC bypass compared with no improvement without operation. However, the baseline blood flow velocity did not change after surgery in the operated group, nor did it differ from the control group postoperatively. The observed group difference was exclusively limited to postoperative acetazolamide activation in the affected hemisphere.

Transcranial Doppler with the acetazolamide test enables us to define a subgroup of patients in whom hemodynamic improvement could be expected by EC-IC bypass surgery. At present, various criteria are used to search for such subgroups. The EC-IC bypass study group failed to identify any such subgroup of patients who might benefit from surgery.1 In 1984 Powers et al22 reported hemodynamic improvement in six of 17 patients examined preoperatively and postoperatively by PET. They studied CBF and oxygen metabolism by the inhalation of carbon monoxide labeled with oxygen-15 and intravenous injection of oxygen-15-labeled water. The shortcoming of the study is that four subjects had a normal CBF preoperatively and only 12 patients showed satisfactory surgical outcome with a good flow through the bypass. In a subgroup consisting of four subjects with transient ischemic attacks and normal computed tomographic scan, they found an increased CBF and a concomitant decrease in the fractional extraction of oxygen from the blood. Samson et al,24 measuring regional CBF, oxygen extraction fraction, and oxygen metabolic rate in 11 patients with ICA obstruction and one with an occlusion of the MCA, reported significant metabolic improvement after EC-IC bypass surgery. In similar studies improvement of cerebral perfusion pressure and improved hemodynamic reserve could be demonstrated after EC-IC bypass.23,26 Vorstrup et al27 studied patients before and after EC-IC bypass with 133Xe-inhalation tomography. Twenty-two patients were selected by low-flow areas exceeding the lesions in computed tomographic scan. Eighteen of these 22 subjects showed no changes in CBF. In a subsequent study the same group used the acetazolamide test in association with CBF measurement.9 However, nine of 18 subjects revealed normal reactivity preoperatively. Only two of nine subjects with a positive acetazolamide test (i.e., a significant redistribution of flow to the nonoccluded side) showed improved focal CBF after shunting. Powers et al28 reported the follow-up of a small group of nonrandomized medically and surgically treated patients with no benefit of surgery in those with hemodynamic compromise as documented by PET.

In our study vasomotor reactivity was used as the hemodynamic criterion. Although blood flow velocity at rest was not altered, 10 of 13 patients (77%) showed a positive response to acetazolamide, demonstrating restored vasomotor reactivity after EC-IC bypass, compared with three of 14 subjects in the conservatively treated control group. These data demonstrate that in patients with insufficient collaterals, the additional anastomosis by EC-IC bypass increases the vasodilatory capacity in the region distal to an ICA occlusion. We found no differences in the functioning of the bypass or other clinical or hemodynamic parameters between responders and nonresponders.

Considering these results, TCD together with the acetazolamide test permits noninvasive evaluation of vasomotor reactivity in patients with ICA occlusion. This method can identify subjects with decreased vasodilatory capacity, which may be improved by EC-IC bypass in about 75% of the cases. This patient group with reduced vasomotor reactivity distal to an ICA occlusion may represent a subgroup that is prone to transient ischemic attacks or permanent strokes caused by critically reduced CBF.

Acknowledgment

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References

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