Effect of Acetazolamide on Cerebral Blood Flow in Subacute and Chronic Cerebrovascular Disease

E. Højer-Pedersen, MD

Acetazolamide increases cerebral blood flow. The generalized and regional changes in blood flow after administration of acetazolamide were evaluated by the xenon-133 inhalation technique in a series of patients with subacute or chronic focal cerebral ischemia. Acetazolamide augmented interhemispheric asymmetry of cerebral blood flow in patients with unilateral occlusion of major cerebral arteries, whereas no significant side-to-side asymmetry was evident in patients with minor arterial lesions. Low flow areas in relation to computed tomography-verified infarcts tended to be larger after administration of acetazolamide. Hyperfrontality was present at rest and during stimulation with acetazolamide. A decline of cerebral blood flow with advancing age was greater in patients than in normal controls. The vasodilator response to acetazolamide did not change with age. (Stroke 1987;18:887-891)

Acetazolamide increases cerebral blood flow (CBF) by 5–80%. After i.v. injection in humans, CBF begins to increase within 15 minutes, reaches a maximum in about 25 minutes, and then gradually declines with a half-time of about 95 minutes. The only known pharmacologic effect of acetazolamide is carbonic anhydrase inhibition, and the exact mechanism of CBF increase is unknown. Cerebral metabolic rate for oxygen is unaffected by acetazolamide, arterial PCO₂ is unchanged, and blood pressure is usually unaffected also.

The present study evaluated both the generalized and focal changes of regional cerebral blood flow (rCBF) after i.v. administration of acetazolamide in a series of patients with focal cerebral ischemia at a subacute or chronic stage. The changes in rCBF were compared with patient age, type of arterial lesion, and computed tomography (CT) findings.

Subjects and Methods

There were 17 patients, 6 women and 11 men, aged 27–67 years (mean 53.8 years, SD 9.2), who had a series of investigations because of slight-to-moderate symptoms of focal cerebral ischemia in the carotid territory. Four patients had transient ischemic attacks (TIAs) without infarctions on CT scan, and 13 patients had minor stroke with CT-demonstrated infarcts. The patients were divided into 2 groups according to the angiographic findings (Table 1). Group 1 had unilateral occlusion of a major cerebral artery; 6 involved the internal carotid artery (ICA) extracranially and 3 the main trunk of the middle cerebral artery (MCA). Group 2 had arteriosclerotic changes of the intracranial ICA, the MCA trunk, or the main MCA branches. These arteriosclerotic stenoses were considered of no hemodynamic significance. The patients in the 2 groups were comparable in age (Table 1) and severity of the ischemic symptoms. Group 1 + 2 includes all patients.

There were 23 controls, 11 women and 12 men, aged 29–70 years (mean 51.3 years, SD 11.0), who by history had no cerebral disease, hypertension, or diabetes. The controls were either members of the staff or patients who were seen for minor surgery or in the course of treatment for fractures of the extremities. They comprised a normal group for comparison of CBF.

Each subject gave informed consent.

Measurement of Cerebral Blood Flow

CBF was measured once between 5 and 179 days (mean 101 days) after the most recent TIA or the stroke by the xenon-133 inhalation technique, using a Novo cerebrograph (Denmark) with 16 external scintillation detectors for each side of the head. rCBF was calculated as the initial slope index (ISI) and was measured first at rest, with the subject lying in a quiet room with eyes closed and ears plugged, and again at test, 20 minutes after i.v. injection of 1 g acetazolamide dissolved in 10 ml distilled water. Paco₂ was estimated from capnograph recordings of end-tidal CO₂ concentrations during the examination; ISI was not corrected for changes in Paco₂. Mean arterial blood pressure (MABP) was measured by auscultation after the CBF measurement.

Statistical Analyses

Differences between ISI at rest and at test were evaluated with the paired t test. Between-group comparisons were made with the unpaired t test. The ISI vs. age relation was evaluated with linear regression analysis. Values are reported as mean ± SD.
Table 1. Arterial Lesions and Clinical Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (yrs) mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>ICA occlusion</td>
<td>53.9±11.9</td>
</tr>
<tr>
<td>MCA occlusion</td>
<td>53.8±5.6</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
</tr>
<tr>
<td>Arterial stenoses</td>
<td>65.8±9.8</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack; ICA, internal carotid artery; MCA, middle cerebral artery.

Results

Interhemispheric Asymmetry

CBF in the asymptomatic and symptomatic hemispheres at rest and at test are indicated in Table 2. At rest, a significant side-to-side asymmetry was found in Groups 1 and 1+2, with the highest flow in the asymptomatic hemisphere, whereas the hemispheric difference was not significant in Group 2. Administration of acetazolamide induced a change in CBF of 10 to 78% (34 ± 18.2%) in the asymptomatic hemisphere and of -2 to 82% (32 ± 18.7%) in the symptomatic hemisphere, with persistence of the interhemispheric asymmetry (Figure 1). In Group 1 patients, the asymmetry was significantly larger at test than at rest because CBF increased less in the symptomatic hemisphere than in the asymptomatic hemisphere (p < 0.02) (Table 2).

In the patients, Paco₂ and MABP at rest were 43 ± 5 and 109 ± 12 mm Hg, respectively, not different from Paco₂ and MABP at test (40 ± 6 and 109 ± 15 mm Hg, respectively) (p>0.05) (Table 3). In the controls, resting mean hemispheric ISI (average of 2 hemispheres) was 52.5 ± 8.5. There was no significant difference in the mean CBF of right and left hemispheres (difference 0.1 ± 0.7). Paco₂ was 41 ± 4 mm Hg, and MABP was 99 ± 13 mm Hg (Table 3) at the time of the CBF measurements.

Cerebral Blood Flow in Relation to Age

The mean hemispheric CBF decreased significantly with advancing age. In the 23 controls, the regression equation was \( Y = 70.82 - 0.35X \) \( (r = -0.46, p<0.05) \) (Figure 2). CBF declined by 15% \( (p<0.05) \) from an ISI of 55.8 ± 7.9 in controls below the median age (53 years) to an ISI of 48.3 ± 7.8 in those above age 53.

In the 17 patients with cerebrovascular disease (CVD) measured at rest and at test, CBF declined with age in both hemispheres (Table 4). The resting CBF in the symptomatic hemisphere (Figure 3) decreased by 33% \( (p<0.01) \) from an ISI of 55.4 ± 8.2 in 8 patients below age 53 to an ISI of 41.5 ± 5.9 in 9 patients above age 53. During the test, CBF in the symptomatic hemisphere (Figure 3) decreased by 27% \( (p<0.01) \) from an ISI of 70.6 ± 10.6 in patients below age 53 to an ISI of 55.7 ± 5.7 in those above age 53.

There was only 1 patient below age 44. When this patient was omitted from the calculations, the correlation coefficient between flow and age for the symptomatic hemisphere was \( r = -0.60 \) \( (p<0.02) \) at rest and \( r = -0.68 \) \( (p<0.01) \) during test.

Administration of acetazolamide increased CBF at rest for the symptomatic hemisphere to 28 ± 10.2% in the 8 patients below age 53 and to 36.4 ± 23.8% in the 9 patients above age 53. The difference between the age groups was not significant \( (p>0.1) \).

ISI in the frontal regions of the symptomatic hemisphere declined significantly with advancing age both in the controls \( (r = -0.49, p<0.02) \) and in the patients at rest \( (r = -0.67, p<0.01) \) and at test.
Table 3. Paco₂ and MABP at rCBF Measurements

<table>
<thead>
<tr>
<th>Patients</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>At test</td>
</tr>
<tr>
<td>Paco₂</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>MABP</td>
<td>109 ± 12</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; rCBF, regional cerebral blood flow. Values are mean ± SD, mm Hg.
*No significant differences between rest and test.

(r = −0.81, p < 0.001) (Table 4). The regression lines for regional frontal ISI reduction with age paralleled those for hemispheric ISI.

The decline of CBF with age was not evaluated separately in Group 1 and Group 2 patients since the number in each group was too small for such an evaluation.

Hyperfrontality

In the controls, rCBF in the frontal region was 2.7 ± 1.5% higher than the hemispheric CBF (p < 0.001). The same flow pattern with significant hyperfrontality was observed in the resting CBF of patients in Group 1 and Group 2, in both the symptomatic and asymptomatic hemispheres. After acetazolamide injection, the hyperfrontal flow distribution was still present (symptomatic hemisphere, p < 0.001; asymptomatic hemisphere, p < 0.02).

Focal Changes

Focal changes in CBF at rest or at test were defined as present when the rCBF of 2 or more adjacent detectors in a hemisphere differed from the rCBF of the corresponding detectors in the other hemisphere by ≥ 2 SD of the mean interhemispheric flow difference in the 17 patients.

Focal low perfusion areas were found in relation to subcortical-cortical infarcts in 7 stroke patients at rest. The interhemispheric asymmetry was distinct. After administration of acetazolamide, rCBF increased diffusely in both hemispheres but with a tendency to less increase in the focal low perfusion areas and their periphery. The low perfusion areas thus become more marked (Figure 4). Six patients had occlusion of the ICA or MCA, 1 had minor arterial lesions. Para-doxical reactions, areas with absolute reduction of rCBF, or appearance of new low perfusion areas after administration of acetazolamide were not seen.

No focal abnormalities and minimal hemispheric asymmetry were observed in the resting CBF of 10 patients. A uniform rCBF increase appeared in 7 of these patients after administration of acetazolamide. These 7 patients had none or small, deep infarcts and minor arterial lesions. In the other 3 patients, acetazolamide induced none or lesser increase in rCBF of nearly the entire symptomatic hemisphere, resulting in a considerable interhemispheric asymmetry. These 3 patients had occlusion of the ICA, 2 without infarction and the third with several small, deep infarcts.

Discussion

Acetazolamide is a potent vasodilator of the cerebral vessels in patients with subacute-chronic CVD. The characteristics of the flow response are related to the severity of the arterial lesions and to the age of the patients.

In the patients of Group 1, those with occlusion of major cerebral arteries, a significantly larger hemispheric difference occurred during acetazolamide test than at rest, whereas patients in Group 2, those with minor arterial lesions, demonstrated no significant hemispheric difference. Three patients in Group 1, with occlusion of the ICA, had no infarcts (2 cases) or small deep infarcts (the third case). In these patients, the observed lesser CBF increase on the occluded side

![Figure 2. Significant decline in cerebral blood flow (CBF) with advancing age in 23 normal controls.](image-url)

Table 4. Regression Analyses for rCBF vs. Age in 17 Patients at Rest and at Acetazolamide Test

<table>
<thead>
<tr>
<th>Region</th>
<th>Regression equation</th>
<th>r</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hemisphere</td>
<td>Y = 85.07 - 0.69X</td>
<td>−0.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Asymptomatic hemisphere</td>
<td>Y = 88.74 - 0.72X</td>
<td>−0.68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Symptomatic frontal</td>
<td>Y = 93.92 - 0.82X</td>
<td>−0.67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>At test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hemisphere</td>
<td>Y = 115.26 - 0.98X</td>
<td>−0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymptomatic hemisphere</td>
<td>Y = 114.98 - 0.92X</td>
<td>−0.80</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Symptomatic frontal</td>
<td>Y = 121.33 - 1.06X</td>
<td>−0.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

rCBF, regional cerebral blood flow; r, correlation coefficient.
Figure 3. Significant decline in cerebral blood flow (CBF) of the symptomatic hemisphere with advancing age, at rest (■) and at test with acetazolamide (○). At rest, \( Y = 85.07 - 0.69X \) \((r = -0.64, p < 0.01)\); at test, \( Y = 115.26 - 0.98X \) \((r = -0.81, p < 0.001)\).

after administration of acetazolamide may have been caused by insufficient collaterals in accordance with the observations of Norrving et al., who demonstrated impaired CO\(_2\) response in patients with reduced collateral capacity. In the other 6 patients of Group 1, subcortical-cortical infarcts were present at CT scan, and these areas with tissue loss and poor or absent perfusion may explain the results of the CBF measurements. In contrast to Group 1 patients, all but 1 in Group 2 had none or small, deep infarcts and no significant interhemispheric difference in CBF at rest or at test.

In accordance with other studies, a significant decline in rCBF with advancing age was found in the controls, and a much larger decline with age in patients with CVD was seen in both the asymptomatic and symptomatic hemispheres. The resting CBF in the elderly patients were considerably lower than in the younger ones; however, the increase in CBF from baseline (at rest) to acetazolamide test was of the same magnitude in the 2 age groups. Thus, in these patients with CVD, the vasodilator response appeared unchanged with advancing age. Davis et al., in a study of cerebrovascular CO\(_2\) reactivity in stroke-age normal controls, found no change in CO\(_2\) reactivity with age. Other studies have given conflicting results. Fazekas et al., in a study of cerebral hemodynamics in elderly persons with cerebral arteriosclerosis, found changes in CBF with CO\(_2\) inhalation, with i.v. aminophylline, and during hyperventilation that were similar to but less marked than those of younger subjects with no evident CVD. Scheive and Wilson reported a small, nonsignificant change in vascular reactivity to CO\(_2\) with age in normal subjects, whereas stroke patients had a reduced response to CO\(_2\). Ackerman and Ackerman et al. demonstrated in patients with subacute-chronic ischemic CVD that a change in CBF in response to a change in CO\(_2\) was proportional to the resting CBF. Yamamoto et al. showed that vasodilator response to hypercarbia decreased with advancing age in normal healthy volunteers and found a severe reduction in the vasodilator response to hypercarbia in patients with chronic hemispheric ischemia.

In the present study, the cerebral hemodynamics were evaluated after administration of acetazolamide. The precise mechanism of the vasodilator effect of acetazolamide is not known, but it may result from a decrease in cerebral pH. In accordance with other studies, Paco\(_2\) and MABP were unchanged after injection of acetazolamide. The applied dose of acetazolamide supposedly reversibly inhibits carbonic anhydrase in all organs for at least 30 minutes. Acetazolamide has a low toxicity and was tolerated without side effects.

rCBF in the controls at rest showed a characteristic intrahemispheric distribution with a consistent, slightly higher CBF in the frontal region. Other investigators have reported a hyperfrontal distribution of 5–10%, 5–15%, 10–15%, and 20–40%. In several of these investigations, the flow parameter \( F_s \) (gray matter flow) was used, whereas ISI was used in the present study. This may explain the value of about 3% lower in this study due to the relative flatness of the ISI pattern. Hyperfrontality is supposedly caused by the intrahemispheric psychological organization. It persisted in CBF, in both symptomatic and asymptomatic hemispheres at rest, and was not lost after vasodilation with acetazolamide. Furthermore, it was present in the elderly controls, as well as in the patients with CVD. This was in contrast to the findings of Mamo et al., who, in patients with vascular risk factors, observed disappearance of the frontal hyperperfusion during the fifth and sixth decades.

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References

Key Words • acetazolamide • cerebral blood flow • cerebrovascular disease
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