Influence of Acetazolamide and CO\textsubscript{2} on Extracranial Flow Volume and Intracranial Blood Flow Velocity

B.M. Eicke, MD; E. Buss, MD; R.R. Bähr, MD; G. Hajak, MD; W. Paulus, MD

Background and Purpose—The vasomotor response can be tested by means of transcranial Doppler sonography. If a constant vessel diameter is assumed, the flow velocity changes will reflect blood flow volume changes. This hypothesis is difficult to verify. Simultaneous assessment of intracranial flow velocity and extracranial flow volume changes may solve this problem.

Methods—We tested vasomotor response in 32 volunteers (age, 42±18 years) with 5% CO\textsubscript{2}. Acetazolamide (1 g) was tested in 15 volunteers (age, 28±8 years). To evaluate drug-dependent flow changes in the external carotid artery territory, acetazolamide was administered in 7 patients with unilateral occlusion of the internal carotid artery without evidence of collateralization through the ophthalmic artery (age, 67±12 years). Simultaneous recording included measurements of flow volume in the common carotid arteries (M-mode color duplex system) and flow velocity in the middle cerebral arteries.

Results—With CO\textsubscript{2} and acetazolamide, intracranial flow velocity increased by 31% and 39%, respectively, with a simultaneous increase of common carotid artery flow volume of 47% and 50%, respectively. No change in extracranial flow volume was observed in patients with an occluded internal carotid artery.

Conclusions—These data show not only the expected increase of flow velocity in the middle cerebral artery but also suggest an increase in cross-sectional vessel diameter of 6% and 4% with CO\textsubscript{2} and acetazolamide, respectively. It remains unresolved whether this observation is due to a direct effect of the drug on the vessel walls or is simply pressure dependent. 

Key Words: acetazolamide ▪ blood flow velocity ▪ carbon dioxide ▪ cerebral blood flow ▪ ultrasonography, Doppler, transcranial ▪ vasomotor reactivity

The vasomotor response (VMR) reflects the capacity of the cerebral blood vessels to react to agents causing vasodilation or vasoconstriction. The main clinical value of these tests is the identification of hemodynamically critical carotid stenoses or occlusions.\textsuperscript{1–6} To date, VMR assessment is usually performed by means of transcranial Doppler sonography (TCD), with insonation of the middle cerebral artery (MCA). It is assumed that the induced changes of cerebral perfusion are predominantly due to changes of blood flow velocity, with only insignificant changes of vessel diameter.\textsuperscript{7} Thus, it would be acceptable to determine the cerebral flow volume from the measured flow velocity. However, comparative regional cerebral blood flow (rCBF) and TCD data are controversial. These results indicated a slight narrowing of the vessel diameter.\textsuperscript{8,9}

The introduction of color duplex M-mode systems (Figure 1) offers the potential to constantly and noninvasively estimate the carotid flow volume.\textsuperscript{10–12} The direct comparison of intracranial flow velocity and extracranial flow volume data may help to differentiate between intracranial flow velocity increases due to either local vasoconstriction or hyperperfusion. The goal of this study was the simultaneous assessment of intracranial blood flow velocity and extracranial blood flow volume during VMR testing. The question of potential vasodilation or vasoconstriction due to vasoactive drugs was addressed.

Subjects and Methods

In this trial we monitored the following parameters simultaneously: (1) extracranial peak systolic and end-diastolic flow velocity, peak systolic and end-diastolic vessel diameter, and flow volume rate in the common carotid arteries (CCA); (2) intracranial blood flow velocity in the MCA bilaterally; and (3) end-expiratory CO\textsubscript{2} pressure.

Extracranially, peak systolic and end-diastolic flow velocity, peak systolic and end-diastolic vessel diameter, and flow volume rate in the CCA (raw data) were measured bilaterally with a specifically developed color duplex M-mode system (P700 with CVI-Q, Philips Medical Systems). These systems offer the potential to constantly and noninvasively estimate the carotid flow volume.\textsuperscript{10,11} Specifically developed color M-mode software (CVI-Q), as well as a time-domain–based color duplex system (with improved temporal and spatial resolution and accuracy of velocity display), offers easy
We performed off-line analysis using the event marker of the DWL system, averaging TCD and CO₂ data over the time the flow volume data on the duplex system were sampled.

We studied the CO₂-dependent VMR in 32 normal, age-matched volunteers (age range, 21 to 82 years; mean age, 42±18 years). Samples were taken with the volunteers breathing normal air and with inhalation of 5% CO₂ through a mask (half-open system). Flow volume data were sampled when TCD measurements (flow velocities) showed a plateau phase, usually after 60 to 90 seconds. Hyperventilation for 1 to 2 minutes was performed after a minimum resting time of 5 minutes with the volunteers breathing normal air.

In 15 volunteers (age range, 32 to 74 years; mean age, 28±8 years), we tested the VMR with acetazolamide. Simultaneous recordings of intracranial blood flow velocity, extracranial flow, and CO₂ data were sampled at baseline and after injection of acetazolamide 1 g IV. Maximum MCA flow velocity data were observed 12 to 20 minutes after injection (Figure 2).

To study the vasomotor effects of acetazolamide on the territory of the external carotid artery (ECA) exclusively, we additionally studied 7 patients (age range, 62 to 75 years; mean age, 67±12 years) with unilateral ICA occlusion without collateral flow through the ophthalmic artery before and after administration of acetazolamide 1 g IV. These patients were studied only ipsilateral to the side of the occlusion.

The study protocol required written informed consent and was approved by the local ethics committee.

All values are given as mean±SD. Statistical evaluation was performed to compare the induced relative changes of intracranial blood flow velocity and extracranial flow volume with CO₂ and acetazolamide. These data were tested for normal distribution (Kolmogoroff-Smirnov test), and the 2-tailed paired t test was applied. Results were considered (locally) significant for P<0.05.

Results

We did not find a significant side-to-side difference of flow volume and flow velocity data in the volunteer groups before and after stimulation with CO₂ or acetazolamide. For further analysis, a mean value of right and left sides was used.

Volunteers Tested With CO₂

The end-expiratory CO₂ content at baseline was 4.0% and changed to 4.9% with inhalation of a gas mixture with 5% CO₂ (Table 1). Blood flow velocity in the MCAs increased...
from baseline values by 19 cm/s (+31%) (Table 2). Simultaneously, the flow volume in the CCAs increased by 163 mL/min (+47%) (Table 3). The relative increase of extracranial flow volume compared with the increase of intracranial flow velocity was significantly higher ($P<0.0001$) (Figure 3).

The extracranial changes were predominantly but not exclusively due to increases of blood flow velocity, especially in diastole. Systolic flow velocity in the CCAs increased by 9 cm/s (+10%) and diastolic blood flow velocity by 7 cm/s (+42%). The calculated mean temporal velocity in the CCAs increased by 8 cm/s (+20%). Systolic vessel diameter in the CCAs increased by 0.3 mm (+4%) and diastolic vessel diameter by 0.4 mm (+7%). Calculated mean temporal diameter in the CCAs increased by 0.4 mm (+6%) (Table 3).

**Volunteers Tested With Hyperventilation**

With hyperventilation, end-expiratory CO$_2$ levels dropped from 4.0% to 2.5% (Table 1), and intracranial flow velocity dropped by 18 cm/s (−28%) (Table 2). Flow volume dropped simultaneously by 121 mL/min (−35%) (Table 3). The relative drop of extracranial flow volume compared with the decrease of intracranial flow velocity was significantly more pronounced ($P<0.05$).

The extracranial changes were most obvious in diastole, with a velocity drop of 6 cm/s (−32%) and a diameter drop of 0.9 mm (−15%). In systole, a velocity decrease of 10 cm/s (−12%) and a diameter decrease of 0.4 mm (−5%) were noted. Calculated mean temporal velocity dropped by 7 cm/s (−17%), and mean temporal diameter decreased by 0.6 mm (−10%) (Table 3).

**Volunteers Tested With Acetazolamide**

The end-expiratory CO$_2$ content at baseline was 4.4% and changed to 3.9% 15 to 20 minutes after intravenous injection (Table 1). Blood flow velocity in the MCAs increased from baseline values by 6 cm/s (+39%) (Table 2). Simultaneously, the flow volume in the CCAs increased by 215 mL/min (+50%) (Table 3). The relative increase of CCA flow volume was significantly higher ($P<0.005$) than the increase of MCA flow velocity (Figure 3).

As with CO$_2$, the most decisive factor altering the extracranial flow volume was the increase of diastolic flow velocity. Systolic flow velocity in the CCAs increased by 6 cm/s (+6%) and diastolic flow velocity by 9 cm/s (+43%). Calculated mean temporal velocity in the CCAs increased by 8 cm/s (+16%). Systolic vessel diameter in the CCAs increased by 0.5 mm (+6%) and diastolic vessel diameter by 0.7 mm (+13%). Calculated mean temporal diameter in the CCA increased by 0.6 mm (+10%) (Table 3).

**Acetazolamide in Patients With Occluded ICA**

Despite a moderate increase of blood flow velocity in the ipsilateral MCA of 13 cm/s (+28%) (Table 2), no significant increase in flow volume in the corresponding CCA was observed (3 mL/min; +2%) (Table 3) (Figure 3).

**Discussion**

Acetazolamide and CO$_2$ are both known to increase cerebral blood flow. Clinically, the VMR is predominantly used for diagnostic purposes to identify patients with hemodynamically critical high-grade carotid stenosis or occlusion. In these patients arterioles and the capillary bed are dilated to a maximum to compensate for the reduced cerebral blood flow. Therefore, the VMR is predominantly used for diagnostic purposes to identify patients with hemodynamically critical high-grade carotid stenosis or occlusion. In these patients arterioles and the capillary bed are dilated to a maximum to compensate for the reduced cerebral blood flow.

The VMR can be measured by means of single-photon emission CT (SPECT), with $^{133}$Xe or hexamethylpropyleneamine oxime (HMPOA) as tracers. A disadvantage of these methods is the requirement of radioactive material and difficulties in monitoring changes over time. Flow velocity of the basilar intracerebral arteries can be monitored continuously and noninvasively with TCD devices. If a constant vessel diameter is assumed, relative flow velocity changes correlate directly with flow volume changes.

With acetazolamide (1 g IV), maximum flow velocity increases in the MCA of 34% to 60% of the increase of rCBF. Comparative rCBF and TCD data are controversial, since a slightly less pronounced increase of rCBF compared with intracranial flow velocity was observed. Sorteberg et al reported a MCA flow velocity increase with acetazolamide of 36% to 42% versus a rCBF increase of only 24% to 26%; Dahl et al found a MCA flow velocity increase of 35% with a corresponding rCBF increase of only 30%. It was assumed that acetazolamide may cause additional vasoconstriction of the major intracerebral vessels. In contrast to the published SPECT data, we noticed not only the anticipated increase of flow velocity in the MCA but also an even more pronounced flow volume increase in the extracranial brain-supplying arteries, predominantly in diastole.

It was possible to exclude that the flow volume changes in the CCA were due to increased perfusion in the ECA territory. For this reason, patients with unilateral occlusion of the ICA who had no evidence of collateral flow through the ophthalmic arteries were studied. Flow volume in these patients did not change after injection of acetazolamide. These results are in contrast to published data by Demolis et al.

### TABLE 1. End-Expiratory Concentration of CO$_2$ in All Arteries

<table>
<thead>
<tr>
<th>End-Expiratory CO$_2$, %</th>
<th>Rest</th>
<th>WS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO$_2$ Inhalation</td>
<td>4.0±0.5</td>
<td>4.9±0.5</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>4.0±0.5</td>
<td>2.5±0.4</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>4.4±0.2</td>
<td>3.9±0.3</td>
</tr>
<tr>
<td>Acetazolamide (patients)</td>
<td>4.1±0.4</td>
<td>3.8±0.6</td>
</tr>
</tbody>
</table>

WS indicates with stimulation.

### TABLE 2. Flow Velocity and Diameter of MCAs

<table>
<thead>
<tr>
<th>Flow Velocity, cm/s</th>
<th>Diameter,*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>WS</td>
</tr>
<tr>
<td>CO$_2$ Inhalation</td>
<td>61±12</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>61±12</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>68±10</td>
</tr>
<tr>
<td>Acetazolamide (patients)</td>
<td>49±10</td>
</tr>
</tbody>
</table>

WS indicates with stimulation.

*Estimated (see text).
†Not estimated.
TABLE 3. Flow Volume, Flow Velocity, Diameter, Systolic and Diastolic Flow Velocity, and Systolic and Diastolic Vessel Diameter in CCAs

<table>
<thead>
<tr>
<th></th>
<th>Flow Volume, mL/min</th>
<th>Flow Velocity, cm/s</th>
<th>Diameter, mm*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Rest</td>
<td>WS</td>
</tr>
<tr>
<td>CO₂ inhalation</td>
<td>349±56</td>
<td>349±56</td>
<td>+47</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>349±56</td>
<td>228±55</td>
<td>-35</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>432±63</td>
<td>647±103</td>
<td>+50</td>
</tr>
<tr>
<td>Acetazolamide (patients)</td>
<td>159±44</td>
<td>162±46</td>
<td>+2</td>
</tr>
</tbody>
</table>

Systolic Flow Velocity, cm/s

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>WS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ inhalation</td>
<td>85±19</td>
<td>94±19</td>
<td>+10</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>85±19</td>
<td>75±17</td>
<td>-12</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>104±14</td>
<td>110±13</td>
<td>+6</td>
</tr>
<tr>
<td>Acetazolamide (patients)</td>
<td>48±12</td>
<td>45±12</td>
<td>-6</td>
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</table>

Diastolic Flow Volume, cm/s

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>WS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ inhalation</td>
<td>25±5</td>
<td>+42</td>
<td>6.8±0.6</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>12±3</td>
<td>-32</td>
<td>6.8±0.6</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>30±3</td>
<td>+43</td>
<td>7.0±0.6</td>
</tr>
<tr>
<td>Acetazolamide (patients)</td>
<td>6±3</td>
<td>+14</td>
<td>6.9±0.8</td>
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</tbody>
</table>

Systolic Vessel Diameter, mm

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>WS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ inhalation</td>
<td>7±4</td>
<td>+14</td>
<td>6.9±0.8</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>3±3</td>
<td>+15</td>
<td>6.3±0.4</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>10±10</td>
<td>+15</td>
<td>6.6±0.1</td>
</tr>
</tbody>
</table>

Diastolic Vessel Diameter, mm

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>WS</th>
<th>%</th>
</tr>
</thead>
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<td>CO₂ inhalation</td>
<td>6±3</td>
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<td>6.9±0.8</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>5±5</td>
<td>+15</td>
<td>6.3±0.4</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>7±7</td>
<td>+15</td>
<td>6.6±0.1</td>
</tr>
</tbody>
</table>

WS indicates with stimulation.

*Calculated mean value=(1×peak systolic value+2×end-diastolic value)/3.

al., who showed a moderate increase of blood flow of 34% in the ECA territory induced by acetazolamide as measured by cutaneous facial blood flow.

A potential explanation for the contradictory results of the aforementioned rCBF studies and our findings is the absolute simultaneous assessment of blood flow velocity and flow volume in our study. SPECT data are based on one-time measurements, and the time course of vasomotor responses may differ.22 It appears possible that the documented rCBF data did not represent the highest flow increase. Continuous TCD monitoring allows exact determination of the maximum flow velocity. Possibly the maximum increase of flow velocity was compared with a submaximal increase of rCBF. Another explanation is a possible underestimation of rCBF by SPECT due to low first-pass extraction in high blood flow regions.26

The discrepancy between extracranial flow volume and intracranial flow velocity data indicates a minor to moderate increase in cross-sectional intracranial vessel diameter and area. This area increase can be estimated as follows:

\[
\text{Volume Flow (m}^3/\text{s}) = \text{Flow Velocity (m/s) × Area (m}^2\text{)}
\]

or

\[
\text{Area} = \frac{\text{Volume Flow}}{\text{Flow Velocity}}
\]

In case of CO₂ testing with an extracranial flow volume increase of 47% and an intracranial flow velocity increase of 31%, a relative intracranial area increase of 12% (diameter +6%) can be calculated. Acetazolamide induced a flow volume increase of 50% with a flow velocity increase of 39%, and thus an area increase of 8% (diameter +4%) can be estimated. This calculation remains inaccurate because the flow volume measurements in the CCA include considerable amounts of ECA flow, which was unchanged with acetazolamide. Since ECA flow is estimated to constitute 20% to 30% of the CCA flow,27 the estimated intracranial area and diameter changes may even be slightly more pronounced. Theoretically, volumetric measurements of the ICA appear to be advantageous and should replace the CCA measurements. Unfortunately, extracranial ICA flow volume measurements are problematic because of physiological turbulent flow in the proximal sections and potential lack of color filling in the more distal segments.

It remains unresolved whether the reported observation is due to a direct effect of the drug on the vessel walls or is strictly pressure dependent. The relative increase of vessel diameter in CCA and MCA appears to be similar.

No major clinical consequences arose from these results. It could be demonstrated that relative intracranial flow velocity changes are within acceptably close limits compared with changes of flow volume. Testing of VMR with TCD is easy to perform and correlates directly with the volumetric changes in the brain-supplying arteries.

One future application of simultaneous assessment of extracranial flow volume and intracranial flow velocity will be in patients with subarachnoid hemorrhage. High flow velocities, as shown by TCD, were interpreted in the past as functional stenoses due to vasospasm28,29 and consecutive hypovolemic flow. Recently it has been hypothesized that some of these flow velocity increases may instead be due to physiological hypervolemic flow or luxury perfusion.30,31

Simultaneous assessment of flow volume and flow velocity according to the protocol of this study may help to solve this diagnostic problem noninvasively.
References


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