Cerebral Vasoreactivity in Unilateral Carotid Artery Disease

A Comparison of Blood Flow Velocity and Regional Cerebral Blood Flow Measurements

Arve Dahl, MD; David Russell, MD, PhD; Rolf Nyberg-Hansen, MD, PhD; Kjell Rootwelt, MD, PhD; Søren Jacob Bakke, MD

Background and Purpose Hemodynamic information obtained by assessing cerebral vasoreactivity is of clinical interest and may have prognostic significance in patients with occlusive carotid disease. The aim of this study was to compare the results of transcranial Doppler and regional cerebral blood flow studies when used to assess cerebral vasoreactivity.

Methods Blood flow velocities in both middle cerebral arteries and regional cerebral blood flow in their respective perfusion territories were compared in 52 patients with severe unilateral carotid stenosis or occlusion. The studies were first performed under basal conditions and repeated after the intravenous administration of 1 g acetazolamide.

Results Asymmetry (normal compared with pathological side) in middle cerebral artery blood velocity increase was significantly greater than the asymmetry in cerebral blood flow increase in the perfusion territories of the arteries. A significant correlation ($r=.63$, $P<.0001$) was found between asymmetry in percent velocity increase and asymmetry in absolute cerebral blood flow increase. The two methods agreed in their assessment of either a normal or a reduced vasoreactivity in 38 subjects and disagreed in 14. In six of the latter patients, who had no evidence of cerebral infarction, the asymmetry in velocity increase was abnormal, whereas asymmetry in flow increase was assessed as normal.

Conclusions We found a good correlation between the asymmetry in regional cerebral blood flow increase in the middle cerebral artery perfusion territories and asymmetry in the velocity increase in the middle cerebral arteries after administration of acetazolamide. These results suggest that transcranial Doppler examination combined with the acetazolamide test may be used in clinical situations to assess cerebral vasoreactivity. (Stroke. 1994;25:621-626.)

Key Words • acetazolamide • carotid artery diseases • cerebral blood flow • cerebral vasoreactivity • ultrasonics

Information regarding intracranial hemodynamics is of clinical interest in patients with cerebrovascular disease, especially those who have a stenosis or occlusion of the internal carotid artery (ICA). This is especially true following recent reports that have documented a significant increased risk of stroke or transient ischemic attacks ipsilateral to a stenotic or occluded ICA if the patients also have an impaired vasoreactivity. Cerebral vasoreactivity may be assessed by measuring regional cerebral blood flow (rCBF) before and after a potent vasodilatory stimulus. Another possibility is transcranial Doppler ultrasonography (TCD). This is a noninvasive and relatively inexpensive method that enables measurement of blood flow velocities in the main intracranial arteries.

Blood flow velocity measurements can theoretically provide information regarding changes in volume flow in a supply artery and in its perfusion territory if both the diameter of the artery and the size of the perfusion territory remain constant after a vasodilatory stimulus. This is due to the fact that volume flow ($Q$) in a vessel is related to blood velocity ($V$) according to the equation $Q=V \cdot \pi R^2$, where $R$ is the vessel radius.

The TCD method is increasingly being used to assess cerebral vasoreactivity by measuring flow velocity change after a vasodilatory stimulus. However, before this method can be accepted for this purpose, it is mandatory to compare findings with those obtained using more established methods. We have previously compared TCD and rCBF findings when assessing cerebral vasoreactivity with acetazolamide in an unselected group of patients with cerebrovascular disease. The aim of the present study was to examine in detail the relation between velocity and rCBF increase after administration of acetazolamide in a selected group of patients with unilateral ICA occlusion or marked stenosis of the ICA and to describe possible limitations of the TCD method when used to assess intracranial vasoreactivity.

Subjects and Methods

Fifty-two patients (48 men and 4 women aged 40 to 77 [mean, 61] years) took part in the study after giving informed consent. rCBF and velocity findings from 7 of these patients were included in a previous publication. Thirty-one had unilateral ICA occlusion and 21 severe unilateral ICA stenosis that caused a diameter reduction of more than 75% (pathological side). Patients were included if they had a contralateral ICA or common carotid stenosis of less than 50% (normal side). Patients with cerebral infarction diagnosed by computed tomography ($n=20$) were included only if the infarct was...
TABLE 1. Clinical Data and Cerebral Computed Tomographic Findings in 52 Patients With Severe Unilateral Carotid Stenosis or Occlusion

<table>
<thead>
<tr>
<th>Presenting signs and symptoms</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck bruit</td>
<td>4</td>
</tr>
<tr>
<td>TIA</td>
<td>29</td>
</tr>
<tr>
<td>RIND</td>
<td>4</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>13</td>
</tr>
<tr>
<td>Major stroke</td>
<td>2</td>
</tr>
<tr>
<td>Clinical findings at time of rCBF and TCD assessments</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>34</td>
</tr>
<tr>
<td>Minor sequela</td>
<td>18</td>
</tr>
<tr>
<td>Major sequela</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral CT findings</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>32</td>
</tr>
<tr>
<td>Small infarction</td>
<td>5</td>
</tr>
<tr>
<td>Medium infarction</td>
<td>7</td>
</tr>
<tr>
<td>Large infarction</td>
<td>8</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; RIND, reversible ischemic neurological deficit; rCBF, regional cerebral blood flow; TCD, transcranial Doppler; and CT, computed tomographic. All infarctions were in the middle cerebral artery perfusion territory. Small infarction indicates cerebral infarction with largest diameter <1 cm; medium infarction, largest diameter 1-3 cm; and large infarction, largest diameter >3 cm.

Localized to the hemisphere ipsilateral to the pathologic neck vessel. The most important clinical data are summarized in Table 1.

Cerebral angiography was performed in 19 of the 21 patients with ICA stenosis and in 18 of the 31 patients with ICA occlusion. Diagnosis in the remaining patients was made using Doppler ultrasound examination of both the precerebral and major intracranial arteries. An ultrasound diagnosis of ICA stenosis or occlusion was made only when both extracranial and transcranial Doppler findings were typical. In two (asymptomatic) patients with a carotid stenosis in whom angiography was not performed, Doppler criteria for stenosis assessment were used.\textsuperscript{11} rCBF was measured using dynamic single-photon emission-computed tomography (SPECT) and xenon-133 inhalation (Tomomatic-64, Medimatic Inc). This instrumentation and method have previously been described in detail.\textsuperscript{12,13} Using high-sensitivity collimators, three slices of brain are studied simultaneously. They are 2 cm thick and routinely positioned 2, 6, and 10 cm above the orbitomeatal plane (OM). The resolution in the plane of each slice is 1.7 cm (full width, half maximum). rCBF was calculated in milliliters per 100 g per minute from slice OM to OM+6 cm in a standardized region of interest in each hemisphere corresponding approximately to the perfusion territories of the middle cerebral arteries (MCAs) (rCBF\textsubscript{ave}). This value was obtained using a software package for automatic calculation of flow values in regions of interest.\textsuperscript{13} rCBF was measured before and 20 minutes after the intravenous administration of 1 g acetazolamide. Because previous studies have not shown a correlation between rCBF increase and basal rCBF values, we considered it most appropriate to use absolute flow increase and not percent increase when assessing the rCBF response.\textsuperscript{10,13}

Blood flow velocities were measured using Doppler ultrasound (TC2-64, Eden Medical Electronics Inc) before the first and after the second rCBF measurement. The instrumentation and the procedure for artery identification have been described elsewhere.\textsuperscript{7,14} Mean velocities were first measured from both MCAs using a hand-held probe after the subjects had rested in the supine position for at least 5 minutes. The mean velocity (V\textsubscript{ave}) was measured as the time mean of the spectral outline. Average values from at least 15 cardiac cycles were calculated. The Doppler sample depth and the temporal acoustic window giving the highest MCA velocities were used for all measurements. The second ultrasound examination was completed within 45 minutes after the acetazolamide administration in all patients. When assessing the velocity increase, we used the percent increase because studies in normal subjects have shown a positive correlation between the absolute velocity increase and basal values (Dahl A, Russell D. 1993. Unpublished data).

The velocity and rCBF values found in this study were compared with normal limits for vasoreactivity obtained from a study of 20 healthy subjects (12 men and 8 women aged 37 to 74 [mean, 52] years) (Table 2). The mean of the two MCA perfusion territories was used for each subject when assessing increases in each hemisphere individually. We assumed that the acetazolamide response is normally symmetrical when assessing side-to-side differences.

All values are expressed as mean (with standard deviation in parentheses) if not stated otherwise. The difference between groups was assessed using Student's t test. Correlations between variables were analyzed using the Pearson correlation model and linear regression analysis. The significance of the correlation coefficients was evaluated using the Fisher z test. All statistical tests were two-tailed, and differences were considered statistically significant if the probability value was less than or equal to 0.05. When defining control limits we used fractiles (percentiles) because these values are more robust than standard deviations when the control group is small and control values do not have a normal distribution.

TABLE 2. Cerebral Blood Flow and Transcranial Doppler Ultrasound Findings in 20 Control Subjects

<table>
<thead>
<tr>
<th>rCBF, mL·100 g\textsuperscript{-1}·min\textsuperscript{-1}</th>
<th>Baseline</th>
<th>Increase</th>
<th>Range</th>
<th>5% Fractile</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF\textsubscript{ave}</td>
<td>52.0 (4.4)</td>
<td>13.7 (4.6)</td>
<td>4.8 to 22</td>
<td>4.9</td>
</tr>
<tr>
<td>V\textsubscript{ave}</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Asymmetry in increase (right to left side)</td>
<td>...</td>
<td>0.03 (1.9)</td>
<td>-3 to 3.5</td>
<td>3.5*</td>
</tr>
</tbody>
</table>

Basal values, increase, and the 5% fractile of the increase in regional cerebral blood flow (rCBF) in the middle cerebral artery perfusion territory (rCBF\textsubscript{ave}) and in middle cerebral artery flow velocity (V\textsubscript{ave}) before and after 1 g acetazolamide. Values are the mean of the right and left side and (SD).

*95% fractile; this value is used as control value when assessing asymmetry in rCBF increase.
The velocity and rCBF findings are shown in Table 3. The results were calculated for the group as a whole and after dividing the patients into two groups depending on whether they had unilateral ICA occlusion or stenosis.

The side-to-side difference (comparing normal side with pathological side) in mean V_max and in rCBF_max under basal conditions was significant for the occlusion group but not for the group of patients with stenosis. The side-to-side asymmetry in percent velocity increase and in rCBF increase (measured in milliliters per 100 g per minute or percent) after acetazolamide administration was highly significant for both patient groups. The side-to-side asymmetry in percent velocity increase (20.2%) was significantly (P < .0001) larger when compared with the asymmetry in percent rCBF increase (10.7%). A similar significant difference was also found for the two subgroups of patients.

In the total group we found a significant positive correlation between basal velocity values in centimeters per second and the absolute velocity increase after administration of acetazolamide on both the normal side (r = .42, P < .02) and on the stenotic/occluded side (r = .57, P < .01). These correlations also reached statistical significance for the occlusion group (ipsilateral to the occlusion, r = .56, P < .01; normal side, r = .43, P < .02) but not the stenotic group (ipsilateral to the stenosis, r = .39, P = .09; contralateral side, r = .43, P = .06).

The increase in rCBF did not correlate significantly with basal rCBF values (normal side, r = .20, P = NS; ipsilateral to the pathological vessel, r = .06, P = NS). When assessing hemispheres ipsilateral to the pathological vessel separately, we found a relatively poor but significant relation between the percent increase in velocity and the absolute increase in rCBF (r = .32, P < .05) (Fig 1). The correlation coefficients had similar values for the two subgroups but did not reach statistical significance, probably due to the relatively small number of subjects in each group.

Normal limits for vasoreactivity regarding velocities and rCBF that were obtained from the control group are shown in Figs 1 and 2 by broken lines. Fig 1 shows that 18 cerebral hemispheres with a reduced vasoreactivity assessed by TCD had a normal rCBF increase. However, when side-to-side asymmetry in rCBF increase was assessed, 13 of these territories were also diagnosed as having a reduced vasoreactivity by this method, and in one asymmetry was just below the limits for abnormal asymmetry (3.0 mL/100 g per minute).
The correlation between the increase in rCBF and velocity on the contralateral (normal) side was not significant \( r = 0.20, P < 0.15 \), as shown in Fig 2. Correlation coefficients were similar when assessing the occlusion and stenotic subgroups. Fig 2 shows that almost all subjects with a normal rCBF increase also had a normal or close to normal percent velocity increase.

A comparison of the side-to-side difference in percent velocity increase and in absolute rCBF increase is shown in Fig 3. The Pearson correlation coefficient was \( r = 0.63 (P < 0.0001) \) for the group as a whole \( (0.54 \ P < 0.05) \) for the stenotic group and \( 0.64 \ P < 0.01 \) for the occlusion group.

When findings were compared with normal limits (shown by broken lines in Fig 3), the two methods agreed in 38 subjects regarding the assessment of either a normal or a reduced vasoreactivity. The methods disagreed in 14 patients who were subsequently studied in more detail. In 6 of these patients, the percent velocity increase was outside normal limits, but the side-to-side difference in rCBF increase was normal. In 2 additional subjects who also had abnormal velocity findings, the rCBF findings were just outside normal limits. One of these 8 subjects had a large posterior watershed cerebral infarction rostral to the slice used to assess rCBF findings. The remaining 7 subjects had normal cerebral computed tomographic scan findings.

In the 8 remaining subjects with disagreeing results, the asymmetry in velocity increase was within normal limits, but the asymmetry in rCBF increase was abnormal. In 6 of these patients, the rCBF values were just outside our normal limits for asymmetry. In 1 patient with a side-to-side rCBF asymmetry of 15 mL/100 g per minute, the percent velocity increase in the normal hemisphere was only 16% and in the pathological hemisphere 6%, which gave an asymmetry within normal limits.

**Discussion**

The main purpose of the present study was to compare TCD and rCBF measurements in the assessment of cerebral vasoreactivity. Both of these methods are more sensitive when used for this purpose if attention is paid to asymmetry rather than changes in absolute values (Dahl A, Russell D. 1993. Unpublished data). Explanations for this observation may include inaccuracy in the measurements and possible effects of acetazolamide on the diameter of the large intracranial arteries or on the magnitude of their perfusion territories. In the present study possible differences in \( \text{PCO}_2 \) levels during the rCBF and TCD studies may also be of importance, and the vasoreactive effect of acetazolamide may have decreased in some subjects between the second rCBF and TCD measurements. The lack of a good correlation suggests that care should be taken when attempting to predict volume flow changes in a cerebral hemisphere on the basis of arterial velocity values alone. This is especially true when assessing values on one side independently from those on the contralateral side. The use of a lower limit for normal vasoreactivity when assessing findings in only one hemisphere also seems to be of limited value. A reduced vasoreactivity may be detected despite flow increase above the lower normal limit when values are compared with those on the contralateral hemisphere.
side. However, the assessment of each hemisphere independently is necessary when vasoreactivity is reduced bilaterally.

The two methods agreed in the assessment of normal vasoreactivity in the hemisphere contralateral to the pathological vessel in most subjects. However, on the pathological side several MCA perfusion territories had a normal rCBF increase despite a low velocity increase. These disagreements are probably due to the same reasons as discussed above. The relatively good correlation found when comparing changes in asymmetry, compared with that found when comparing the findings on each side independently, emphasizes the importance of assessing asymmetry in the acetazolamide test.

In several subjects without cerebral infarction we observed a considerable asymmetry in MCA velocity increase without concomitant asymmetry in rCBF increase. Studies have been performed that indicate individual differences in the size of the perfusion territories of the main cerebral arteries. These variations seem to be greater than previously believed. Therefore, measurements of flow velocities in the MCA may in some subjects only partly reflect rCBF in the assumed MCA perfusion territory that we used in this study. The anterior or posterior cerebral artery may in some subjects contribute to blood supply in the assumed MCA perfusion territory. In some patients with ICA disease perfusion in the MCA territory may also be partly supplied by leptomeningeal collaterals. It is also possible that collaterals outside the circle of Willis may be recruited only after a potent vasodilatory stimulus.

The comparison of rCBF and velocity findings when assessing vasoreactivity has previously been performed in only a few studies.piegres et al. compared TCD and rCBF findings when assessing vasoreactivity with acetazolamide in 21 patients with carotid artery disease. They found a significant correlation between increases in absolute velocity and in rCBF on both the symptomatic and asymptomatic side. Vorstrup et al. found in their study of 11 patients with common carotid artery occlusion a significant positive correlation between velocities and rCBF only when comparing their compiled data. They did not assess asymmetries in the response, and the number of subjects was small. We have previously compared the two methods when assessing an unselected group of patients with cerebral vascular diseases. We found a good relation between asymmetries in responses and a reasonably good agreement between the two methods in their assessments of reduced or normal vasoreactivity.

We found in the present study a larger percentage of patients with a greater asymmetry in velocity than in rCBF increase. There are several possible explanations for this observation. One is the effect of scattered radiation and a partial volume effect that may cause an overestimation of rCBF values in localized small areas of reduced flow. It should be stressed, however, that the percent rCBF increase on the pathological side after administration of acetazolamide was similar to the percent velocity increase on this side. Therefore, the differences in the side asymmetry between the two methods seems to be explained by the lower increase in rCBF on the normal side. This observation suggests that the SPECT method may underestimate high flow values and thereby the calculation of flow increase. It is also important to remember that the use of velocity measurements to predict perfusion changes in the brain assumes no change in vessel diameter or change in the magnitude of the perfusion territory of the artery after the vasodilatory stimulus. A slight change of MCA diameter after the administration of acetazolamide cannot be excluded and may partly explain the discrepancies between the rCBF and the velocity increase.

Cerebral infarction in the MCA perfusion territory may make the comparison between difference in absolute rCBF increase and difference in relative velocity increase inappropriate in several ways. This may depend on the topography of the infarct with respect to the brain slice in which rCBF was measured and which was assumed to be representative of the whole MCA perfusion territory. An infarction located unilaterally in the brain slice under study may cause overestimation of the rCBF difference without affecting the percent velocity difference to the same degree, and a large infarction outside the slice may possibly lead to an underestimation of changes in the whole MCA perfusion territory. The TCD and rCBF methods are supplementary to each other when assessing vasoreactivity. By measuring velocities in the vessels related to the circle of Willis, the TCD method gives information about the pattern of collateral supply to the brain regions thought to be affected by the pathological supply vessel. In contrast, rCBF measurements provide information regarding perfusion in regions of interest.

In conclusion, the present study shows a relatively good correlation between asymmetries in rCBF and MCA velocities when assessing vasoreactivity using the acetazolamide test. The TCD method detected reduced vasoreactivity in most subjects, with a marked asymmetry in rCBF increase. This strongly suggests that the TCD may be used for this purpose in the clinical situation. However, there are some limitations for the TCD method when vasoreactivity is assessed only in the MCA because this may fail to take into account potential collateral blood supply to the MCA perfusion territory in some subjects.

References


Cerebral vasoreactivity in unilateral carotid artery disease. A comparison of blood flow velocity and regional cerebral blood flow measurements.
A Dahl, D Russell, R Nyberg-Hansen, K Rootwelt and S J Bakke

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