A Comparison of Transcranial Doppler and Cerebral Blood Flow Studies to Assess Cerebral Vasoreactivity

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Background and Purpose: The aim of this study was to determine the ability of transcranial Doppler ultrasonography when used to assess cerebral vasoreactivity. The results of this method were compared with regional cerebral blood flow measurements.

Methods: Forty-three patients with symptoms suggesting cerebrovascular disease took part. Transcranial Doppler findings in the middle cerebral arteries were compared with regional cerebral blood flow in the corresponding perfusion territories before and after acetazolamide administration.

Results: There was a significant positive correlation between the absolute increase in cerebral blood flow in milliliters per 100 g per minute and the percent increase in velocity (r=0.63). The right–left, side-to-side difference of the acetazolamide response obtained by the two methods also showed a positive correlation (r=0.80). Control limits obtained from healthy subjects were used for both the blood flow increase (absolute values and asymmetry in absolute values) and the velocity increase (percent increase and asymmetry in percent increase). The two methods then agreed in their evaluation of vasoreactivity in 74 (86%) of the 86 middle cerebral artery perfusion territories; 20 (23%) were assessed by both methods as having a reduced vasodilatory reserve. Eleven hemispheres with a slightly reduced regional cerebral blood flow response to acetazolamide were not detected by transcranial Doppler, whereas all territories with a marked reduction were identified by Doppler. Only one hemisphere with a normal cerebral blood flow increase after acetazolamide administration was assessed by Doppler as having reduced vasoreactivity.

Conclusions: Transcranial Doppler and the acetazolamide test may be used in clinical situations to assess cerebral vasoreactivity. (Stroke 1992;23:15-19)

The assessment of cerebral vasoreactivity provides information regarding the reserve capacity of the cerebral circulation in patients with cerebrovascular disease. Established methods measure the increase in cerebral blood flow (CBF) after a vasodilatory stimulus, with a reduced CBF response indicating hemodynamic impairment. Transcranial Doppler ultrasonography (TCD) permits the noninvasive measurement of blood flow velocities in the basal brain arteries. This method has several practical advantages compared with tracer methods when used to assess cerebral vasoreactivity. It is inexpensive, relatively simple to perform, and, therefore, well suited for routine clinical use. However, the future use of TCD for this purpose first requires a favorable comparison with established techniques.

The aim of this study was to determine the ability of TCD to assess cerebral vasoreactivity. Transcranial Doppler and regional CBF (rCBF) findings with single-photon emission computed tomography (SPECT) were compared before and after a vasodilatory stimulus (1 g acetazolamide i.v.) in patients with symptoms suggesting cerebrovascular disease.

Subjects and Methods

Forty-three patients, 30 males and 13 females 16–74 years of age, took part in the study. The only criterion for entering the study was a history suggest-
ing cerebrovascular disease. Three patients were not included in the study because of difficulties in obtaining a satisfactory Doppler signal. The referral diagnoses are shown in Table 1. Twenty healthy subjects, 10 men and 10 women 24–51 (mean, 37) years of age, served as controls.

The rCBF studies were carried out using xenon-133 inhalation and SPECT (Tomomatic 64, Medomatic Inc., Copenhagen, Denmark).9,9 Measurements were made before and approximately 20 minutes after the intravenous administration of 1 g acetazolamide. Three slices of brain were studied simultaneously using high-sensitivity collimators. The slices were 2 cm thick and were routinely positioned 2, 6, and 10 cm above the orbitomeatal plane (OM). Regional cerebral blood flow was calculated in milliliters per 100 g per minute from slice 2 (OM+6 cm) in a standardized region of interest in each hemisphere corresponding approximately to the perfusion territory of the middle cerebral artery (MCA) at that slice level. This was obtained using a software package for automatic calculation of flow values in regions of interest.9 Correction of rCBF values for PCO2 was not carried out.

The TCD studies were performed using a 2-MHz range-gated pulsed-wave Doppler instrument with on-line spectrum analysis (TC2-64, Eden Medical Electronics Inc., Uberlingen, FRG). Flow velocities in the patients were measured using a hand-held probe from the proximal part of both MCAs before the first and immediately after the second rCBF study. Time mean velocities (the time mean from the spectral outline) were measured from at least 10 cardiac cycles at the sample depth giving the highest values. PCO2 measurements were not performed. In the control group, the MCA velocity increase was measured on both sides using self-retaining probes.

The relationship between cross-sectional average blood flow velocity in centimeters per second (V) and volume flow (Q) in an artery and its perfusion territory is given by the equation Q=V-A, where A is the arterial lumen area. Using tracer methods, rCBF is measured in milliliters per 100 g of brain tissue per minute; thus, volume flow (Q') in the perfusion territory of an artery is Q'=rCBF·T, where T is the weight of the perfusion territory in 100 g.10 Combining these two equations and remembering that Q=1/60 Q', we obtain the following relationship10:

\[ rCBF \times T = V \times A \times 60 \text{ or } V = \frac{1}{60} \times rCBF \times T/A \]

This equation shows that changes in blood velocity (V) will reflect changes in volume flow if the luminal area A and the perfusion territory T remain constant. This equation may also be applied to TCD maximum velocity measurements since there is normally a constant relationship between cross-sectional average and maximum velocities.11 The TCD method, therefore, theoretically may be used to assess vasoreactivity in the perfusion territory of a defined basal cerebral artery.

The rCBF and flow velocity values are given as mean with the standard deviation in parentheses. Correlations between variables were analyzed using the Pearson correlation model and linear regression analyses.12 All statistical tests were two-tailed, and differences were considered statistically significant for \( p \leq 0.05 \). Correlation coefficients were tested using the Fisher z test. We used fractiles (percentiles) when defining control limits because these values are more robust than standard deviations when the control group is small and control values do not have a normal distribution.

**Results**

The increases in CBF and velocities in the control group are shown in Tables 2 and 3, where the lower control limits (5% fractile) are given. When assessing asymmetry, we subtracted findings on the left side from those on the right and used the interval between the 5% and the 95% fractile of these values as the normal range.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral ICA stenosis &gt;50%</td>
<td>11</td>
</tr>
<tr>
<td>Bilateral ICA stenosis &gt;50%</td>
<td>3</td>
</tr>
<tr>
<td>ICA occlusion and contralateral stenosis &lt;50%</td>
<td>9</td>
</tr>
<tr>
<td>ICA occlusion and contralateral ICA stenosis &gt;50%</td>
<td>4</td>
</tr>
<tr>
<td>Bilateral ICA occlusion</td>
<td>2</td>
</tr>
<tr>
<td>Variations (cerebral infarction, TIA, operated ICA stenosis)</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
</tr>
</tbody>
</table>

Diagnoses were based on clinical, ultrasonic, or radiological examination. ICA, internal carotid artery; TIA, transient ischemic attack. %, percent diameter reduction.

<table>
<thead>
<tr>
<th>Basal values (ml/100 g/min)</th>
<th>Increase (ml/100 g/min)</th>
<th>Range (ml/100 g/min)</th>
<th>5% fractile (ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right rCBF&lt;sub&gt;MCA&lt;/sub&gt;</td>
<td>56.0 (7.8)</td>
<td>16.5 (4.7)</td>
<td>7.5–23.5</td>
</tr>
<tr>
<td>Left rCBF&lt;sub&gt;MCA&lt;/sub&gt;</td>
<td>55.2 (7.8)</td>
<td>16.4 (4.3)</td>
<td>7.5–25</td>
</tr>
<tr>
<td>Both sides</td>
<td>55.6 (7.8)</td>
<td>16.5 (4.5)</td>
<td>7.5–25</td>
</tr>
<tr>
<td>Asymmetry in increase (right–left side)</td>
<td>0.14 (1.9)</td>
<td>–3 to 4.5</td>
<td>–3, 4.4*</td>
</tr>
</tbody>
</table>

Basal values, increase, and 5% fractile of increase in regional cerebral blood flow (rCBF) in middle cerebral artery perfusion territory (rCBF<sub>MCA</sub>) after administration of 1 g acetazolamide. Values are mean with standard deviations in parentheses.

*Represents the 95% fractile when subtracting increase on the left from the right side.
TABLE 3. Transcranial Doppler Ultrasound Findings in 20 Controls

<table>
<thead>
<tr>
<th></th>
<th>Basal (V_{MCA}) (cm/sec)</th>
<th>Increase (%)</th>
<th>Range (%)</th>
<th>5% fractile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right (V_{MCA})</td>
<td>63.6 (12.9)</td>
<td>33.4 (11.0)</td>
<td>18.3-53.0</td>
<td>19</td>
</tr>
<tr>
<td>Left (V_{MCA})</td>
<td>63.7 (13.5)</td>
<td>34.6 (11.0)</td>
<td>18.6-53.3</td>
<td>19</td>
</tr>
<tr>
<td>Asymmetry in increase (right-left side)</td>
<td>-1.6 (7.6)</td>
<td>-14.5 to 12.5</td>
<td>-14, 12*</td>
<td></td>
</tr>
</tbody>
</table>

Basal values, the increase, and 5% fractile of increase in time mean middle cerebral artery velocities (\(V_{MCA}\)) after injection of 1 g acetazolamide. Values are mean with standard deviations in parentheses.

*Represents the 95% fractile when subtracting increase on the left from the right side.

In the 43 patients, a comparison of the absolute increase in mean MCA velocity after acetazolamide administration and baseline velocity showed a significant positive correlation on both the right (R) and left (L) sides (R: \(r=0.66, p<0.01\); L: \(r=0.67, p<0.01\)). The absolute increase in rCBF in the perfusion territory of the MCA did not, however, correlate with baseline values (R: \(r=0.21, p\) not significant [NS]; L: \(r=0.05, p=NS\)). The percent increase in MCA blood velocity and the absolute increase in rCBF after acetazolamide administration showed a significant positive correlation (R: \(r=0.67, p<0.01\); L: \(r=0.55, p<0.01\)). Figure 1 shows values for both sides (\(r=0.63, p<0.01\)). When the increases in rCBF and mean MCA velocity for each perfusion territory were compared with control values (Tables 2 and 3), the two methods agreed in 77 (90%) of the 86 MCA territories; 15 (17%) territories were assessed by both methods as having a reduced vasodilatory reserve (Figure 1). When SPECT was used as the reference method, there were three false-positive and six false-negative detections of reduced vasoreactivity with TCD.

There was a significant (\(r=0.80, p<0.01\)) positive correlation between asymmetry in the absolute rCBF increase (right–left side) and the asymmetry in the percent velocity increase after acetazolamide (Figure 2).

The following criteria were used in an attempt to improve the detection of reduced vasoreactivity: rCBF, absolute rCBF increase after acetazolamide or asymmetry of this increase; TCD, percent velocity increase after acetazolamide or asymmetry in percent velocity increase. When these criteria were used, 10 additional hemispheres with reduced vasoreactivity were identified with SPECT and three more with TCD. The two methods agreed in the assessment of 74 (86%) of the 86 MCA perfusion territories, with 20 (23%) territories assessed as having a reduced perfusion reserve.

When using these criteria for defining reduced vasoreactivity, one hemisphere assessed as normal by SPECT showed reduced vasoreactivity by TCD. Velocity increase and asymmetry in increase in this hemisphere were outside control limits, whereas asymmetry in flow increase was just inside control limits.
 Eleven hemispheres with reduced vasoreactivity on rCBF assessment were not detected by the TCD method. Six patients had a normal rCBF increase in each individual hemisphere, but the side-to-side asymmetry in the flow increase (range 4.5–8.0 ml/100 g/min) was just outside our control limits. Three patients with an acceptable asymmetry in hemispheric flow increase had an increase on one side just below control limits (6.0, 6.7, and 7.5 ml/100 g/min). In two patients with a relatively symmetrical but bilaterally low increase in flow, TCD findings indicated that the hemisphere with the greatest increase was normal.

Discussion

The measurement of rCBF with tracer methods is an accepted method for the assessment of cerebral vasoreactivity; the SPECT findings were, therefore, used as a reference in this study. There is, however, no consensus as to how vasoreactivity using SPECT and the acetazolamide test may best be assessed.\textsuperscript{13,14} We found further evidence that suggests that the rCBF increase after acetazolamide administration is not dependent on baseline flow values.\textsuperscript{11,15} The measurement of absolute rCBF increase rather than the percent increase may thus provide a more accurate assessment of vasoreactivity. Unilateral reduced vasoreactivity may be best detected by assessing side-to-side asymmetry in the acetazolamide response, especially in those patients whose absolute values are within normal limits on both sides. Furthermore, by comparing the degree of asymmetry in the acetazolamide response, random changes in absolute flow values become less important. Changes in Pco\textsubscript{2} caused by hyperventilation during one of the studies as well as Pco\textsubscript{2} differences between patients and control subjects will probably also be less important when asymmetry is assessed. However, to detect a bilateral reduction in vasoreactivity, it is necessary to consider the absolute increase in flow on each side separately.

The use of absolute velocity changes (in centimeters per second) for vasoreactivity assessment is less relevant for TCD. In this study, we assessed the percentage of velocity increase because we previously found a positive correlation between basal velocity and velocity increase after acetazolamide administration.\textsuperscript{15} The normal range of MCA velocities is large and probably reflects a substantial variation in vessel diameter, and, as shown in the equation in “Methods,” the absolute change of flow velocity following a given change in volume flow will depend on vessel diameter. The positive correlation between basal velocity and velocity increase that we found in this study supports our decision.

A significant positive correlation was observed between the percent increase in mean MCA velocity and the absolute increase in rCBF after acetazolamide administration. More MCA perfusion territories with moderately reduced vasoreactivity were found with rCBF and TCD when side-to-side differences in the acetazolamide response, in addition to lower control limits, were considered. It is not surprising that the classification of patients according to TCD and rCBF findings showed some discrepancies, especially when values were close to our control limits. We would like to stress, however, that there was a relatively good correlation between TCD and rCBF findings. When using asymmetry in increase and a lower limit, there was only one false-positive finding with TCD when SPECT was used as the reference method, but 11 hemispheres with moderate changes were not detected with TCD. Piepgras et al\textsuperscript{16} compared TCD and SPECT findings when vasoreactivity was assessed with acetazolamide in 21 patients with carotid occlusive diseases. They found one false-positive and six false-negative detections of reduced vasoreactivity with TCD when SPECT was used as the reference method. Their results and ours suggest that the disagreement may partly be due to a slightly lower sensitivity of the TCD method in detecting reduced vasoreactivity.

There are other possible explanations for those cases in our study in which the two methods disagreed in the assessment of vasoreactivity. First, according to the equation in “Methods,” velocity changes will reflect changes in rCBF only as long as vessel diameter and perfusion territory remain constant or change in parallel. During a vasodilatory stimulation, the equilibrium between adjacent brain arteries and their perfusion territories may change. In normal subjects, a redistribution of blood flow within one cerebral hemisphere may occur.\textsuperscript{17} Intracranial hemodynamics may change in patients with cerebrovascular disease so that the anterior and posterior cerebral arteries contribute to the blood supply of brain areas that are normally perfused by the MCA or vice versa. The measurement of velocity increases in the MCA alone after administration of acetazolamide may therefore lead to an underestimation or overestimation of this potential collateral supply. Recordings from all the basal intracranial arteries may be of help in answering this question.

We measured Pco\textsubscript{2} during the rCBF but not during the TCD studies. A relative hyperventilation during the rCBF measurements may therefore have led to disagreement in at least some hemispheres in which there was a decreased rCBF response after acetazolamide administration but normal TCD findings.

Furthermore, rCBF was measured in a standardized region of interest at the level OM+6 cm corresponding approximately to the perfusion territory of the MCA at that level. Perfusion changes in this area may not reflect flow changes in the entire MCA perfusion territory.

In conclusion, the present study strongly suggests that the TCD method may be used to assess cerebral vasoreactivity when combined with the acetazolamide test. We stress that all patients with a marked reduction in vasoreactivity detected by rCBF studies were also correctly identified by TCD. This is important because the measurement of vasoreactivity in the clinical situation is most rele-
vant for patients who have a marked reduction. It is now possible to use TCD for extensive studies where the aim is to evaluate the clinical significance of a reduced perfusion reserve.

References

**KEY WORDS** • acetazolamide • blood flow velocity • cerebral blood flow • tomography, emission computed
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