Cerebrovascular Reserve in Patients With Carotid Occlusive Disease Assessed by Stable Xenon-Enhanced CT Cerebral Blood Flow and Transcranial Doppler

Ronda R. Pindzola, PhD; Jeffrey R. Balzer, PhD; Edwin M. Nemoto, PhD; Steven Goldstein, MD; Howard Yonas, MD

Background and Purpose—Cerebrovascular reserve (CVR) by both transcranial Doppler ultrasonography (TCD) and quantitative cerebral blood flow (CBF) can identify subgroups of patients at increased risk for stroke. A direct comparison of CVR measurements obtained with both technologies in patients with cerebrovascular occlusive disease is lacking.

Methods—CVRs before and after acetazolamide administration (1 g IV) were measured by TCD insonation of the middle cerebral artery (MCA) and CBF obtained with stable xenon CT (Xe/CT) in 38 patients with carotid occlusive disease. Sensitivity/specificity calculations were based on 2 Xe/CT MCA values: an average over 4 levels and the level with the lowest percent change in CBF. Compromised CVR was defined as no reactivity or a decrease in reactivity.

Results—Using the analysis of the systolic TCD, we found that velocity changes compared with the average Xe/CT MCA CVR showed a sensitivity of 33%, specificity of 90.6%, positive predictive value of 54.5%, and negative predictive value of 80%. The sensitivity of TCD compared with the lowest Xe/CT CBF CVR was 35.5%, specificity and positive predictive values were 100%, and negative predictive value was 66.7%. The index of validity was between 72% and 76%.

Conclusions—TCD is much less sensitive than Xe/CT CBF in identifying patients with compromised CVR. This may be a result of the inability of TCD to identify patients with compromised reserves when their MCA blood flow comes from collateral sources. The lack of correlation between TCD and Xe/CT CBF for identifying patients with compromised CVR should be considered when stroke risk assessments are made by TCD. (Stroke. 2001;32:1811-1817.)

Key Words: acetazolamide ■ carotid artery occlusion ■ cerebral blood flow ■ ultrasonography, Doppler, transcranial ■ vasoreactivity

S
tenosis or occlusion of the internal carotid artery is associated with a high rate of a subsequent stroke: ~24% for the first 18 months for high-grade symptomatic stenosis, 6% per year for occlusion, and 33% to 40% per year for those with stenosis on one side and occlusion on the other.1-3 In a retrospective study, Webster and colleagues4 reported a stroke rate of 28.9% in 2 years (21% the first year, unpublished results) in symptomatic patients with carotid stenosis or occlusion and a negative cerebrovascular reserve (CVR) of ~5% or lower determined by xenon-enhanced CT (Xe/CT) cerebral blood flow (CBF) in response to a vasodilatory challenge with acetazolamide. PET has also been used to evaluate patients at risk for stroke. High oxygen extraction fraction, indicating a lack of autoregulation, correlated with a stroke rate of 28% over 31.5 months.5 Yamauchi et al6 found that the area of lowest perfusion and highest oxygen extraction fraction has the highest risk for infarction. Several studies indicate that transcranial Doppler ultrasonography (TCD) can identify patients at increased risk for stroke (Table 1). Vernieri et al7 showed that impaired CVR as revealed by TCD with breath holding is predictive of cerebral ischemic events in patients with carotid artery occlusion. Kleiser and Widder8 reported that with TCD and a CO2 challenge, patients with exhausted CVR ipsilateral to a stenotic or an occluded carotid artery had a significantly elevated rate of stroke similar to but less than that found with Xe/CT by Webster et al.4 Silvestrini et al9 reported that the risk of stroke or transient ischemic events in patients with asymptomatic carotid artery stenosis is related to impaired cerebrovascular reactivity to hypercapnia measured by TCD. Gur et al10 demonstrated that TCD was useful for evaluating CVRs and identifying patients with a higher risk of transient ischemic attacks (TIAs) or ischemia. Chimowitz et al11 found an association between compromised reserves and TIA and...
TABLE 1. Comparison of Annual Risk for Stroke Found With Different Technologies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method</th>
<th>Sample Size, n</th>
<th>Symptomatic</th>
<th>Degree of Stenosis</th>
<th>Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubb et al†‡</td>
<td>1998</td>
<td>PET/OEF</td>
<td>81</td>
<td>Yes</td>
<td>ICA occlusion</td>
<td>28.0*</td>
</tr>
<tr>
<td>Gur et al10</td>
<td>1999</td>
<td>TCD/AZ</td>
<td>44</td>
<td>No</td>
<td>&gt;70% ICA stenosis</td>
<td>10.5</td>
</tr>
<tr>
<td>Kleiser and Widder§</td>
<td>1992</td>
<td>TCD/CO₂</td>
<td>85</td>
<td>Both</td>
<td>ICA occlusion</td>
<td>17.0</td>
</tr>
<tr>
<td>Silvestrini et al‡‡</td>
<td>2000</td>
<td>TCD/BRH</td>
<td>94</td>
<td>No</td>
<td>&gt;70% ICA stenosis</td>
<td>13.9</td>
</tr>
<tr>
<td>Vernieri et al§§</td>
<td>1999</td>
<td>TCD/BRH</td>
<td>42</td>
<td>Yes</td>
<td>ICA occlusion</td>
<td>11.9</td>
</tr>
<tr>
<td>Webster et al¶¶</td>
<td>1995</td>
<td>Xe/CT CBF/AZ</td>
<td>95</td>
<td>Yes</td>
<td>&gt;70% ICA stenosis/occlusion</td>
<td>28.9*</td>
</tr>
<tr>
<td>Yamauchi et al¶¶</td>
<td>1996</td>
<td>PET/OEF</td>
<td>40</td>
<td>Yes</td>
<td>&gt;70% ICA stenosis/occlusion</td>
<td>57</td>
</tr>
</tbody>
</table>

OEF indicates oxygen extraction fraction; ICA, internal carotid artery; AZ, acetazolamide; and BRH, breath holding.
*Based on follow-up period, not annual rate.
†Data is based on 31.5 mo.
‡Annual ipsilateral ischemic event rate.
§Annual ipsilateral ischemic event rate for symptomatic patients.
¶Data based on 19.6 months and include 2 contralateral strokes that also occurred in territories with compromised reserves; there was a 21% annual risk for stroke (unpublished).
††Small number of subjects (4 of 7 patients with high OEF had a stroke).

suggested that TCD with acetazolamide may allow identification of patients who are at higher risk for stroke.

Several studies have compared changes of TCD velocity measurements with changes in CBF obtained with single-photon emission CT and xenon-133 (133Xe) inhalation. Dahlin et al,12 Piepras et al,13 and Bishop et al14 found a correlation between TCD and 133Xe CBF measurements. Brauer et al15 compared CVR measured by TCD and by Xe/CT CBF in 32 patients who had various clinical indications, including subarachnoid hemorrhage, head trauma, and liver failure. The authors speculated that their finding of a lack of correlation between TCD and CBF CVR could be a result of collateral flow, which is included in the Xe/CT CBF results but not assessed by TCD when insonating the middle cerebral artery (MCA). They also stated that the relationship of velocity changes may depend on the underlying diagnosis.

This study examined the relationship between TCD assessment of CVR compared with quantitative Xe/CT CBF. If TCD provides sensitivity, specificity, positive predictive value, negative predictive value, and index of validity equal to that of Xe/CT CBF–measured CVR, this widely available and less expensive technology could be used routinely to identify patients at increased risk for stroke. If the results are different, an understanding of this difference should help to guide the clinical role of each technology in studies of CVR.

Subjects and Methods
Over 4 years, 38 patients, 12 women (32%) and 26 men (68%) 53 to 88 years of age (mean, 71 years), were entered in the study. Informed consent was obtained by the principal investigator from all patients entered. The study was approved by the University of Pittsburgh Institutional Review Board. The patients were diagnosed with internal carotid artery stenosis (≥70%, 3 patients) or occlusion (34 patients) determined by angiography or CT angiography. One additional patient had occlusion of the left common carotid artery. Of these patients, 20 (53%) had ≥70% stenosis or complete occlusion contralaterally. Twelve additional patients (32%) had between 50% and 70% stenosis contralaterally. All but 4 patients were diagnosed with a TIA or nondisabling stroke. TCD insonation of the MCA could not be performed in 5 patients because of failure to obtain an adequate bone window. In 3 patients, velocities could be obtained from only 1 side. Four patients had Xe/CT CBF and TCD studies both before and after contralateral carotid endarterectomy, and 2 patients had a Xe/CT CBF and TCD study only after contralateral carotid endarterectomy. Seventy-six percent of the patients had hypertensive disease, 16% had diabetes, and 61% had smoked or were still smoking.

Blood Flow Measurements

Xe/CT Method
During Xe/CT CBF studies, patients inhaled through a face mask a 28% concentration of medical-grade Xe gas in 40% oxygen (XeScan stable xenon in oxygen USP, Praxair Pharmaceutical Gases, Praxair, Inc) for 4.3 minutes, during which time rapid sequential CT scanning (General Electric) of 3 or 4 preselected levels (slices) of the brain was performed. Studies covered either 55 or 65 mm of brain tissue. CVRs were assessed by inducing a vasodilatory challenge with 1 g acetazolamide (diamox), a carbonic anhydrase inhibitor16 injected intravenously after the baseline Xe/CT CBF study. The Xe/CT CBF study was repeated 15 to 20 minutes later. The cerebral tissue acidosis caused by acetazolamide dramatically increases the blood flow to uncompromised territories of the brain by 30% to 40%, whereas territories that are hemodynamically compromised are unchanged presumably because vessels are already maximally dilated. Those that are most severely compromised demonstrate a "steal" phenomenon (ie, a decrease in CBF).17

The signal-to-noise ratio was ~8:1 when Xe/CT CBF studies were performed. With this amount of signal, reliable, quantitative CBF values have been obtained when regions of interest (ROIs) include >120 measurements because at that point the measurement error is <12%.18 The 2 studies were done only 15 to 20 minutes apart, and the same planes were located and scanned. There were no misregistration effects from the use of separate baseline and acetazolamide studies unless the patient moved during image acquisition. Misregistration could be detected from the confidence images, and ROIs with poor confidence were deleted from the analysis.

TCD Method
The TCD ultrasonography was performed to measure blood velocity in the MCA before the standard Xe/CT scan and within 25 to 55 minutes of administration of acetazolamide. The TCD method used a transtemporal approach permitting insonation of the M1 segment of the MCA. The TCD system (Medasonics) used was a pulsed Doppler that operates at 2 MHz (EME TC 2-64). Cranial depths of 35 to 60 mm were sampled at 5-mm steps. The power output of the transducer was set at 100 mV/cm², allowing for optimal insonation via the transtemporal window. Systolic MCA velocities were used for this analysis.

A normal response in mean TCD values after acetazolamide is an increase of 29 cm/s for women and 21 cm/s for men,19 which is equivalent to a 49.3% and a 38.9% change, respectively. This
amount of augmentation found with TCD is similar to the amount found with Xe/CT CBF methods in normal subjects. Therefore, the percent change (reserve status) was calculated the same way for the 2 technologies.

Data Analysis
The percent change between baseline and acetazolamide studies in these patients was calculated on the basis of systolic TCD values and the Xe/CT CBF values of the MCA. This constituted the CVR measurement. The formula for calculating percent change for both types of studies was as follows: postacetazolamide (velocity, cm/s) divided by preacetazolamide (velocity, cm/s) minus 1 times 100, and postacetazolamide (CBF, mL · 100 g⁻¹ · min⁻¹) divided by preacetazolamide (CBF, mL · 100 g⁻¹ · min⁻¹) minus 1 times 100.

For the Xe/CT CBF study, cortical flow values were obtained by placement of a series of 6 contiguous 2-cm ROIs (more than ~300 pixels each) within the MCA territory²⁰ for each of 4 levels (3 levels in 4 patients). Level 1 included the basal ganglia and paralleled the frontal skull base near the orbitomeatal line. Each of the 3 additional levels were cut 1.5 cm above the lowest level. The mean MCA CBF for each level was calculated by summing the values of the ROIs and dividing by the number of ROIs for each level. Results also were analyzed by averaging the percent change for all ROIs of all levels of the MCA territory. For each Xe/CT study, the CT scan was analyzed separately for alterations consistent with stroke, and individual ROIs showing infarction were deleted from the analysis. If an MCA territory >3 ROIs (ie, >50% infarction) with densities indicating infarction, the whole territory for that level was eliminated from the analysis.

Table 2: Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Index of Validity for Diagnostic Accuracy of TCD in Predicting Patients With Compromised Reserves With Xe/CT CBF Methods

<table>
<thead>
<tr>
<th>Threshold at 0%</th>
<th>Threshold at −5 to 5 for Marginal Group and &gt;5 for Positive Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest MCA (1 level), %</td>
</tr>
<tr>
<td></td>
<td>Both</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>35.5</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
</tr>
<tr>
<td>PPV</td>
<td>100</td>
</tr>
<tr>
<td>NPV</td>
<td>66.7</td>
</tr>
<tr>
<td>Index of validity</td>
<td>72</td>
</tr>
</tbody>
</table>

Lowest MCA indicates that the calculations were based on the MCA territory that had the lowest Xe/CT CBF value; Average MCA, calculations were based on the average of all 4 levels for the MCA territory for the Xe/CT CBF data; PPV, positive predictive value; NPV, negative predictive value; and both, all of the data—ipsilateral (ipsil) and contralateral (contri) hemispheres combined.

Results
The sensitivity and specificity of the TCD velocity changes compared with the Xe/CT CBF CVR data were calculated different ways: (1) the MCA territory with the lowest percent change for the Xe/CT CBF or the average over 4 levels of the MCA territory for the Xe/CT CBF, and (2) all data, including both sides, only the occluded side, and only the contralateral side (Table 2). The greatest sensitivity was found for the ipsilateral data with the lowest MCA analysis (43%). The lowest sensitivity was found with the analysis of the lowest MCA values for the contralateral side (20%). The sensitivity for all data (both sides) was 33% for the average MCA calculation and 35.5% for the lowest MCA calculation. Although the sensitivity of CVR for TCD compared with the Xe/CT CBF method was marginal, the specificities were relatively high, indicating that there was agreement between the 2 methods for the true negatives (patients correctly identified as negative for compromised reserves, ie, positive reserves). The index of validity was 71% for the lowest MCA analyses and 76% for the average MCA analyses.

A subanalysis of the marginal reserves (between −5 and 5) and the positive reserves (>5) showed that the sensitivity was low for TCD compared with Xe/CT CBF (22% for the lowest MCA calculation of Xe/CT CBF values and 16.6% for average values; Table 2).

For the Cohen’s 𝜅 analysis, the patients were separated into the following 2 groups on the basis of their percent change in Xe/CT CBF values: positive reserves (>0% and compromised reserves <0%). The Cohen’s 𝜅 analysis showed comparatively low agreement between the TCD and Xe/CT CBF CVR measurements (κ=0.38 for the lowest MCA level, Table 3; 0.27 for the averaged MCA levels, Table 3).

Figure 1 shows the Xe/CT CBF results for a patient who had right symptomatic internal carotid artery occlusion and 50% contralateral carotid stenosis. Two Xe/CT CBF studies (baseline and acetazolamide) are included, each showing 4 different levels through the brain. It was determined that this patient’s blood flow did not augment in the right MCA of levels 2, 3, and 4 after acetazolamide in the Xe/CT CBF study but did augment in the TCD study.

A graph of the CVR (Figures 2 and 3) shows that most patients who had positive reserves by Xe/CT CBF also had positive reserves by TCD. More important, it also shows that there were patients who had negative reserves by the Xe/CT CBF method and positive reserves by TCD (false negatives). There were 12 data points in this category for the averaged data (Figure 2) and 20 data points for the lowest MCA territory data (Figure 3).
A Spearman correlation test revealed that there is a moderate correlation between CVR measured by the 2 tests. The Spearman correlation estimate was 0.35 ($P=0.003$) for the lowest category and 0.32 ($P=0.007$) for the average Xe/CT CBF category when the hypothesis that TCD and Xe/CT CBF tests were independent was tested.

**Discussion**

We have compared CVR assessed with both TCD and quantitative CBF to understand how differences between these technologies may affect the identification of patients with compromised reserves who may be at increased risk for stroke. The primary result of this study is that changes in velocity measured within the initial portion of the MCA do not reliably predict the changes in tissue perfusion that accompany a vasodilatory stress induced by intravenous acetazolamide. The negative predictive value of TCD is lower if the single level of the brain with the most severe compromise of CVR rather than the average flow change in all levels is compared with MCA velocity changes. A lack of sensitivity to a negative CBF response can be explained in part by the observation that this type of flow response is statistically associated with the absence of blood supply via the circle of Willis and instead a dependence on pial and retrograde ophthalmic collaterals. Thus, it does not seem physiologically reasonable to expect that the rate of blood movement within the trunk MCA should be able to reflect changes in CBF when the MCA is not the primary route of blood supply to the MCA territory.

**TABLE 3. Agreement of TCD and Xe/CT CBF Assessed by Cohen’s $\kappa$**

<table>
<thead>
<tr>
<th>TCD CVR</th>
<th>≤0</th>
<th>&gt;0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest MCA Territory for Xe/CT CBF (1 level)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>&gt;0</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>40</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TCD CVR</th>
<th>≤0</th>
<th>&gt;0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averaged MCA Territory (All 4 Levels Averaged Together)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>&gt;0</td>
<td>12</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>53</td>
<td>71</td>
</tr>
</tbody>
</table>

*K*=0.38; 95% CI, 0.20–0.56; exact 2-sided $P=0.000$.

†*k*=0.27; 95% CI, 0.02–0.53; exact 2-sided $P=0.025$.

**Figure 1.** Xe/CT CBF results for a patient who had right symptomatic internal carotid artery occlusion and 50% contralateral carotid stenosis. Included are 2 Xe/CT CBF studies (baseline and acetazolamide), each showing 4 different levels through the brain. This patient had compromised reserves on the occluded side of $-8.7\%$ change in level 3. The percent change for level 4 was $-8.4\%$ change and for level 2 was $-1.2\%$ change. The right MCA of level 1 was not compromised. TCD results for this patient indicated a $16.7\%$ change in the right MCA. It was determined that this patient’s blood flow did not augment in the right MCA of levels 2, 3, and 4 after acetazolamide in the Xe/CT CBF study (arrows) but did augment in the TCD study. Color bar provides the quantitative blood flow reference (from 0 to 160 mL/100 g tissue per minute).
The use of a tomographic high-resolution CBF study appears physiologically sound because it provides the ability to assess flow changes not only within an entire vascular territory but also within the cortical or subcortical regions on each of the levels of study. From the perspective of predicting subsequent ischemic events, only the most severely compromised level that was consistently a level above the basal ganglia was predictive of individuals at increased stroke risk.\textsuperscript{4,17} Quantitative CBF studies have also shown that the most dramatic flow changes in patients with chronic occlusive vascular disease are within the periventricular white matter that is the region most prone to infarction in low-flow conditions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Percent change of the preacetazolamide and postacetazolamide values for Xe/CT CBF vs TCD velocity measurements for 71 hemispheres of patients with occlusive carotid artery disease. Xe/CT CBF values were calculated on the average of the MCA ROIs across all 4 levels.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Percent change of the preacetazolamide and postacetazolamide values for Xe/CT vs TCD. Xe/CT CBF values used in this analysis were based on the territory of lowest percent change.}
\end{figure}
states and is clinically associated with symptoms of ischemic claudication. This higher resolution to especially low flow within subcortical structures may help explain why Brauer et al, who used stable Xe/CT CBF, may have had conclusions similar to those of our study, which were different from those of Dahl et al and Piepgras et al, who used either quantitative CBF or regional CBF that has little to no perception of flow changes within subcortical structures.

Although the measurement of oxygen extraction with PET is a useful tool for identification of patients at increased ischemic risk, studies that involve a physiological stress and the repeated measurement of a single flow-related variable also have this capacity. By changing only 1 variable, a flow-related stress test examines only the ability of the circulation to respond to a well-understood and predictable physiological stress. Whether a rise in local tissue hydrogen ions is induced by an increase in the level of PCO₂ or by intravenous injection of acetazolamide, the result is the same. This type of challenge can only induce dilatation, and if no elevation in CBF is observed, one can only assume that the vascular bed in question is already maximally vasodilated. A maximal CBV is integral to the state of severe hemodynamic compromise reported by Grubb et al and is associated with a rise in oxygen extraction. Nariai et al have reported a correlation between elevated oxygen extraction fraction and decreased Xe/CT CBF in patients with carotid occlusion. It has been our preference to use acetazolamide because it is well tolerated at a dose of about 17 mg/kg (about 1 g for an adult) and it produces a reliable significant physiological challenge. Although a CO₂ challenge is theoretically simpler to induce by breath holding or the inhalation of 3% to 5% CO₂, the resulting PCO₂ change is very unpredictable and is often associated with anxiety and hypertension, thus confounding the interpretation of CBF data.

Consideration must be given to the potential design problems of the study. The time of the TCD study was between 40 and 70 minutes after acetazolamide administration, whereas the second Xe/CT CBF study was done 20 minutes afterward. Considering that after 90 minutes half of the acetazolamide is still active, we are within the limits for observing an increase in vasoreactivity. The second potential problem is that we did not measure CO₂ during the time the TCD studies were performed. Although CO₂ probably decreased during this study because of an increased respiratory rate, the acidification of cerebrospinal fluid by acetazolamide persists despite the counteracting effect of the relative hypocapnia. Consideration must be given to the potential problems of using TCD, such as the inability to obtain TCD values in 5% to 15% of patients and the operator dependence of the TCD measurements. A potential problem of Xe/CT CBF is the belief that Xe increases blood flow, but this is not significant until 5 minutes of inhalation, which is longer than the 4.3 minutes used in this study. Modeling has provided further support by confirming a minimal effect of Xe inhalation on the calculated versus “real” CBF values using the currently employed method for calculated CBF. Xe also has an effect on the sensorium, but with the reduction in Xe from 33% to 28%, there has been a significant reduction in even minimal symptoms.

TCD velocity changes by acetazolamide have been shown to be insensitive to areas of negative reactivity compared with quantitative CBF and therefore may not be the optimum method for assessing cerebral hemodynamic compromise in patients with carotid occlusive disease. Further studies are needed to determine whether CVRs measured by TCD or quantitative or qualitative CBF or oxygen extraction fraction measured by PET are comparable in predicting risk for stroke.

Acknowledgments
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References


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