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 n carotid artery occlusion n cerebral blood flow n ultrasonography, Doppler, transcranial n vasoreactivity

Several studies indicate that transcranial Doppler ultrasonography (TCD) can identify patients at increased risk for stroke (Table 1). Vernieri et al1 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 Widder4 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...
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 ($^{133}$Xe) inhalation. Dahl et al,12 Piepgras et al,13 and Bishop et al14 found a correlation between TCD and $^{133}$Xe CBF measurements. Brauer et al15 compared CVR measured by TCD and by $\text{Xe}/\text{CT}$ 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 $\text{Xe}/\text{CT}$ 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 $\text{Xe}/\text{CT}$ CBF. If TCD provides sensitivity, specificity, positive predictive value, negative predictive value, and index of validity equal to that of $\text{Xe}/\text{CT}$ 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 ($\geq 70\%$, 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 $\geq 70\%$ 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 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) was used with 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/cm, allowing for optimal insonation via the transtemporal window. Systolic MCA velocities were used for this analysis.

**TCD Method**

The TCD ultrasonography was performed to measure blood velocity in the MCA before the standard $\text{Xe}/\text{CT}$ 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) was used with 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/cm, 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.
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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>Both</td>
<td>Ipsil</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 (contral) hemispheres combined.

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 territory 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.

Sensitivity, specificity, positive predictive value, negative predictive value, and an index of validity were calculated for comparison of the TCD and the Xe/CT CBF CVRs. The formula for the index of validity was true positives plus true negatives divided by the total number of cases.21 Cohen’s κ statistic was used as a chance-corrected measure of agreement between the 2 methods. For the κ analysis, the results of each patient’s blood flow were classified into 1 of 2 groups (≥0, <0). To take into account the continuous nature of the data, Spearman correlations were also calculated.

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 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 κ**

<table>
<thead>
<tr>
<th>TCD CVR</th>
<th>Xe/CT CVR ≤0</th>
<th>Xe/CT CVR &gt;0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<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>

*κ = 0.38; 95% CI, 0.20–0.56; exact 2-sided P = 0.000.
†κ = 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 an 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. 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 states.

Figure 2. 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.

Figure 3. 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.
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 qualitative 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 ischemic risk, studies that involve a physiological stress and 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


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.


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