Cerebral Blood Flow Asymmetry in the Detection of Extracranial Cerebrovascular Disease

Wendy M. Robertson, PA-C, K.M.A. Welch, MD, Barbara C. Tilley, PhD, and James R. Ewing, MS

Regional cerebral blood flow was measured by the 133Xe inhalation technique in patients with unilateral carotid occlusion, unilateral carotid occlusion and contralateral carotid stenosis, bilateral carotid occlusion, or normal arteriograms. After adjusting for age, sex, and history of stroke, hemispheric blood flow asymmetry was shown to be a predictor of unilateral carotid occlusion with a sensitivity of 80.6% and a specificity of 80.5%. Asymmetry of regional cerebral blood flow is useful in the assessment of patients with extracranial cerebrovascular disease. (Stroke 1988;19:813–819)

There is a need for functional measures to identify asymptomatic and transiently symptomatic patients with impending cerebral infarction. Accordingly, an inexpensive, atraumatic, reliable, and readily available technique for patients at risk for cerebrovascular disease would be of great value. One such technique is the measurement of regional cerebral blood flow (rCBF) by 133Xe inhalation. Measurement of rCBF has proved of little utility in the evaluation of stroke patients, but assessment of rCBF asymmetries may be of greater value, as in our study of patients with carotid occlusion. Our study was undertaken to determine the efficacy of the 133Xe inhalation rCBF technique in the detection and evaluation of extracranial carotid occlusive disease.

Subjects and Methods

We studied 104 patients (74 men, 30 women) who had cerebral arteriography and rCBF measurement for the evaluation of suspected cerebrovascular disease (Table 1). In most patients arteriography was performed with four-vessel selective injections via femoral catheterization. A few patients had aortic arch studies or bilateral carotid artery injections. Patients were grouped into those with unilateral carotid occlusion (UCO), unilateral carotid occlusion and contralateral carotid stenosis of >50% (UCO + CS), bilateral carotid artery occlusion (BCO), and normal arteriograms or carotid artery stenosis of <50% (NA). Clinical presentation included stroke, transient ischemic attacks (TIAs), other nonfocal symptoms, or no symptoms (Table 2). Of the 62 patients with a history of stroke, 23 had mild deficits (subtle findings on neurologic examination), 36 had moderate deficits (clear neurologic signs and limitation of function), and three had severe deficits (preventing ambulation). The overall median time since the last ictus was 2 months (range 3 days–108 months).

We also studied young (20–30 years old) and aged (>60 years old) controls (19 men, 19 women) who had rCBF measured but no arteriography (Table 1). Controls were hospital employees, their relatives, or retirees from a local retirement activity center. Controls had no history or physical examination findings to suggest neurologic disease.

rCBF was measured by the 133Xe inhalation technique. The subject reclined with eyes open in a quiet, dimly lit room. Sixteen Nal (Ti) scintillation detectors with 1 x 3/4 in. cylindrical collimation were placed in a hemispheric array of contralaterally symmetric pairs against the subject’s head (Figure 1). After a 1-minute inhalation of a mixture of air and trace amounts of radioactive 133Xe, the cerebral washout curves of the indicator were followed for approximately 15 minutes. Ten-minute portions of the washout curves were used as response functions, with the end-tidal trace amount of radioisotope in expired air as the input function. The flow parameters of a two-compartment cerebral clearance curve were estimated by a maximum-
TABLE 1.  Patient Population

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>Range</th>
<th>Male</th>
<th>%</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral carotid occlusion</td>
<td>36</td>
<td>61.2</td>
<td>34-81</td>
<td>72.2</td>
<td>80.6</td>
<td></td>
</tr>
<tr>
<td>Unilateral carotid occlusion and contralateral carotid stenosis</td>
<td>31</td>
<td>62.7</td>
<td>31-75</td>
<td>80.7</td>
<td>90.3</td>
<td></td>
</tr>
<tr>
<td>Bilateral carotid occlusion</td>
<td>12</td>
<td>57.2</td>
<td>47-71</td>
<td>58.3</td>
<td>91.7</td>
<td></td>
</tr>
<tr>
<td>Normal arteriograms</td>
<td>25</td>
<td>57.0</td>
<td>35-83</td>
<td>64.0</td>
<td>76.0</td>
<td></td>
</tr>
<tr>
<td>Aged controls</td>
<td>16</td>
<td>66.1</td>
<td>60-77</td>
<td>43.8</td>
<td>68.8</td>
<td></td>
</tr>
<tr>
<td>Young controls</td>
<td>22</td>
<td>26.7</td>
<td>20-30</td>
<td>54.5</td>
<td>95.4</td>
<td></td>
</tr>
</tbody>
</table>

likelihood procedure. Estimates produced by this procedure are within a few percent of the more commonly used unweighted least-squares procedure. Flow values obtained in young normal subjects with this model have been found to correspond to values obtained with the $^{133}$Xe intracarotid injection technique. The initial slope index (ISI), related primarily to the faster clearance rate of indicator from gray matter, corrected for recirculation, was the measure of blood flow used in this study.

Logarithmic transformations of ISI stabilized the variance of the raw data. Student's two-sample $t$ tests were used to compare mean ISI for each patient group and the aged controls. Probe pair differences (nonoccluded minus occluded ISI for UCO and UCO+CS; left minus right ISI for NA and aged controls) were computed as a measure of asymmetry. Paired $t$ tests were used for analysis of asymmetries within groups. All statistical tests were adjusted for multiple comparisons using the method of Bonferroni with $p<0.0125$ considered significant. Fisher's exact $\chi^2$ test was used to determine sex distribution between each patient group and the aged controls.

As another way of characterizing asymmetry, an asymmetry score was developed. Probe pair differences were calculated. A positive difference obtained a score of 1, a negative difference of -1, and no difference of 0. Asymmetry scores for the individual probe pairs in a subject were summed, and the absolute value of this total asymmetry score was used to determine whether one hemisphere more frequently had a lower blood flow than the other. For example, a score of 0 implied four positive and four negative values, or a symmetric distribution of probe pair differences between hemispheres. A score of 8 implied that all eight probes were lower in the same hemisphere, or maximal asymmetry. The possible values for the score were 0, 2, 4, 6, or 8. The $\chi^2$ test for trend was used to compare combined UCO and UCO+CS with combined NA and aged controls.

Logistic regression was performed to determine the information added by various measures of asymmetry in distinguishing patients with UCO from NA and aged controls after adjusting for age, sex, race, and history of stroke. Sensitivity and specificity were calculated as sensitivity = true positive/true positive + false negative × 100; specificity = true negative/true negative + false positive × 100. The model was then validated using 28 additional subjects (15 men, 13 women), 15 with unilateral carotid occlusion, 10 with normal arteriograms, and three normal controls.

Results

Mean ISI for all 16 probes and for each probe pair was higher in young controls than in aged controls (mean ± SEM, 63.9 ± 2.0 vs. 47.4 ± 2.1; $p<0.0002$). Since mean age of the aged controls was similar to that of the patients, only the aged control group was used for comparison. Fisher's exact $\chi^2$ test detected no significant difference in sex distribution between the aged controls and any patient group.

Mean hemispheric ISI was lower than aged controls in the occluded hemisphere of UCO and UCO+CS and in the nonoccluded hemisphere of UCO+CS. No significant difference in mean hemispheric ISI could be detected between aged controls and NA or BCO (Table 3).

Asymmetry of hemispheric blood flow (HBF), the mean difference in hemispheric ISI, was pronounced in both UCO and UCO+CS compared with aged controls (Figure 2). UCO patients with stroke or TIAs showed greater hemispheric differences than controls (Figure 3). In contrast, NA patients did not differ significantly from aged controls, regardless of clinical presentation. No significant asymmetry was found in BCO patients or in young controls or aged controls.

Mean ISI of individual probes in the occluded hemisphere of UCO patients was significantly lower.

<table>
<thead>
<tr>
<th>Group</th>
<th>Stroke</th>
<th>Computed tomography</th>
<th>Transient ischemic attacks</th>
<th>Median time from last event (mo)</th>
<th>Persons with</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCO</td>
<td>36</td>
<td>23</td>
<td>64</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>UCO + CS</td>
<td>31</td>
<td>19</td>
<td>61</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>BCO</td>
<td>12</td>
<td>10</td>
<td>83</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>NA</td>
<td>25</td>
<td>10</td>
<td>40</td>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

UCO, unilateral carotid occlusion; UCO+CS, unilateral carotid occlusion and contralateral stenosis; BCO, bilateral carotid occlusion; NA, normal arteriograms.
in two probes (inferior frontal and superior frontal) and borderline (p<0.03, not significant because of the multiple tests performed) in the other six probes compared with aged controls (Figure 4). However, mean ISI in all probes was lower than aged controls in both hemispheres of UCO+CS patients. No significant differences were found in mean ISI of any probe in NA patients, and only borderline differences were found in the two frontal probes in BCO patients compared with aged controls.

Comparison of the mean differences in ISI for each probe pair within groups revealed asymmetries in all eight probe pairs in UCO and UCO + CS (Figure 5). The differences in probe pair ISI fluctuated around 0 in the aged controls and in BCO and NA. Regional asymmetries in these groups were not significant, with the exception of the aged controls, where differences from 0 in the asymmetry of the superior frontal and parietal probes were detected.

ISI asymmetry is the distinctive measure in UCO and UCO + CS, as demonstrated in Figure 6. Regardless of the magnitude of asymmetry, the number of probes per hemisphere with ISI lower than the contralateral probes was considered. Asymmetry score was calculated for combined UCO and UCO + CS and combined NA and aged controls (Table 4). χ² analysis of the association of asymmetry score with carotid occlusion revealed an increase in the proportion of patients with occlusion for each increase in asymmetry score. Seven or eight probes lower in one hemisphere was highly suggestive of unilateral carotid occlusive disease. Patients with bilateral carotid occlusions demonstrate symmetry of ISI.

Regardless of the magnitude of asymmetry, the number of probes per hemisphere with ISI lower than the contralateral probes was considered. Asymmetry score was calculated for combined UCO and UCO + CS and combined NA and aged controls (Table 4). χ² analysis of the association of asymmetry score with carotid occlusion revealed an increase in the proportion of patients with occlusion for each increase in asymmetry score. Seven or eight probes lower in one hemisphere was highly suggestive of unilateral carotid occlusion.

Logistic regression was used to compare the prediction of occlusion based on stroke history alone or on the difference in HBF alone. History of

### TABLE 3. Mean Initial Slope Index in Patient Groups and Aged Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Initial slope index</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Occluded hemisphere</td>
<td>Nonoccluded hemisphere</td>
<td></td>
</tr>
<tr>
<td>UCO</td>
<td>36</td>
<td>40.5 ± 1.3*</td>
<td>42.6 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>UCO + CS</td>
<td>31</td>
<td>36.9 ± 1.3*</td>
<td>39.6 ± 1.2*</td>
<td></td>
</tr>
<tr>
<td>BCO</td>
<td>12</td>
<td>41.9 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>25</td>
<td>-</td>
<td>45.2 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Aged controls</td>
<td>16</td>
<td>-</td>
<td>47.4 ± 2.1</td>
<td></td>
</tr>
</tbody>
</table>

UCO, unilateral carotid occlusion; UCO + CS, unilateral carotid occlusion and contralateral stenosis; BCO, bilateral carotid occlusion; NA, normal arteriograms. Values are mean ± SEM. *p<0.009, two-sample t test, different from aged controls.

### TABLE 4. Asymmetry Score for Patients With Unilateral Carotid Occlusion and Normal Subjects

<table>
<thead>
<tr>
<th>Asymmetry score</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probes lower than contralateral hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCO and UCO + CS (n = 67)</td>
<td>6</td>
<td>40</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>NA and aged controls (n = 40*)</td>
<td>3</td>
<td>21</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

UCO, unilateral carotid occlusion; UCO + CS, unilateral carotid occlusion and contralateral stenosis; NA, normal arteriograms. x² test for linear trend p<0.008.

*One aged control was omitted because of a missing probe value.
stroke alone correctly predicted occlusion in 70% of the subjects (UCO, NA, and aged controls), with a sensitivity of 65.7% and a specificity of 78.0%. Difference in HBF alone correctly predicted occlusion in 75%, with a sensitivity of 80.6% and a specificity of 65.9%. After adjusting for age, sex, race, and history of stroke, logistic regression revealed that the difference in HBF was significant in distinguishing occluded from nonoccluded subjects (p<0.005). Regional asymmetries and asymmetry score did not add to the distinction. Based on the logistic regression equation, a one-unit increase in the difference in HBF resulted in a risk estimate of 1.54, or a 54% increase in risk of occlusion (Table 5). After adjusting for age, sex, race, and stroke history, comparison of patients predicted to have occlusion based on difference in HBF with patients having true (arteriographic) occlusion demonstrated a sensitivity of 80.6% and a specificity of 80.5% (Table 6), an improvement in specificity over either stroke history alone or difference in HBF alone.

The logistic regression model developed with the first group of subjects was tested on the additional group of 28 subjects, resulting in a sensitivity of 80.0% and a specificity of 69.2%.

Discussion

Consistent CBF abnormalities have not been demonstrated by intracarotid techniques in cases with arteriographic evidence of carotid occlusion.12–14 However, injection techniques are limited by difficulties with isotope delivery to tissue in the distru.

**Figure 3.** Absolute value of mean difference in hemispheric initial slope index (ISI) in patients with unilateral carotid occlusion (UCO) or normal arteriograms (NA) with no symptoms (ASX), transient ischemic attacks (TIA), or stroke. Bars represent SEM. *hemispheric difference greater than that for aged controls (p<0.008). +hemispheric difference in patients with UCO and TIA different from that in patients with NA and TIA (p<0.03).**

**Figure 4.** Mean initial slope index (ISI) in each probe pair. ○, unilateral carotid occlusion; solid line, occluded hemisphere; dashed line, nonoccluded hemisphere; □, unilateral carotid occlusion and contralateral stenosis; solid line, occluded hemisphere; dashed line, nonoccluded hemisphere; ●, bilateral carotid occlusion; ◊, normal arteriograms; ▲, aged controls. *mean ISI was lower than that for aged controls in all eight probes in both hemispheres of patients with unilateral carotid occlusion and contralateral stenosis (p<0.0125 all probes except temporal, nonoccluded hemisphere, where p<0.015); ×, significant difference compared with aged controls in regional probes in occluded hemisphere of patients with unilateral carotid occlusion (p<0.002).**

**Figure 5.** Mean difference in initial slope index (ISI) in each probe pair. ○, unilateral carotid occlusion; □, unilateral carotid occlusion and contralateral stenosis; ●, bilateral carotid occlusion; ◊, normal arteriograms; ▲, aged controls. Note marked asymmetry of ISI in all eight probes in patients with unilateral carotid occlusion both with and without contralateral stenosis. Regional differences fluctuated around 0 in patients with bilateral carotid occlusion or normal arteriograms. Two regional probes with significant asymmetry were found in aged controls. *differences in all eight probes differ from 0 (p<0.007); ×, differences in regional probes differ from 0 (p<0.007).
TABLE 5. Logistic Regression Analysis of Patients With Unilateral Carotid Occlusion and Normal Arteriograms and Aged Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.03</td>
<td>1.03</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.48</td>
<td>0.62</td>
</tr>
<tr>
<td>Race</td>
<td>1.19</td>
<td>3.29</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.60</td>
<td>4.95</td>
</tr>
<tr>
<td>ΔHBF</td>
<td>0.43</td>
<td>1.54</td>
</tr>
</tbody>
</table>

βs are derived from fit of logistic regression model that includes all variables listed. Each β is calculated in presence of all other variables and represents contribution of that variable to prediction of occlusion beyond predictive ability of other variables. Risk estimate = $e^β$, change in risk of occlusion related to a one-unit change in the variable. If β is negative, risk estimate represents decrease in risk; if β is positive, risk estimate represents increase in risk. ΔHBF, difference in hemispheric blood flow.

FIGURE 6. Mean initial slope index (ISI) in each probe pair plotted for occluded vs. nonoccluded or right vs. left hemispheres. Solid line, line of identity right of which patients with unilateral carotid occlusion, with or without contralateral carotid stenosis, but there was no significant asymmetry in patients with bilateral carotid occlusions or normal arteriograms. Although a bilateral diffuse decrease of rCBF was reported in one previous study of patients with unilateral carotid occlusion who had TIAs or completed stroke,1 other studies strongly support our findings.5,6,15

Although one subgroup of UCO patients with hemispheric ISI asymmetry had cortical infarction (see Figure 3), UCO patients with TIAs also demonstrated significant asymmetry of ISI, so parenchymal damage alone is unlikely to account for the hemispheric asymmetries found in our study. Computed tomograms (CT scans) were unavailable in all of our TIA patients, some of whom may have had CT-demonstrated infarcts. However, it is unlikely that the low-volume infarcts seen in TIA patients16 could account for the degree of asymmetry found. Furthermore, based on logistic regression analysis, stroke history alone was less sensitive in predicting occlusion than difference in HBF alone, implying that more patients with occlusion would be missed using only stroke history. When both stroke history and difference in HBF were considered along with age, sex, and race, there was an improvement in specificity; few patients without occlusion were misclassified. However, there was no increase in sensitivity over the use of difference in HBF alone. When the logistic regression model was tested with the additional subjects, the sensitivity remained high (80.0%). Sensitivity is the important measure of the utility of the rCBF measurement as a screening test. The lower specificity (69.2%) in the additional subjects reiterated the importance of considering the clinical features of individual patients before pursuing further, more invasive diagnostic procedures if rCBF measurement is used as a screening test.

Contralateral carotid stenosis, when arteriographically significant, reduced perfusion of the nonoccluded hemisphere. Although some arteriographic evidence was significant, and ISI in the occluded hemisphere tended to be lower than in patients without contralateral carotid stenosis. Norrving et al15 found that resting CBF does not correlate with the arteriographically demonstrated source of collateral blood flow. Our results suggest that rCBF asymmetries are valuable in assessing the adequacy of contralateral carotid collateral sources. No significant rCBF asymmetries were found in patients with unilateral carotid occlusion who had symmetric cortical filling demonstrated by digital subtraction angiography.17 Patients with delayed filling ipsilateral to carotid occlusion had variable rCBF results,17 which our study suggests could be related to the clinical features of the patients studied, perhaps identifying...
those at risk for developing further symptoms of cerebral ischemia based on rCBF asymmetry.

Decreases in mean CBF are found with aging as well as with nonatherosclerotic cerebral diseases, as we found. Nevertheless, two significantly asymmetric probe pairs were found in the aged control group (superior frontal and parietal probes), raising the possibility that the development of regional asymmetry rather than the decrease in mean CBF with age may be important.

In patients with bilateral carotid occlusions, a decrease in mean ISI was found compared with aged controls; however, significance was not obtained because of the small number of BCO patients studied. Of interest is the lack of asymmetry in these patients with advanced, yet symmetric, extracranial vascular disease.

Carotid occlusion can present clinically with a spectrum of symptoms, ranging from asymptomatic occlusion to devastating cerebral infarction. The demonstration of an arteriographic abnormality alone is insufficient to establish the clinical significance of the lesion. Long-term studies have demonstrated an increase in stroke and death rate among patients with carotid occlusion, underlining the need to detect patients at risk for postocclusive symptoms.

Varying mechanisms of occlusive and postocclusive ischemia have been suggested. Hemodynamic impairment or emboli may be involved in the pathogenesis of neurologic symptoms due to carotid occlusion. CT and cerebral arteriography may help to identify the possible etiology of postocclusion ischemia, but these tests cannot be definitive. As a physiologic measure of cerebral perfusion, rCBF could potentially add to the differentiation between sources of ischemic symptoms by identifying those patients with a hemodynamic deficit. This is supported by our finding of asymmetries in patients with TIAs and occlusion and the lack of asymmetries in TIA patients without significant arteriographic abnormality.

133Xe inhalation could be useful in prearteriographic screening of patients with extracranial cerebrovascular disease. For example, patients with a unilateral asymptomatic bruit with normal or minimally reduced rCBF, who show no asymmetry of blood flow distribution, might be at less stroke risk than those with major interhemispheric asymmetry and decreased HBF. The use of rCBF measurement could be extended to the evaluation of patients in whom cerebral arteriography is contraindicated, patients with indefinite hemispheric symptoms resembling TIAs, and patients with documented obstructive extracranial vascular disease and continuing symptoms of transient ischemia.

In conclusion, we found several measures that might identify unilateral carotid artery occlusion before cerebral arteriography: 1) differences in HBF, 2) degree of rCBF asymmetry, and 3) number of asymmetric probe pairs. Logistic regression analysis suggested that difference in HBF is useful in predicting carotid occlusion. A substantial increase in the estimated risk of occlusion was found for each unit increase in difference in HBF. Measurement of rCBF in the nonoccluded hemisphere and magnitude of asymmetry have potential for the additional evaluation of contralateral carotid collateral supply.

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References


**KEY WORDS** • carotid artery diseases • cerebral blood flow • xenon • cerebrovascular disorders
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