Increased stroke risk predicted by compromised cerebral blood flow reactivity

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The authors sought to determine risk for stroke in individuals with symptomatic carotid stenosis or occlusion based upon an assessment of cerebral blood flow (CBF) reserves. Vascular reserve was assessed by two consecutive xenon/computerized tomography (Xe/CT) CBF studies with intravenous acetazolamide introduced 20 minutes prior to the second study. Patients were assigned to one of two vasoreactivity groups. Group 2 included individuals who experienced a CBF reduction of more than 5% in at least one vascular territory and had a baseline flow of 45 cc/100 gm/min or less. Group 1 included all other individuals. Any territory with volume loss on CT of more than 50% was eliminated from analysis.

Sixty-eight individuals were followed at 6-month intervals for a mean of 24 months. In Group 1 two strokes were observed contralateral to the side with lowest reserve, for a stroke incidence of 4.4%; in Group 2 eight strokes were observed ipsilateral to the side with lowest reserve, for a stroke incidence of 36%. The latter group had a 12.6 times greater chance of stroke (p = 0.0007). History of stroke, history of transient ischemic attacks, baseline CBF, and degree of stenosis were not associated with an increased stroke rate. In this study, significantly compromised vascular reserves accompanied by relatively low initial flow identified individuals who subsequently demonstrated a significantly increased rate of ipsilateral stroke.

KEY WORDS - cerebral flow - stroke - occlusive vascular disease - acetazolamide

The role played by compromised cerebral hemodynamics in the likelihood of subsequent infarction has not been clearly defined. Until recently, it has not been possible to properly identify significant numbers of individuals who may be at increased hemodynamic risk for infarction. This is due in part to our inability to identify and accurately measure relevant physiological parameters. With the availability of positron emission tomography (PET), which provides an integrated assessment of cerebral blood flow (CBF), blood volume, oxygen extraction fraction (OEF), and metabolism, it was assumed that we would be able to overcome previous limitations.

Positron emission tomography studies have shown that, while moderately compromised perfusion pressure is compensated for by vasodilatation (Stage I), it is only after a state of maximum vasodilatation that CBF falls with further perfusion pressure compromise and increased oxygen extraction (Stage II). This severe hemodynamic compromise was labeled "miser perfusion" by Baron, et al. However, as of 1983, no significant predictor of subsequent stroke had been defined by PET studies.

Because maximum vasodilatation accompanies severely compromised cerebral hemodynamics, CBF response to a vasodilatory challenge has been examined as a more accessible means of identifying patients with compromised vascular reserves. Whether a vasodilatory challenge is induced by inhaling a gas mixture containing 3% to 5% CO₂ or is chemically induced with the intravenous injection of acetazolamide, the resultant regional OEF-flow response has proven useful for identifying individuals with disturbed cerebral hemodynamics. Utilizing 1 gm of intravenous acetazolamide with ¹³³Xe single-photon emission computerized tomography CBF imaging, Leinsinger, et al., defined a spectrum of reactivity that ranges from a normal increase in CBF of approximately 25% to a decrease of CBF in one or more vascular territories. In 1988, Kanno, et al., and Herold, et al., individually reported that patients with compromised CO₂ reactivity tended to have not only increased CBF but also elevated
FIG. 1. Baseline computerized tomography (CT) scans (A and C) obtained during acquisition of xenon/CT cerebral blood flow (CBF) studies prior to (B) and after acetazolamide (Diamox) administration (D). After acetazolamide infusion, CBF is reduced primarily within the right middle cerebral artery territory. The color key shows CBF in cc/100 gm/min. The numbers in B and D indicate mean CBF values in the relevant regions of interest (circled areas).

OEF. It was observed by Lassen, Vorstrup, and Rogg, et al. all of whom used tomographic CBF techniques, that patients who demonstrated not only a lack of vasodilatory capacity but also a “steal” response to an acetazolamide (Diamox) challenge are the most clinically unstable and thus appear to be the most at risk for stroke.

In this retrospective study of 68 symptomatic persons with high-grade carotid artery stenosis or occlusion, we attempted to define whether patients with the most severely compromised CBF reserves had an increased risk for subsequent stroke.

Clinical Material and Methods

Patient Data

Patients were selected for this retrospective study from among patients at the University of Pittsburgh Medical Center who had undergone xenon/computerized tomography (Xe/CT) CBF studies with acetazolamide challenge within the previous 50 months or more. To be included in the study, a patient had to have had greater than 70% stenosis or occlusion of an internal carotid artery (ICA) accompanied by symptoms of transient ischemic attacks (TIA’s) or moderate nondisabling stroke appropriate to the involved artery. In compliance with the guidelines of our institution’s Investigational Review Board, qualifying individuals were contacted initially by means of a mailed questionnaire that requested their consent to participate. After consent was obtained, we reviewed each patient’s medical record to determine whether the diagnosis of ICA occlusive vascular disease had been confirmed by angiography. Patients were contacted by telephone either immediately after consenting to participate (patients who had undergone the Xe/CT procedure longer than 6 months previous to consent) or 6 months after they had undergone the procedure. At that time, we requested an account of medical history, a description of symptoms that had occurred immediately before the Xe/CT CBF studies with acetazolamide were performed, and symptoms that had occurred since the studies were performed. Additional data were collected at 6-month intervals from the date of the initial baseline
Stroke risk predicted by compromised CBF reactivity

![Graph showing patient's baseline and acetazolamide-enhanced cerebral blood flow (CBF) coordinates by group for the territory with the least reactivity. Open circles = patients in Group 1 who did not suffer stroke; closed circles = patients in Group 1 who suffered stroke (these two were contralateral); open triangles = patients in Group 2 who did not suffer stroke; closed triangles = patients in Group 2 who suffered stroke (these eight were ipsilateral).](image)

Fig. 2. Graph showing each patient's baseline and acetazolamide-enhanced cerebral blood flow (CBF) coordinates by group for the territory with the least reactivity. Open circles = patients in Group 1 who did not suffer stroke; closed circles = patients in Group 1 who suffered stroke (these two were contralateral); open triangles = patients in Group 2 who did not suffer stroke; closed triangles = patients in Group 2 who suffered stroke (these eight were ipsilateral).

Five patients in the initial group of those diagnosed as having occlusive vascular disease were eliminated from the study because of inadequate follow-up information, and four were eliminated due to technically poor studies. Those who underwent cerebrovascular surgical procedures before 12 months of follow-up evaluation were excluded from the study, and those who underwent surgical procedures after 12 months were terminated from follow-up evaluation as of the date of surgery. In all, 68 patients (44 men and 24 women) were identified and followed for this report.

To confirm the occurrence of new stroke, a CT scan without contrast enhancement was obtained and compared with initial CT studies. Patients who suffered persistent hemispheric neurological deficits with (nine cases) or without (one case) CT-defined evidence of a new cerebral infarction were classified as having had a new stroke.

Stable Xe/CT CBF Methodology

Cerebral blood flow was measured using the stable Xe/CT CBF technique described by Gur and colleagues. Within 5 minutes after a baseline CBF study, the patient received 1 gm acetazolamide by rapid intravenous infusion; approximately 20 minutes later, a repeat CBF measurement was made. The patient maintained the same position in the scanner for the duration of the two studies. Cerebral blood flow measurements were taken on two levels. Level 1 was at the basal ganglia, a level that provided bilateral mixed cortical CBF measurements of the anterior, middle, and posterior cerebral artery distributions. Level 2 was approximately 20 mm higher, at the level of the centrum semiovale. This level also provided bilateral measurements of the anterior, middle, and posterior cerebral artery distributions. Contiguous 2-cm diameter circular regions of interest (ROIs) were placed around the cortical mantle on each of the two CBF images. Individual ROI's encompassed approximately 314 voxels, each measuring $1 \times 10 \times 10 \text{ mm}$. The CBF values for each vascular territory were computed by averaging the three to six ROIs within each territory on each level before and after acetazolamide administration (Fig. 1B and D). The change in CBF following the administration of acetazolamide was computed for each of the 12 vascular territories per study. Territories that included more than 50% infarction demonstrated on CT were excluded from analysis.

Patients were initially assigned to one of two groups based on the percent of CBF change that occurred following administration of acetazolamide. However, preliminary analysis revealed that patients with a baseline flow of 45 cc/100 gm/min or less were more at risk, which led us to group patients as follows: Group 2 included patients with a baseline flow of 45 cc/100 gm/min or less accompanied by a decrease greater than 5% in any vascular territory; Group 1 patients had all other combinations of percent change and baseline CBF. In each case, the most hemodynamically compromised, artifact-free, noninfarcted vascular territory was used to determine group classification. Patients who had undergone more than one CBF study with acetazolamide challenge were placed in a group according to data from the most recent study.

Statistical Analysis

Statistical analyses, including cross-tabulations and t-tests, were employed to identify relationships among group classification, gender, age, type of angiographic lesion, medical history, and occurrence of subsequent stroke. Kaplan-Meier cumulative failure curves were used to identify the cumulative stroke rate and the cumulative stroke and death rate of the two groups. Statistical analysis was performed using the SAS statistical package* ($p \leq 0.05$ was considered significant).

Results

New stroke was recorded in 10 of the 68 individuals at a mean incidence of 5 months after assessment of CBF reserves (Table 1 and Fig. 1). Of these, only one patient (in Group 2) died as a result of the stroke. One patient in each group died due to other causes. In Group 1, a new stroke was recorded in two individuals (Fig. 2). Both of these patients had ICA stenosis and each had a stroke opposite to the side of the brain determined to have the most compromised reserves. In Group 2, a new stroke was recorded in eight individuals (Fig. 2). Three of these individuals had ICA stenosis and five

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had ICA occlusion. All Group 2 strokes were ipsilateral to the compromised territory. The incidence of stroke in Groups 1 and 2 was 4.4% and 36%, respectively (p = 0.0001, Fisher's exact test, Table 2). Kaplan-Meier cumulative failure curves confirmed the higher incidence of stroke (p = 0.0003) (Fig. 3) and of stroke and death (p = 0.0001) in Group 2. Multivariate analysis demonstrated a 12.6 times (p = 0.0007) greater chance of stroke based on the response of CBF to acetazolamide for patients in Group 2. No variable examined (age, gender, history of TIA's or stroke, or degree of stenosis) other than CBF response to acetazolamide challenge was significantly associated with the occurrence of a new stroke. However, patients who developed a new stroke did have significantly lower baseline flow values (Table 3).

We found that, of 16 patients in Group 2 with carotid artery occlusion, five had a new stroke, showing a significantly increased risk of new stroke compared to similar patients in Group 1 (0 of 25) (p = 0.0005, Table 2). There was no significant difference in risk of stroke between Groups 1 and 2 for patients with severe stenosis (p = 0.056). When baseline and postacetazolamide values were compared, carotid occlusion was associated with significantly decreased CBF (Table 4). However, stenosis was not associated with a difference between baseline and postacetazolamide CBF values.

**Discussion**

Since 1985, when the International Extracranial/Intracranial (EC-IC) Bypass Study failed to show that this procedure significantly reduced the risk of subsequent stroke, both the procedure and the concept of compromised hemodynamics as a cause of stroke lost favor in the medical community. However, it has been shown that abnormal hemodynamic parameters not measured in the EC-IC bypass study have been repeatedly identified in some patients with severe occlusive vascular disease and subsequently improved with bypass surgery. The results from the previously mentioned case reports as well as retrospective studies that describe relief from recurring TIA's following bypass surgery support continued speculation that a relatively small subgroup of patients may be at increased hemodynamic risk for recurrent TIA's and stroke and may benefit from efforts to augment the supply of CBF.

Support for this concept began to appear in 1991 as more patients were followed for longer periods of time. Powers observed a 29% increase in stroke rate (four of 14 cases) in Stage II patients who were followed for 2 years. A group of patients with ICA occlusion who had exhausted flow reserves defined by transcranial Doppler velocity response to a CO2 vasodilatory challenge.

**TABLE 1**

<table>
<thead>
<tr>
<th>Age (yrs), Sex</th>
<th>Medical History</th>
<th>Symptoms</th>
<th>Degree of Vessel Disease</th>
<th>Territory of Least Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Territory</td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59, M</td>
<td>TIA</td>
<td>rt arm/leg weakness, aphasia</td>
<td>stenosis, ICA</td>
<td>rt ACA</td>
</tr>
<tr>
<td>65, M</td>
<td>TIA</td>
<td>rt arm/leg weakness, it facial weakness, it body numbness, slurred words</td>
<td>stenosis, rt ICA</td>
<td>rt ACA</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>58, M</td>
<td>TIA</td>
<td>rt arm/leg weakness, it body numbness, slurred words</td>
<td>occlusion, rt ICA</td>
<td>rt MCA</td>
</tr>
<tr>
<td>58, M</td>
<td>Stroke</td>
<td>rt arm/leg weakness, bilat body numbness, unable to speak, it hearing loss</td>
<td>occlusion, bilat ICA</td>
<td>rt ACA</td>
</tr>
<tr>
<td>72, F</td>
<td>TIA</td>
<td>rt vision loss</td>
<td>stenosis, ICA</td>
<td>It ACA</td>
</tr>
<tr>
<td>77, F</td>
<td>Stroke</td>
<td>rt arm/leg weakness, aphasia</td>
<td>occlusion, ICA</td>
<td>It MCA</td>
</tr>
<tr>
<td>55, M</td>
<td>Stroke</td>
<td>It arm/leg weakness, it facial weakness</td>
<td>occlusion, ICA</td>
<td>It MCA</td>
</tr>
<tr>
<td>64, F</td>
<td>TIA</td>
<td>rt arm/leg weakness, bilat body numbness, balance problems, fainting</td>
<td>occlusion, rt ICA</td>
<td>rt ACA</td>
</tr>
<tr>
<td>71, M</td>
<td>TIA</td>
<td>rt arm/leg weakness, it facial weakness, aphasia, memory impairment, it hearing loss</td>
<td>stenosis rt ICA</td>
<td>rt MCA</td>
</tr>
<tr>
<td>76, M</td>
<td>Stroke</td>
<td>rt arm/leg weakness, facial weakness, slurred words</td>
<td>occlusion, rt ICA</td>
<td>rt MCA</td>
</tr>
</tbody>
</table>

* Reactivity = percent change in cerebral blood flow (CBF) from baseline study to postacetazolamide study. TIA = transient ischemic attack; ICA = internal carotid artery; ACA = anterior cerebral artery; MCA = middle cerebral artery. Group 2 = patient with a baseline CBF ≤ 45 cc/min and > 5% decrease of flow in any vascular territory; Group 1 = all other patients in this series.

**TABLE 2**

<table>
<thead>
<tr>
<th>Vascular Disease</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe stenosis</td>
<td>2/21 (9.5%)</td>
<td>3/6 (50%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Occlusion</td>
<td>0/25</td>
<td>5/16 (31%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total</td>
<td>2/46 (4.4%)</td>
<td>8/22 (36%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Data show the number of patients with new stroke/total patients in that group, with percentages in parentheses. For explanation of groups see footnote to Table 1.
Stoke risk predicted by compromised CBF reactivity

![Graph showing the cumulative failure rate (stroke) in Group 1 and Group 2 patients over 24 months. Numerals on the curve indicate number of events during 1-month intervals. This analysis uses the Kaplan-Meier cumulative failure curves, p < 0.0001.](image)

The 36% ipsilateral stroke risk observed in our Group 2 patients further supports these findings that a group at increased risk for subsequent stroke due to hemodynamic compromise does exist.

Powers, et al., observed that PET-defined Stage II patients frequently displayed incompetence of collateral flow about the circle of Willis and a dependence on leptomeningeal collateral vessels. These patients are most likely to display not only a lack of vasoreactivity but also a redistribution of available CBF and decreased flow ("steal" response) in response to acetazolamide challenge. Cerebral perfusion in patients who display a "steal" response must also be critically dependent on perfusion pressure, so even small reductions may produce neurological deficits. It follows that individuals with severely compromised hemodynamics are also at increased risk for stroke due to embolic events.

In our analysis, no individual variable other than flow change with acetazolamide challenge was predictive of stroke. The postanalysis addition of a low baseline flow cut-off point of 45 cc/100 gm/min or less increased our ability to define the group at greatest risk from p = 0.014 to p = 0.0001 (a 26% to 36% stroke rate). While group criteria should ideally have been defined prior to data collection, the relationship between low initial flow values and subsequent stroke has been observed previously and our stroke victims did have significantly lower baseline flow values. This factor alone, however, was not a good discriminator of those patients at increased risk for subsequent stroke. This is because it is not possible to determine whether low flow was due to reduced metabolic demand or to compromised blood supply.

Our hemodynamically compromised patients not only had a higher percentage of strokes at the 24-month follow-up evaluation (36% vs. 14%) than the medical group of the EC-IC bypass study but, like Kleiser and Wilder, we also demonstrated that these strokes occurred relatively early (mean 5 months), suggesting that strategies for identification and treatment must be implemented early if they are to have the maximum impact. Only follow-up evaluation of larger numbers of Group 2 patients will determine if the rate of stroke will continue to climb for 5 years or if patients at increased risk will have been selected out by earlier infarctions.

As with any clinical study based on the retrospective review of clinical and physiological parameters, this report has limitations due to patient selection and methodological constraints. Our patients were obtained from a highly selected referral population. While we included all eligible candidates at our institution, selection criteria for CBF studies were not consistent within and between different clinical services. Also, CBF studies were often obtained only after angiography indicated the possibility of compromised collateral flow. However, the fact that the stroke rate in our study was 15% (10 of 68 cases) at 24 months suggests that our population was not greatly different from those medically treated patients in the EC-IC bypass study, who had a similar stroke rate.

The Xe/CT CBF examination with acetazolamide challenge is a good tool for identifying patients at increased risk for stroke because it provides quantitative CBF information in a tomographic format that is coupled with CT-defined anatomy. The ability to integrate anatomy and physiology is vital for proper interpretation of data, especially when volume loss due to prior ischemic events is common. Without this ability to identify and exclude from analysis those territories with significant prior infarction, our results would have been far less conclusive. The ability to test and retest CBF within one session also minimizes normal flow variations over time, while the ability to measure changes of flow in response to a specific physiological challenge minimizes the dependence on unmeasured variables.
Clinically, the importance of Xe/CT CBF with vasodilatory challenge rests in its ability to guide in the management of individuals with severe occlusive vascular disease. In some patients, Xe/CT studies may dissuade physicians from continuing or instituting potentially dangerous hypotensive therapy and instead lead them to prescribe hypertensive therapy. If CBF reserves are compromised in all regions, then any surgical procedure that provides increased intracranial supply may prove beneficial. However, if only a symptomatic middle cerebral artery territory displays a steal response, then flow augmentation should be directed to this territory. Only when future randomized studies examine the role of EC-IC bypass surgery in patients with appropriate focal hemodynamic disorders will the role for this procedure be appropriately established.

If subsequent studies confirm that an examination of CBF combined with vasodilatory stress does identify patients at increased hemodynamic risk for stroke, then such methodologies should play a central role in the assessment of individuals with symptomatic occlusive vascular disorders.

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Stroke risk predicted by compromised CBF reactivity


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