Background and Purpose—Misery perfusion, identified by increased oxygen extraction fraction (OEF), predicts subsequent stroke in patients with carotid occlusion. The purpose of this investigation was to determine the relationship of angiographic findings to increased OEF in these patients.

Methods—Forty-seven patients with carotid occlusion were studied with cerebral angiography and positron emission tomography (PET). The following angiographic data were collected blind to PET results: (1) pial collateralization, defined as retrograde filling of the MCA branches to the level of the insula; (2) presence of border zone shift; (3) presence of delayed venous phase; and (4) measurement of posterior communicating artery size. Patients were divided into 2 groups based on the PET measurement of normal or increased OEF.

Results—Seventeen of 47 patients had increased OEF distal to the occluded carotid artery. No significant relationship between increased OEF and any angiographic finding was found. Pial collateralization was present in only 2 patients, both with increased OEF ($P = 0.105$). Border zone shift was equally distributed between the 2 groups (12 of 30 with normal OEF and 6 of 15 with increased OEF). Delayed venous phase was present in 4 patients, 3 of whom had increased OEF ($P = 0.073$). The relationship between the size of the posterior communicating artery and OEF was not significant by linear regression analysis ($P = 0.242$).

Conclusions—With the possible but infrequent exceptions of delayed venous phase and pial collateralization, anatomic findings made on routine angiographic studies of patients with carotid occlusion do not correlate with increased OEF.

Keywords: angiography • carotid artery occlusion • collateral circulation • hemodynamics • oxygen
correlated with stage 2 hemodynamic compromise. In the St Louis Carotid Occlusion Study, however, neither pattern correlated with increased OEF. In this study, reconstitution of the internal carotid artery siphon from retrograde ophthalmic artery flow was present in 19 of 31 patients with increased OEF and in 10 of 28 patients with normal OEF. Pial collaterals, defined as any retrograde filling of middle cerebral artery (MCA) branches, was identified in 2 of 29 patients with increased OEF and 5 of 23 patients with normal OEF.

The purpose of this retrospective analysis was to determine whether other findings made on routine clinical angiographic examinations, which were not prospectively evaluated in the St Louis Carotid Occlusion Study, could be used to identify stage 2 hemodynamic compromise in a large group of patients with carotid occlusion. Specifically, these findings included (1) pial collateralization as the primary angiographic source of MCA territory supply (defined here as retrograde filling of the MCA branches to the level of the insula (M2) rather than any retrograde MCA branch flow); (2) the presence of border zone shift; (3) the presence of delayed venous phase; and (4) measurement of posterior communicating artery (PCoA) size. Small or absent PCoAs have been associated with prior MCA territory infarction in patients with and without carotid occlusion. In addition, the clinical outcomes of the patients in this analysis were reviewed in order to examine the relationship between these angiographic findings and subsequent ischemic stroke.

Subjects and Methods

Patients

The laboratory records of 117 patients with symptomatic or asymptomatic atherosclerotic carotid artery occlusion enrolled in the St Louis Carotid Occlusion Study, a blinded prospective study of cerebral hemodynamics and ischemic stroke, were reviewed. This study began enrollment in 1992 and ended in 1996. An analysis of the baseline risk factors of these patients has been published. Patients with cerebral angiograms available for review were identified from laboratory records.

A range of normal control cerebral hemodynamic and metabolic values was established from 18 normal control subjects aged 19 to 77 years (mean±SD, 45±18 years) recruited by public advertisement. Eight were women, 10 were men. All underwent neurological evaluation, MRI of the head, and duplex ultrasound imaging of the extracranial carotid arteries. None had (1) signs or symptoms of neurological disease other than mild distal sensory loss in the legs consistent with age, (2) pathological lesions on MR scan (mild atrophy and punctate asymptomatic white matter abnormalities were not considered pathological), or (3) <50% stenosis of the extracranial carotid arteries. All studies were performed under protocols approved by the Human Studies Committee.

Positron Emission Tomography Measurements

After positioning the patient on the scanner gantry, an individually molded thermoplastic face mask was applied to ensure that the patient’s head remained in a constant position during the scanning period. The exact position of the patient’s head relative to the scanning plane was recorded on a lateral skull film obtained after head immobilization. Venous and arterial catheters were placed for intravenous radiotracer administration and for arterial blood gas analyses and arterial time-activity curve determination, respectively. All PET studies were performed on 1 of 2 scanners (ECAT 953B or ECAT EXACT HR, Siemens). A transmission scan was performed before radiotracer administration using 68Ge/68Ga rotating rod sources. The skull film and attenuation data from this scan were used to define the limits of the calvarium for quantitative processing of PET data.

Each PET study consisted of 3 separate physiological studies. During each, arterial blood samples were drawn by hand or automatically in order to convert quantitative regional radioactivity data to quantitative physiological measurements. Additional arterial samples were drawn at intervals during the examination for determina-
tion of PaCO2 stability, average hematocrit (for mean arterial oxygen content calculations), and carboxyhemoglobin content. CBF was measured using a bolus intravenous injection of 15O-labeled water.22,24 CBV was measured after inhalation of air containing trace amounts of carbon monoxide labeled with 15O.25 OEF was measured after 1 or 2 breaths of 15O-labeled oxygen in combination with data from the CBV and CBF measurements.26 When technical difficulties precluded the determination of quantitative OEF, a ratio image of the counts in the oxygen image divided by the water image and normalized to a whole-brain mean of 0.40 was substituted for the quantitative OEF image.27 The counts in this count-based ratio image are linearly proportional to quantitative OEF except for small contributions from intravascular oxygen and recirculating water.26 The entire PET examination could be performed within 1 hour because of the short half-life (123 seconds) of 15O. All radionuclides were produced in the Washington University cyclotron facility.28,29

PET Processing

PET images from the ECAT 953B and ECAT EXACT HR scanners were reconstructed to a uniform resolution of 16 mm full-width half-maximum with use of a 3D Gaussian filter. All PET data were converted to uniform stereotaxic atlas space to allow reproducible placement of regions of interest. For each patient and normal volunteer, 7 spherical regions of interest 19 mm in diameter were placed in the cortical territory of the MCA in each hemisphere using stereotaxic coordinates.11,23 Areas of prior infarction were identified by review of CMRO2 images as well as CT or MR examinations. Neither the regions within these areas nor the corresponding contralateral regions were used for analysis.

The mean OEF in each cerebral hemisphere was calculated from the remaining regions. The ratio of the mean OEF in the hemisphere ipsilateral to the occluded carotid artery to the mean OEF contralateral to the occlusion was calculated for each patient. Hemodynamic stage for each individual patient was assigned by comparing the ipsilateral/contralateral hemispheric OEF ratios of each study patient to left/right and right/left hemispheric mean OEF ratios from the 18 normal control subjects. For each patient, the OEF ratio was considered abnormal if it fell outside the range observed in the normal population (a normal range for the count-based ratio image of 15O oxygen and 15O water was also generated).

Angiographic Assessment

Patients with cerebral angiograms performed at our institution or with complete copies of outside studies in the laboratory files were analyzed. All studies had been obtained for clinical purposes before PET examination. A neuroradiologist reviewed each examination blinded to the PET results.

Anatomic information recorded on a standardized data collection sheet included the site of carotid occlusion and the measurement of stenosis in ipsilateral and contralateral carotid and vertebralbasilar arteries. Measurements of stenoses were expressed as percent stenosis of the narrowest luminal diameter relative to the diameter of the normal distal lumen. The following 3 angiographic findings were recorded as present, absent, or indeterminate: (1) pial collateralization, specifically defined as retrograde MCA flow reaching the surface of the insula (Figure 1); (2) border zone shift (anteroposterior projection). The distal left ACA branches continue further over the convexity (beyond the superior frontal sulcus) than do the right ACA branches. PET examination revealed normal OEF. She remained asymptomatic during 58 months of follow-up.

Figure 2. Border zone shift in a 65-year-old asymptomatic woman with a left carotid artery occlusion. Midarterial phase after right common carotid injection in the anteroposterior projection. The distal left ACA branches continue further over the convexity (beyond the superior frontal sulcus) than do the right ACA branches. PET examination revealed normal OEF. She remained asymptomatic during 58 months of follow-up.

Data Analysis

The null hypothesis tested was that the frequency of each angiographic finding would be the same for patients with increased OEF as for patients with normal OEF. The statistical significance of the difference between these 2 categories of hemodynamic status and the angiographic findings was determined by χ2 and Fisher exact test analyses of 2×2 contingency tables. Statistical significance was accepted at P<0.05. Linear regression analysis of the relationship between the OEF ratio and the size of the PCoA was performed. A 1-way ANOVA comparing each angiographic finding as a nominal variable with the OEF ratio as a continuous variable were also performed. If the data failed either the normality or the equal variance tests, the Kruskal-Wallis 1-way ANOVA was performed instead. A post hoc Tukey’s test was also performed, if indicated. Statistical analyses were performed with SPSS 7.0 for Windows (SPSS Inc).

Outcome Data

The patients included in this retrospective analysis represented a subgroup of the patients enrolled in the St Louis Carotid Occlusion Trial. The clinical outcome data of the trial were reviewed, and the outcome of these patients was recorded. The primary end point of the original prospective longitudinal study was subsequent ischemic stroke, defined clinically as a neurological deficit of presumed ischemic cerebrovascular cause lasting longer than 24 hours in any cerebrovascular territory.10 Secondary end points were ipsilateral ischemic stroke and death. Patients were followed by the study coordinator for the duration of the study by telephone contact every 6 months with the patient or next of kin. The interval occurrence of any symptoms of cerebrovascular disease, other medical problems, and functional status was determined. The occurrence of any symptoms suggesting a stroke was thoroughly evaluated by 1 designated blinded investigator based on history from the patient or eyewitness and review of medical records ordered by the patient’s physician. If necessary, follow-up examination and brain imaging were arranged.
Results

Clinical Data
Forty-seven patients with atherosclerotic carotid artery occlusion had both angiographic examinations available for review and complete hemodynamic PET studies. These patients were studied between June 1992 and December 1996. Their mean age was 66 years. Twelve were women and 35 were men. Thirteen patients were asymptomatic. The mean and median times between last symptom and PET examination for the 34 symptomatic patients were 121 and 50 days, respectively. Ischemic symptoms were classified as transient monocular blindness in 11, transient ischemic attack in 8, and cerebral infarction in 15. The mean and median times between angiography and subsequent PET examination were 90 and 49.5 days, respectively. Mean follow up of this cohort was 3.1 years. A total of 4 strokes occurred; all ipsilateral and ischemic in nature. A total of 6 deaths were recorded; 1 was stroke related.

PET Data
The range of left-to-right and right-to-left hemispheric ratios for quantitative OEF in 18 normal volunteers was 0.914 to 1.085. The normal range for the count-based OEF ratio was 0.935 to 1.065. Quantitative studies were obtained in 38 patients. Of these, 24 patients had normal OEF ratios and 14 had increased OEF. Complete quantitative PET studies could not be performed in 9 patients, and the count-based OEF method was used. Of these, 6 patients had normal OEF ratios and 3 had increased ratios.

Angiographic Data
Completeness of Study
Selective digital subtraction angiograms (DSAs) were obtained in 46 patients. One patient had a cut film study. Forty-one had been performed at our institution and 6 at other hospitals. Forty-four studies included bilateral selective carotid cerebral angiograms with least 2 orthogonal views. Three studies combined 1 selective carotid injection and an aortic flush run of the cerebral circulation. Selective vertebral or subclavian artery injections were obtained in 33 patients. The PCoA ipsilateral to the occluded carotid artery was patent in 22 of these 33 patients. Pial collateralization could not be assessed in 5 studies. The presence of border zone shift or delayed venous filling could not be adequately assessed in 2 and 8 studies, respectively.

Angiographic Findings
These data are summarized in Table 1. Pial collateralization to the level of the insula was identified in only 2 patients, both with increased OEF ($P=0.105$). This sign had a high specificity (100%) and a low sensitivity (15.4%). The presence of border zone shift was evenly distributed between patients with increased and normal OEF. Fifteen of the 30 patients with normal OEF had border zone shift, as did 6 of 15 patients with increased OEF. Of 4 patients in whom delayed venous phase was identified, 3 had increased OEF and 1 had normal OEF ($P=0.073$). This finding had a high specificity for increased OEF (96.3%) but a low sensitivity (25%). No statistically significant relationship between these angiographic findings and the OEF ratio was found with Kruskal-Wallis 1-way ANOVA tests. The PCoA diameter was plotted against the OEF ratio for all patients with vertebral or subclavian studies ($n=33$; Figure 3). No significant relationship was found (linear regression, $P=0.242$). Exclusion of asymptomatic patients from this analysis did not affect these results.

Correlation With Outcome
These data are shown in Table 2. Three of the 4 ipsilateral strokes occurred in patients with increased OEF. The frequencies of pial collateralization and delayed venous phase for patients with increased OEF and subsequent stroke were nearly identical to those observed in patients with increased OEF and no stroke during follow up. One of the 4 patients with delayed venous phase suffered an ipsilateral ischemic stroke on follow-up. Both patients with pial collateralization remained neurologically stable. Two of the 33 patients with vertebral or subclavian artery studies suffered a stroke during the follow-up period. The PCoA was absent in one and measured 1.0 mm in diameter in the other.

<table>
<thead>
<tr>
<th>Angiographic Finding</th>
<th>Normal OEF ($n=30$)</th>
<th>Increased OEF ($n=17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pial collateralization</td>
<td>0/26</td>
<td>2/13</td>
</tr>
<tr>
<td>Border zone shift</td>
<td>12/30</td>
<td>6/15</td>
</tr>
<tr>
<td>Delayed venous phase</td>
<td>1/27</td>
<td>3/12</td>
</tr>
</tbody>
</table>

No statistically significant differences were identified between groups by $\chi^2$ and Fisher’s exact tests. The numerator represents the number of patients identified with each finding and the denominator represents the total number of patients in whom that finding could be assessed.

Figure 3. Plot of OEF versus diameter of the PCoA. Thirty-three patients had both selective carotid and vertebral or subclavian artery injections that allowed accurate assessment of the presence and size of the PCoA ipsilateral to the occluded carotid artery. Linear regression analysis found no significant relationship between OEF and PCoA diameter ($P=0.242, R=0.21$). Only 2 of these 33 patients suffered a stroke during follow-up (indicated by black diamonds).
Discussion

The identification of patients with increased OEF may become clinically important. Increased oxygen extraction fraction (OEF) is known to be a reliable angiographic identifier of increased OEF, which has been found to correlate with increased OEF in patients with carotid disease and impaired cerebral vasoreactivity measured by xenon CT. This pattern of collateralization was also present in 2 of 10 patients with normal vasoreactivity. Their definition for pial collateralization was not provided, however. It should be pointed out the degree of correlation between paired-flow methods of hemodynamic assessment (such as xenon CT) and OEF as measured by PET has been variable. While a significant linear relationship between OEF and the degree of flow impairment has been reported by some but not all investigators, the sensitivity and specificity of paired-flow methods for the identification of increased OEF appears to be poor.

Pial collaterals to the surface of the insula have also been observed in patients with M1 occlusion and stage 1 hemodynamic compromise (3 of 5 patients with MCA occlusion). Therefore, while it is possible that the pattern of pial collateralization to the level of the M1 or M2 has a high specificity for increased OEF in patients with carotid occlusion, the frequency of this finding may be too low to be clinically useful.

It is interesting that the presence of border zone shift did not correlate with increased OEF in the cortical regions of the MCA territory. In fact, border zone shift was observed in many patients with normal cerebral hemodynamics (stage 0) in the MCA territory (data not shown). Whether these patients have selective hemodynamic impairment in the arterial border zone remains an unanswered question. If one considers retrograde filling of MCA vessels to the level of the insula as the far end of the spectrum of border zone shift (defined in this study as pial collateralization), then an association with hemodynamic impairment was observed.

These data suggest that delayed venous phase may be an indicator of hemodynamic impairment. This deserves further investigation. The angiographic identification of delayed venous phase in the context of temporary balloon occlusion of the carotid artery has been advocated as an indicator of hemodynamic compromise. However, the assessment of delayed venous phase on static images filmed from routine clinical DSA studies, as performed in this retrospective analysis, is gross at best. These films often included only a single image of the venous phase. Carefully filmed sequential images of both hemispheres obtained after injection of the aortic arch or contralateral carotid artery are required for this measurement. There is a physiological rationale that supports the association of this finding with hemodynamic impair-

<table>
<thead>
<tr>
<th>Normal OEF</th>
<th>Increased OEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>No Stroke</td>
</tr>
<tr>
<td>(n=1)</td>
<td>(n=29)</td>
</tr>
<tr>
<td>Pial collateralization</td>
<td>0/26</td>
</tr>
<tr>
<td>Border zone shift</td>
<td>1/11</td>
</tr>
<tr>
<td>Delayed venous phase</td>
<td>0/1</td>
</tr>
</tbody>
</table>

No statistically significant differences were identified between groups and Fisher’s exact tests. The numerator represents the number of patients identified with each finding and the denominator represents the total number of patients in whom that finding could be assessed.
Figure 4. Increased OEF with an absent PCoA and without pial collateralization, delayed venous phase, or border zone shift. A, The AP projection after selective right common carotid artery injection demonstrates prompt opacification of the left MCA via an anterior communicating artery. B, A later image from the same run demonstrates no definite difference in late arterial phase. Venous phase was normal (not shown). C, The PET study demonstrates increased OEF (stage 2 hemodynamic compromise). Note that left and right are reversed on the PET study relative to the angiogram. Ipsilateral CBF is diminished throughout the left MCA territory (white arrows) despite maximal autoregulatory vasodilation (increased ipsilateral CBV). Normal symmetrical oxygen metabolism (cerebral metabolic rate of oxygen, CMRO₂) is maintained by increased oxygen extraction (white arrows). This patient was a 60-year-old man who presented with an acute infarction of the left internal capsule 30 days before PET examination. Angiography was performed 10 days after presentation. He suffered a stroke in the left carotid territory confirmed by clinical and imaging criteria 38 months after study enrollment.
ment. A linear relationship between the mean transit time (an indicator of autoregulatory vasodilatation) and the angiographic circulation time, a precise measurement of the time between the appearance of the first artery and the first vein on a cerebral angiogram, has been documented. A delay in the appearance of the cerebral veins may indicate the presence of autoregulatory vasodilatation.

Several investigators have examined the relationship between the circle of Willis anatomy and the incidence of prior stroke. In a postmortem pathological study, Battacharji and coworkers examined the brains of 49 patients with cerebral infarction and 88 patients without stroke. An abnormally small PCoA was found in greater frequency in the patients with infarction (59% compared with 39%). Schomer and coworkers correlated the presence of a PCoA > 1 mm by MRA with the absence of preexisting border zone region infarction by MR. In our data, however, the size of the PCoA did not correlate with OEF or with the risk of subsequent stroke. Similar results were reported by van Everdingen and coworkers. They studied 57 patients with carotid occlusion and found no correlation between CO$_2$ reactivity and the route of flow from circle of Willis collaterals, as long as one was present.

Several limitations of this study deserve mention. The angiograms were obtained for clinical purposes and consequently did not allow assessment of each of the angiographic findings examined in this analysis in all patients. All angiographic data were derived from retrospective review of static images. Dynamic information such as delayed venous phase is difficult to assess in this manner. The assessment of arterial border zone shift was subjective, and there is good evidence that considerable anatomic variation exists in the location of the cortical arterial border zone between middle and anterior cerebral arteries. van der Zwan and colleagues demonstrated in anatomic studies of 25 human brains that the MCA/ACA border zone could be located in the superior frontal gyrus, the superior frontal sulcus, the middle frontal gyrus, or in the inferior frontal sulcus. The location of the border zone was symmetrical between the hemispheres in 14 patients and asymmetrical beyond the middle frontal gyrus in 3 (the definition of border zone shift used in this report).

The delay between angiography and PET introduces the possibility of error in the correlation of angiographic findings and hemodynamic status. It is possible that changes in either the anatomic collateralization or the hemodynamic stage may have occurred in the interval. Collateral pathways can increase in size over time, and occlusive lesions have the potential for recanalization. The degree of hemodynamic impairment may improve over time, but this phenomenon appears to occur slowly over months and years. There is no evidence for interval worsening in hemodynamic stage in patients without interval stroke, however.

It should be noted that the method used for defining patients with normal or increased OEF in this study differs slightly from the original method used in the St Louis Carotid Occlusion Study. In that study, we used the ratio of left to right hemispheric mean OEF to categorize patients as normal or abnormal. In the present study we used ipsilateral (to the carotid occlusion) to contralateral ratios. The normal range was established from combining left/right and right/left ratios from the normal volunteers. The reason for this approach was to allow statistical testing of the OEF ratio as a continuous variable. The count-based method used in 9 of the 47 patients in the present study was used to categorize 13 of the 81 patients in the original St Louis Carotid Occlusion Study. A direct comparison of the quantitative and count-based OEF methods found no significant difference between the hemispheric ratios generated with either technique and, more importantly, no difference in the ability to identify patients at risk for subsequent stroke.

In summary, the data from the present study indicate that the anatomic information provided by routine cerebral angiography does not allow the identification of increased OEF in the majority of patients. The static angiographic images can be considered a map of the routes by which blood reaches the brain but not necessarily an indicator of the traffic on them. Dynamic information that can be derived from an angiographic study was not assessed. Although pial collateralization to the level of the insula and delayed venous phase may be associated with increased OEF, the low sensitivity of these findings reduce their clinical usefulness. In addition, these two findings did not achieve statistical significance in this large retrospective analysis. The most severe category of hemodynamic impairment (increased OEF, stage 2 hemodynamic compromise) has been shown to predict subsequent stroke risk in patients with symptomatic carotid occlusion. If a trial of extracranial to intracranial bypass surgery for patients with carotid occlusion is organized, the anatomic information present on review of static images from a cerebral angiogram will not be suitable for identifying the majority of patients with increased OEF.

Acknowledgments
Supported by NIH grants NS28947, NS02029, and NS34050; the Charles A. Dana Foundation; and a Radiological Society of North America/Siemens Medical Systems research fellowship. The authors wish to acknowledge Susanne M. Fritsch, RN, for her critical role as study coordinator for the St Louis Carotid Occlusion Study.

References
10. Grabb RL Jr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EJ, Powers WJ. The importance of hemodynamic factors...


45. Moret J, Panel discussion on aneurysms. Presented at Joint Section of Cerebrovascular Surgery and the American Society of Interventional and Therapeutic Neuroradiology Annual Meeting; Meeting, February 5, 1998; Orlando, Fla.


Lack of Correlation Between Pattern of Collateralization and Misery Perfusion in Patients With Carotid Occlusion

Stroke. 1999;30:1025-1032
doi: 10.1161/01.STR.30.5.1025

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/30/5/1025

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/