The Effect of Hemodynamically Significant Carotid Artery Disease on the Hemodynamic Status of the Cerebral Circulation

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Although the presence of a hemodynamically significant carotid artery lesion is commonly used as an indicator of impaired cerebral circulation, the effect of such lesions on cerebral perfusion pressure and cerebral blood flow has never been determined accurately. We used positron emission tomography (PET) to study 19 patients with unilateral hemodynamically significant carotid artery disease (> 66% diameter reduction) and no evidence of cerebral infarction. According to PET measurements in the cerebral hemisphere distal to the lesion, 7 patients had normal cerebral hemodynamics, 8 had reduced perfusion pressure with normal blood flow, and 4 had reduced blood flow. Neither the percent stenosis nor the residual lumen diameter in the carotid artery was a reliable indicator of the hemodynamic status of the cerebral circulation. However, a significant relationship was found between the PET measurements of cerebral hemodynamics and the arteriographic circulation pattern ($p = 0.006$). The role of hemodynamic factors in the pathogenesis and treatment of cerebrovascular disease cannot be determined from the severity of carotid artery disease alone.

THE IMPORTANCE of hemodynamic factors in the pathogenesis and treatment of ischemic cerebrovascular disease remains unclear. Measurements in the cervical carotid artery have shown that reductions in blood pressure and blood flow distal to a stenosis occur only when the lumen diameter falls below a critical size. This critical point of hemodynamic significance is reached when vessel diameter is reduced by 60% to 65%, producing a residual lumen of 1 to 2 mm (1-3). The presence of a hemodynamically significant carotid artery lesion is generally regarded as an indication of impaired cerebral circulation. Prophylactic carotid endarterectomy is often recommended for patients with asymptomatic but hemodynamically significant carotid stenosis, especially those having major cardiovascular surgery, on the assumption that these patients are at increased risk for cerebral ischemia of hemodynamic cause (4-6). (This approach is far from universally accepted, however, because of the lack of adequate prospective studies confirming its efficacy [7, 8].) The clinical importance ascribed to the presence of a hemodynamically significant lesion in the cervical carotid artery has, in turn, led to the development of various noninvasive tests to aid in its detection (9, 10). These tests are used to screen for possible surgery those patients with asymptomatic carotid artery disease and those with ill-defined cerebral symptoms (4-6, 11, 12).

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Such an emphasis on the hemodynamic significance of a carotid artery lesion ignores the possible contribution of collateral circulatory pathways in maintaining cerebral perfusion. No accurate evaluation of the physiologic effect of hemodynamically significant carotid artery disease on the cerebral circulation and the importance of collateral channels has ever been done in humans. Previous attempts based on analysis of the incidence and extent of cerebral infarction in patients with varied degrees of stenosis and different patterns of collateral flow have not been able to separate hemodynamic from embolic causes of infarction (13-15). Attempts to evaluate cerebral hemodynamics by direct measurements of cerebral blood flow distal to a stenosis (16) are also subject to error, because they cannot detect reductions in cerebral perfusion pressure when cerebral blood flow is maintained by compensatory vasodilation nor can they differentiate cerebral blood flow decreases caused by reduced blood supply from those caused by the reduced metabolic demands of damaged tissue. Some investigators have used the cerebrovascular response to CO_2 inhalation as an indicator of reduced cerebral perfusion pressure (17, 18). Although the normal cerebral blood flow increase during hypercapnea is attenuated when cerebral perfusion pressure falls (19), this reduced CO_2 response is a nonspecific finding that may be produced by various factors other than reductions in perfusion pressure (20-22).

The development of positron emission tomography (PET) has made it practical to do a variety of measurements of human cerebral physiology in addition to cerebral blood flow. When combined with a knowledge of the normal compensatory responses made by the brain to progressive decreases in cerebral perfusion pressure, PET can be used to determine accurately the hemodynamic status of the cerebral circulation in vivo (23). When cerebral perfusion pressure is normal (stage 0), blood flow is regulated by changes in arteriolar size and there is a direct correlation between cerebral blood flow and the intravascular cerebral blood volume. Under these conditions, cerebral blood flow is also closely matched to the resting metabolic rate of the tissue. As a result, there is a uniform value throughout the brain for the fractional extraction of oxygen from the blood. This cerebral oxygen extraction fraction is approximately one third in normal resting humans (24). As perfusion pressure falls, the first compensatory response is arterial vasodilation (stage 1). Flow is then maintained by a decrease in vascular resistance. Both blood volume and the volume/flow ratio will increase, but oxygen extraction will remain normal (Fig-

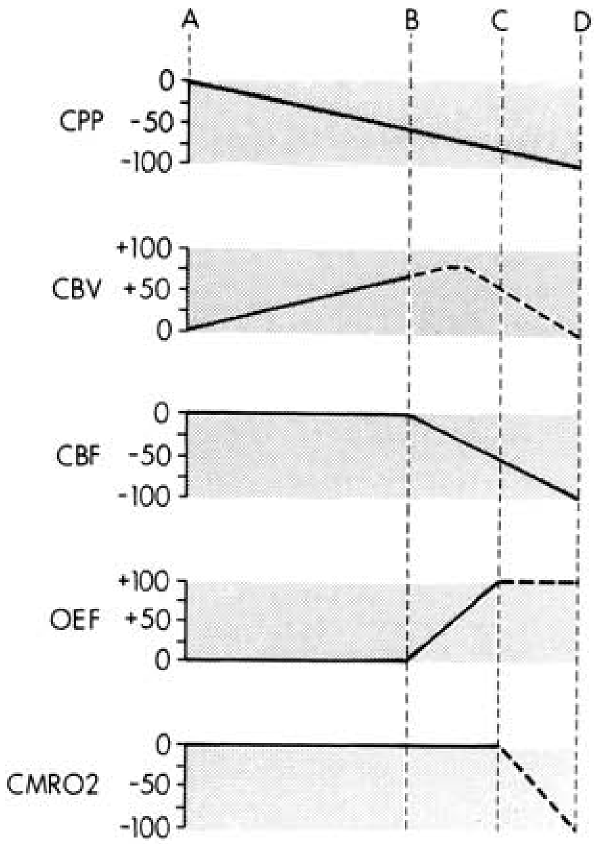

Figure 1. Compensatory responses to reduced cerebral perfusion pressure (numbers shown are the percent change). As cerebral perfusion pressure (*CPP*) falls, cerebral blood flow (*CBF*) is initially maintained by dilation of precapillary resistance vessels. As a result, both cerebral blood volume (*CBV*) and the volume/flow ratio (not shown) increase. When vasodilation can no longer compensate, cerebral autoregulation fails and blood flow begins to fall (*point B*). (This occurs before maximal vasodilation). As perfusion pressure continues to fall, cerebral blood volume may decrease as vessels collapse, but the volume/flow ratio remains elevated. A progressive increase in the oxygen extraction fraction (*OEF*) now maintains cerebral oxygen metabolism (*CMRO2*). Once this mechanism becomes maximal (*point C*), further declines in blood flow cause disruption of normal cellular metabolism and function. (Dashed lines indicate conditions for which data are inadequate to draw firm conclusions.)

ure 1). As perfusion pressure falls further, the capacity for compensatory vasodilation will be overwhelmed and blood flow will begin to fall. At this stage, cerebral oxygen metabolism is maintained by an increase in oxygen extraction (stage 2) (Figure 1). Under these circumstances, cerebral blood volume may decline as vessels passively collapse (25), but the volume/flow ratio will remain elevated. Because the volume/flow ratio is mathematically equivalent to the mean vascular transit time for erythrocytes through the cerebral vessels, an increase in this ratio indicates slowing of the cerebral circulation (26, 27). If cerebral perfusion pressure falls further, the compensatory mechanisms of the brain will be exhausted and cerebral infarction may occur (23).

We have used PET measurements of regional cerebral blood flow, blood volume, and oxygen extraction to evaluate the cerebral circulation in 19 patients with unilateral, hemodynamically significant carotid artery disease (> 66% diameter reduction). Neither the percent stenosis nor the size of the residual lumen was an accurate indicator of the hemodynamic status of the cerebral circulation. There was, however, a significant relation between the cerebral hemodynamic status and the pattern of collateral circulation as determined by carotid arteriography.

Methods

SUBJECTS

Positron emission tomographic measurements were done on 19 patients, aged 45 to 79, with cerebrovascular disease who were selected with the following criteria: no clinical neurologic deficit; normal findings on a computed tomographic scan of the brain; and bilateral, biplane, common carotid arteriography showing unilateral stenosis with greater than 66% diameter reduction. Eleven patients had complete carotid occlusion. All had contralateral stenosis of less than 67% (Table 1). No one had arteriographic abnormalities of the middle cerebral arteries or their branches. Eleven patients had had hemispheric transient ischemic attacks, 5 had had transient monocular blindness, 1 had had both of these conditions, and 2 had arteriography for investigation of asymptomatic carotid disease (1 with an asymptomatic bruit and 1 with an asymptomatic occlusion contralateral to a previously operated symptomatic stenosis). All 19 were asymptomatic at the time of the PET measurements.

Positron emission tomographic studies also were done on 33 normal persons, aged 18 to 84. Twenty-five of these persons, aged 18 to 50, were volunteers who had no history or evidence of neurologic disease and were recruited by public advertisement. The remaining 8, aged 62 to 84, were volunteer participants in the Washington University Memory and Aging Project. Each had a clinical interview, general physical and neurologic examination, standardized 2-hour battery of psychological tests, blood and urine tests, and a computed tomographic scan of the brain. Only those classified as normal and healthy according to previously published criteria (28) were included in our study. Informed written consent was obtained from each subject before the PET measurements. This protocol was approved by the Human Studies Committee and the Radioactive Drug Research Committee of the Washington University School of Medicine.

POSITRON EMISSION TOMOGRAPHY

Measurements of regional cerebral blood flow, blood volume, and oxygen extraction were done on the PETT VI tomograph in the low-resolution mode (29). This tomograph collects seven parallel tomographic slices, 1.4 cm apart. Venous and arterial catheters were placed to permit radiotracer injection and collection of arterial blood samples. Subjects were positioned so that the lowest tomographic slice was near the canthomeatal line. The head was then immobilized by an individual face mask made of heat-molded plastic and attached to a headrest. A plastic plate with seven radioopaque wires was used to record the position of each of the seven PET slices on a lateral skull radiograph. A transmission scan with a $^{68}Ge/^{68}Ga$ ring source was done on each subject to provide data on photon attenuation necessary for quantitative reconstruction of subsequent scans.

Cerebral blood flow was measured after bolus intravenous injection of ^{15}O-labeled water ($H_2{}^{15}O$) (30, 31). Cerebral blood volume was measured after a brief inhalation of ^{15}O-labeled carbon monoxide ($C^{15}O$) (32, 33). The oxygen extraction fraction was measured after brief inhalation of ^{15}O-labeled oxygen ($O^{15}O$) (33). (The cerebral metabolic rate for oxygen can be calculated from the product of cerebral blood flow, oxygen extraction fraction, and arterial oxygen content.) Subjects' eyes and ears were not masked. The short half-life of oxygen-15 (123 s) allowed these studies to be done in rapid succession. Total study duration ranged from 1 to 2 hours. All radiotracers were produced by the Washington University medical cyclotrons (34).

Table 1. Cerebral Circulatory Status Distal to a Hemodynamically Significant Carotid Artery Stenosis

Patient	Age/Sex	Diagnosis	Percent Stenosis (Diameter)		Arterial Supply‡			
			Ipsilateral	Contralateral	Carotid	Willis	Ophthalmic	Meningeal
	yrs		*% (mm)*	*% (mm)*				
Normal hemodynamics (stage 0)								
1	60/M	Transient hemispheric ischemia	100	66(1.5)*	−	+	−	−
2	59/F	Transient monocular blindness	100*	0	−	+	−	−
3	68/F	Transient monocular blindness	100*	0	−	+	−	−
4	63/F	Transient hemispheric ischemia	75(1.0)*†	0	+	−	−	−
5	68/M	Transient hemispheric ischemia, transient monocular blindness	75(1.0)*†	21(3.5)†	+	−	−	−
6	45/F	Transient monocular blindness	72(1.0)*†	0	+	−	−	−
7	76/F	Transient hemispheric ischemia	67(1.5)*†	25(3.5)†	+	−	−	−
Reduced cerebral perfusion pressure, normal flow (stage 1)								
8	65/F	Transient hemispheric ischemia	100*	0	−	+	+	−
9	52/F	Transient hemispheric ischemia	100*	41(2.5)†	−	+	−	−
10	69/M	Transient hemispheric ischemia	100*	17(4.0)†	−	−	+	−
11	63/F	Asymptomatic	100	0	−	+	−	−
12	52/F	Transient hemispheric ischemia	91(0.5)†	36(2.5)*†	−	+	+	−
13	62/M	Transient monocular blindness	86(0.5)*	41(2.5)	+	−	−	−
14	64/F	Transient monocular blindness	71(1.0)*	0	+	−	−	−
15	79/M	Asymptomatic	71(1.5)†	40(3.0)†	+	−	−	−
Reduced cerebral perfusion pressure, reduced flow (stage 2)								
16	70/M	Transient hemispheric ischemia	100*	40(2.5)†	−	−	+	+
17	69/M	Transient hemispheric ischemia	100*	0	−	−	+	+
18	64/M	Transient hemispheric ischemia	100*	65(1.5)†	−	−	+	+
19	47/M	Transient hemispheric ischemia	100*	18(3.5)†	−	−	+	−

* Symptomatic side.
† Multiple lesions in tandem.
‡ − = absent; + = present.

For each subject, seven 1.37×1.37-cm regions of interest in the cortical territory of the middle cerebral artery were defined in each hemisphere using stereotactic coordinates (24, 35). For each PET measurement, the mean value from these seven regions was used to calculate a hemispheric value. Hemispheric ratios were determined by dividing the higher hemispheric value by the lower. Because no age-matched control group with normal carotid arteriograms was available, 17 normal persons, aged 18 to 30, were selected from the larger control group as being epidemiologically unlikely to have significant carotid artery atherosclerosis (36, 37). The hemisphere values for volume/flow ratio and the oxygen extraction fraction, as well as the hemispheric ratios for each of these two measurements, were determined for this group and were used to define the normal range of values for this study. Because the control group was younger than the study group, we examined the influence of age on volume/flow ratio, oxygen extraction fraction, and their respective hemispheric ratios by calculating the correlation coefficients between age and each of the four variables for the entire control population of 33 persons, aged 18 to 84 (38). No significant correlations were seen (all $r^2 < 0.125$, all $p > 0.20$).

The hemodynamic status of the cerebral circulation in the hemisphere ipsilateral to the severe carotid artery lesion was determined for the 19 patients with cerebrovascular disease. Values outside the normal range determined from the 17 controls aged 18 to 30 were considered to be abnormal. If only a hemispheric ratio was abnormal, the hemisphere with the higher value was considered to be abnormal, because both volume/flow ratio and oxygen extraction increase with reduced cerebral perfusion pressure. The 19 patients were divided into three hemodynamic categories according to the PET data (Figure 2): stage 0 (normal), normal volume/flow ratio and normal oxygen extraction fraction; stage 1 (reduced perfusion pressure, normal flow), increased volume/flow ratio and normal oxygen extraction; stage 2 (reduced perfusion pressure, reduced flow), increased volume/flow ratio and increased oxygen extraction. No direct measurements of cerebral perfusion pressure were made.

ARTERIOGRAPHY

All 19 patients with cerebrovascular disease had bilateral, biplane, carotid arteriography for clinical indications. The results of these studies were retrospectively reviewed by two neuroradiologists who were unaware of the PET measurements. The diameter of the internal carotid artery on each side was measured at the origin, the level of the first cervical vertebra (C1), and the siphon. The residual lumen size was also measured at any other site in the internal carotid artery where there was a visible stenosis. Measurements were made on both lateral and anterioposterior projections, and the mean value was taken as a lumen diameter at that site. The percent stenosis for each patient was calculated from the lumen diameter at the site of stenosis and the greater of the two diameters recorded at C1. For patients with multiple carotid lesions in tandem, the severest lesion was used for analysis. All measurements were corrected for magnification.

The arterial supply to the middle cerebral artery territory ipsilateral to the severer carotid lesion was determined from the arteriograms and classified as carotid (antegrade via the ipsilateral internal carotid artery), Willis (via the anterior circle of Willis from the opposite carotid circulation), ophthalmic (via the ipsilateral ophthalmic artery from the external carotid artery), or meningeal (via anastomotic channels across the surface of the brain from the anterior cerebral arterial circulation).

Five patients (Patients 1, 14, 16, 17, and 18) had selective vertebral arteriography to evaluate the posterior circulation. Any collateral circulation from the vertebrobasilar system to the middle cerebral artery in these patients was noted.

DATA ANALYSIS

The statistical significance of relationships between the three PET categories of cerebral hemodynamic status and the percent carotid stenosis or diameter of the residual carotid lumen was determined by one-way analysis of variance. The statistical significance of the relationships between the three PET categories of cerebral hemodynamic status and the four collateral patterns was determined by chi-square analysis of a 3×4 contingency table. Further subgroup analysis of these relationships was done by 2×2 contingency tables with two-tail probabilities from Fisher's exact test (38).

Results

In the hemisphere distal to the hemodynamically significant carotid stenosis, 7 patients had normal cerebral hemodynamic status (stage 0), 8 had reduced cerebral perfusion pressure with a normal cerebral blood flow (stage 1), and 4 had both reduced cerebral perfusion pressure and reduced cerebral blood flow (stage 2) (Table 1, Figure 2). Of the 12 patients classified as having abnormal cerebral hemodynamic findings, 11 were classified on the basis of abnormal hemisphere ratios and only 1 (Patient 12) was classified solely on the basis of quantitative measurements outside the normal range (Table 2).

There was no significant relationship between the hemodynamic status of the cerebral circulation as measured by PET and either the percent carotid stenosis ($F = 2.046$, $p = 0.323$) or the diameter of the residual carotid lumen (in millimeters) ($F = 1.922$, $p = 0.357$). There was, however, a highly significant relationship between the three PET categories of cerebral hemodynamics and the four patterns of arteriographic flow (Table 1) (chi-square $= 18.024$, $p = 0.006$). Meningeal collaterals were present only in patients with reduced cerebral blood flow (3 of 4 patients with stage 2) and not in patients with normal cerebral blood flow (0 of 15 patients with stages 0 and 1, $p < 0.005$). Ophthalmic collaterals were observed only in patients with reduced cerebral perfusion pressure (7 of 12 patients with stages 1 and 2) and not in patients with normal hemodynamics (0 of 7 patients with stage 0, $p < 0.02$).

The value of ophthalmic collaterals as an indicator of reduced cerebral perfusion pressure was further examined by analysis of the contralateral hemispheres. In 17 of the 19 patients, the contralateral hemisphere showed normal cerebral hemodynamics. In 2, there was reduced perfusion pressure with normal blood flow (stage 1). None had ophthalmic collaterals. For both hemispheres, the presence of ophthalmic collaterals as an indicator of reduced perfusion pressure had a sensitivity of 50% (7/14) and a specificity of 100% (24/24).

Of five patients who had vertebrobasilar arteriography, only one (Patient 1) had collateral flow to the middle cerebral artery through the posterior communicating artery ipsilateral to the severe carotid lesion. This patient had normal cerebral hemodynamic findings. The other four patients showed no filling of the middle cerebral artery branches via the posterior communicating artery. All four had abnormal cerebral hemodynamics in that hemisphere with one classified as having stage 1 (Patient 14) and three as having stage 2 (Patients 16, 17, and 18). Three of these four patients (Patients 14, 16, and 17) showed collateral circulation via meningeal vessels from the posterior cerebral artery to the middle cerebral artery.

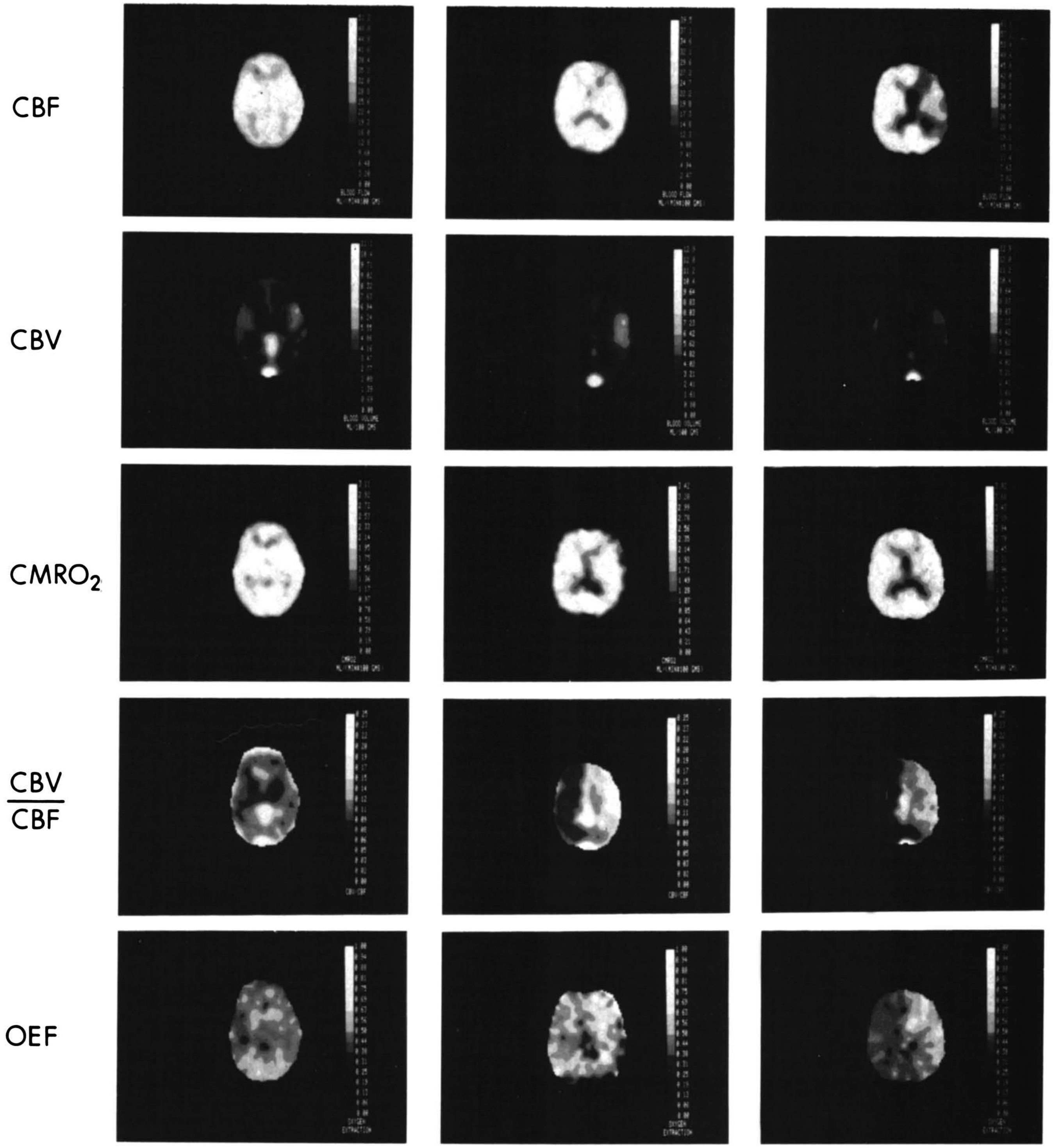

Figure 2. Positron emission tomography (*PET*) of regional cerebral hemodynamics and metabolism in three patients with right internal carotid artery occlusion. Each panel shows one tomographic slice depicting a different physiologic measurement. The right cerebral hemisphere is on the right; the front of the brain is at the top. **Left Column.** A 59-year-old woman (Patient 2) with episodes of transient blindness in the right eye has normal cerebral blood flow (*CBF*), cerebral blood volume (*CBV*), cerebral metabolic rate for oxygen (*$CMRO_2$*), volume/flow ratio (*CBV/CBF*), and oxygen extraction fraction (*OEF*). **Center Column.** A 65-year-old woman (Patient 8) with episodes of transient left-sided weakness shows elevated cerebral blood volume and volume/flow ratio in the right hemisphere. Both blood flow and oxygen metabolism are slightly and proportionately decreased in the right frontal region, as shown by a uniform oxygen extraction fraction throughout the brain. **Right Column.** A 69-year-old man (Patient 17) who had one episode of transient left-sided weakness 6 weeks earlier. Right hemispheric blood flow is reduced relative to oxygen metabolism. Cerebral blood volume, volume/flow ratio, and oxygen extraction fraction are all increased in the right hemisphere.

Table 2. Positron Emission Tomographic Measurement of Cerebrovascular Physiology*

Patient	Blood Flow		Blood Volume		Volume/Flow			Oxygen Extraction		
	Ipsi-lateral	Contra-lateral	Ipsi-lateral	Contra-lateral	Ipsi-lateral	Contra-lateral	Ratio	Ipsi-lateral	Contra-lateral	Ratio
	mL/100 g·min		*mL/100 g*		← s →					
Normal hemodynamics (stage 0)										
1	39.74	44.13	4.28	5.04	6.43	6.82	1.061	0.35	0.37	1.057
2	37.98	36.21	4.10	3.99	6.48	6.61	1.020	0.47	0.47	1.000
3	33.34	37.05	2.98	3.18	5.36	5.15	1.041	0.54	0.51	1.059
4	47.78	51.91	3.66	3.95	4.60	4.57	1.007	0.32	0.33	1.031
5	44.54	48.94	3.56	3.40	4.81	4.18	1.151	0.33	0.30	1.100
6	39.45	41.08	3.81	3.83	5.78	5.59	1.034	0.46	0.48	1.043
7	36.19	38.12	3.49	3.54	5.78	5.54	1.043	0.44	0.44	1.000
Reduced cerebral perfusion pressure, normal flow (stage 1)										
8	25.85	30.59	3.87	2.69	9.04	5.29	1.709	0.38	0.37	1.027
9	35.37	38.91	4.77	4.04	8.11	6.26	1.296	0.44	0.45	1.023
10	56.51	75.31	5.18	4.71	5.47	3.77	1.451	0.39	0.36	1.083
11	35.53	38.00	3.74	3.11	6.32	4.92	1.285	0.49	0.46	1.065
12	39.26	37.81	6.29	6.83	9.60	10.84	1.129	0.45	0.47	1.044
13	35.73	38.67	3.82	3.50	6.30	4.93	1.278	0.33	0.32	1.031
14	34.53	37.05	4.11	3.26	7.14	5.28	1.352	0.58	0.53	1.094
15	44.79	55.18	4.13	4.09	5.53	4.45	1.243	0.31	0.30	1.033
Reduced cerebral perfusion pressure, reduced flow (stage 2)										
16	35.59	51.08	7.50	6.06	12.94	7.42	1.744	0.65	0.53	1.226
17	31.09	43.57	4.02	3.18	7.83	4.39	1.784	0.54	0.42	1.286
18	23.93	38.45	6.76	6.84	17.22	10.65	1.617	0.55	0.42	1.310
19	32.53	40.98	4.78	3.96	8.85	5.75	1.539	0.46	0.38	1.211
Normal range	37.06-64.07		2.72-6.03		4.28-8.49		1.007-1.175	0.21-0.67		1.007-1.143

* Ipsilateral = middle cerebral artery territory in hemisphere ipsilateral to severer carotid artery lesion; contralateral = middle cerebral artery territory in hemisphere contralateral to severer carotid artery lesion; ratio = greater of the two hemisphere measurements divided by the lesser.

Discussion

This study shows that neither the presence nor severity of unilateral, hemodynamically significant carotid artery disease is a reliable indicator of the hemodynamic status of the cerebral circulation in the ipsilateral hemisphere. Similar observations in the coronary circulation have been reported recently (39). Our data suggest that the primary determinant of cerebral perfusion pressure and cerebral blood flow under these circumstances is the adequacy of collateral circulatory pathways. In some patients, flow through the carotid itself (if not completely occluded) and through the circle of Willis is adequate to maintain normal perfusion pressure and flow (stage 0). The simple presence of arteriographic flow through the anterior circle of Willis did not indicate adequacy, however (Table 1). Circulation through ophthalmic arterial collaterals occurred primarily in patients with reduced cerebral perfusion pressure (stages 1 and 2), suggesting that this pathway is functional only when circulation through the carotid artery and circle of Willis is inadequate. In patients with reduced perfusion pressure who do not manifest ophthalmic collaterals, sufficient time may not have elapsed to allow these pathways to dilate or the anatomic connections may not be present. Thus, the absence of ophthalmic collaterals cannot be construed as indicating normal cerebral hemodynamic status. Similarly, collateral circulation through meningeal arterial anastomoses occurred primarily in patients with reduced flow (stage 2), indicating that these channels are called into play only under conditions of even severer reductions in cerebral perfusion pressure.

The present study examined patients with primarily unilateral carotid artery disease who had no evidence of cerebral infarction. The evaluation of the hemodynamic status of the cerebral circulation by PET in patients with cerebral infarction is more difficult because of the various poorly understood changes in cerebral blood flow, blood volume, and oxygen extraction that occur under these circumstances (23). The presence of primarily unilateral carotid artery disease in our study population allowed us to evaluate the role of collateral circulation through the anterior portion of the circle of Willis. Hemodynamic compromise of a cerebral hemisphere distal to a severe carotid lesion implies that collateral circulation from the vertebrobasilar system through the posterior portion of the circle of Willis must be inadequate as well. Although we were unable to evaluate completely the importance of the posterior circulation collaterals because only five patients had vertebrobasilar angiography, we did show absence of arteriographic flow through the posterior communicating artery in those four of the five who had abnormal cerebral hemodynamics.

We used PET measurements to determine the hemodynamic status of the cerebral circulation. The validity and accuracy of this approach are based on fundamental principles of cerebral circulatory physiology outlined in the introduction and have been confirmed by direct experimental and clinical experience. Grubb and coworkers

(40) found cerebral blood volume to be a sensitive indicator of changes in cerebral perfusion pressure. A significant increase in blood volume occurred with as little as a 9% reduction in perfusion pressure. Gibbs and colleagues (26) have shown that the volume/flow ratio is increased in patients with bilateral carotid artery occlusion and in those with clinical features suggesting hemodynamic perfusion failure. These investigators have also reported that surgical revascularization in patients with carotid occlusion causes a significant decrease in the volume/flow ratio that can be ascribed to the expected increase in perfusion pressure (41). The volume/flow ratio was a more sensitive indicator of hemodynamic change than volume or flow alone. A unilateral increase in oxygen extraction in patients having extracranial-intracranial bypass surgery has been a reliable predictor of a postoperative increase in blood flow. Oxygen extraction returns to normal under these circumstances, indicating that the preoperative hemispheric flow was reduced relative to the metabolic demands of the tissue (23, 42). Cerebral blood flow and cerebral oxygen metabolism may not return to normal, however, even in patients with no evidence of cerebral infarction. This suggests that diffuse loss of a small number of neurons may occur in some patients with normal findings on computed tomographic scans of the brain and normal neurologic function (42).

We used both absolute measurements and hemispheric ratios to analyze our data. The wide range of normal values for absolute measurements (Table 2) makes detection of abnormalities difficult. The use of hemispheric ratios takes advantage of the basic symmetry of the brain to improve sensitivity for identifying localized disease. The ratio technique, however, only allows one hemisphere to be classified as abnormal and permits no conclusion about the opposite hemisphere. Hemodynamic status in the hemisphere contralateral to a severe carotid stenosis cannot be assumed to be normal because of the possibility of interhemispheric shunting of blood (43), making quantitative measurements in this hemisphere essential. The two methods of analysis thus complement each other.

Estimation of regional cerebral blood flow and blood volume in patients with cerebrovascular disease by single-photon-emission computed tomography (SPECT) has also been reported (44, 45). Although this technique is seemingly more attractive than PET because it does not require an on-site cyclotron for radiotracer production, SPECT is less accurate due to both inherent problems with the technique (46) and the current lack of validated tracer techniques that permit accurate, quantitative measurements of cerebral blood flow in both physiologic and pathologic circumstances. Furthermore, the measurement of oxygen extraction fraction is not possible with SPECT.

The results of our study have important implications for both clinical research and patient care. For research purposes, classification of patients based on the degree of carotid stenosis will fail to differentiate those with reduced cerebral perfusion pressure or blood flow from those with normal cerebral hemodynamics. This failure will result in the creation of patient groups who are physiologically heterogeneous, making it all but impossible to assess the influence of hemodynamic factors on the pathogenesis and treatment of cerebrovascular disease. Such a deficiency is evident in the recently completed multicenter trial analyzing the value of extracranial-intracranial bypass surgery in the prevention of stroke (47). This operation was primarily designed to improve perfusion to hemodynamically compromised areas of the brain. Although the study showed that the surgery was ineffective in preventing strokes, patients were categorized by the degree and location of arterial stenosis and not by the presence or absence of an abnormal cerebral hemodynamic status. The subgroup of patients with reduced cerebral perfusion pressure, who would have been most likely to benefit from the surgery, could not be identified, and thus the value of surgery in this subgroup could not be analyzed (48). However, with knowledge of the present work, these investigators have analyzed the efficacy of this surgery in a group of patients with ophthalmic collaterals and found no benefit (49). No information about the subgroup with the most severely deranged cerebral hemodynamics manifested by meningeal collaterals or local increases in oxygen extraction is available. However, because of the overwhelmingly negative results of this trial, we believe that the value of extracranial-intracranial bypass surgery in patients with hemodynamic perfusion failure manifested by local increases in cerebral oxygen extraction must be demonstrated and cannot be assumed.

In the clinical area, our results clearly indicate that little rationale exists for using the degree of carotid stenosis to decide whether a patient may be at increased risk for stroke on hemodynamic grounds or whether cerebral symptoms are caused by poor perfusion. It follows that the choice of medical or surgical therapy should not be based on such considerations. What remains to be determined is whether those patients with true cerebral circulatory compromise are at an increased risk for stroke, either spontaneously or during major cardiovascular surgery. Patients with severe carotid artery disease may be at increased risk for subsequent stroke due to nonhemodynamic factors as well. As the size of the atherosclerotic plaque increases, it may become a more likely source for thromboembolism due to the presence of increasingly turbulent flow and the development of complicated, friable lesions that are more thrombogenic.

Studies investigating the relation between the severity of carotid stenosis and the subsequent risk for stroke in patients with asymptomatic carotid artery disease have produced conflicting results. Some have shown an increased risk for stroke with increasing stenosis (50-52), whereas others have not (53-55). These studies have largely failed to account for such confounding prognostic variables as age, hypertension, and different treatment regimens. Their results are therefore difficult to interpret, and the question remains unresolved. For symptomatic patients with transient ischemic attacks or minor stroke in the carotid artery distribution, the data relating severity of stenosis to stroke risk are much clearer and the results somewhat surprising. The best available evidence indicates that the risk for ipsilateral stroke in patients with symptomatic carotid artery disease who are not treated surgically is not influenced by the degree of stenosis (53, 56, 57).

In conclusion, we have shown that the presence of hemodynamically significant carotid artery disease is a poor indicator of the hemodynamic status of the cerebral circulation in the ipsilateral hemisphere. Therefore, any diagnostic test that provides only a direct or indirect measurement of the degree of carotid stenosis cannot provide reliable information about the cerebral circulation. Our data suggest that the effect of unilateral carotid stenosis on the cerebral circulation can be more accurately assessed by analysis of the arteriographic circulation pattern, but further studies are needed to confirm the reliability of these findings. The importance of hemodynamic factors in the pathogenesis of cerebrovascular disease remains to be determined. This can only be done through accurate determination of the hemodynamic status of the cerebral circulation with techniques such as PET scanning.

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