Hemodynamic and Metabolic Effects of Extracranial Carotid Disease

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ABSTRACT: Cerebral blood flow (CBF), cerebral blood volume (CBV), the CBF/CBV ratio – an index of the hemodynamic reserve capacity – the rate of oxygen metabolism ($CMRO_2$), and the fractional extraction of oxygen by the brain (OEF) were studied by positron emission tomography (PET) in the cortical territory of both internal carotid arteries in 15 cases of transiently symptomatic or progressive extracranial atherosclerotic carotid disease. None of the patients had a major stroke or had a significant neurological deficit except 1 whose damaged hemisphere is excluded from study. All were asymptomatic at the time of PET scanning. Values were obtained in the middle cerebral artery (MCA) distribution, and in the anterior and posterior borderzone regions. Eight cases had unilateral carotid stenosis of 80% or greater and 7 had unilateral or bilateral occlusion of the origin of the internal carotid artery. Results obtained in patients were compared using Student's t-test, to those obtained in neurologically normal, elderly volunteers. Patients with carotid stenosis had a significantly decreased CBF ($p<.025$) and CBF/CBV ratio ($p<.025$) selectively in the anterior borderzone regions. This was accompanied by a trend toward elevated OEF and declining $CMRO_2$ values. Patients with carotid occlusion had significantly decreased CBF ($p<.005$), decreased CBF/CBV ratio ($p<.005$) and decreased $CMRO_2$ ($p<.025$) in the ipsilateral anterior borderzone and MCA territories. Similar changes were present in the opposite hemisphere of patients with bilateral carotid disease. These results indicate that carotid stenosis is associated with hypoperfusion and diminished hemodynamic reserve capacity in the anterior borderzone, and that carotid occlusion produces more widespread hypoperfusion and metabolic depression.

RÉSUMÉ: Effets hémodynamiques et métaboliques de la maladie carotidienne extra-crânienne Nous avons étudié le flot sanguin cérébral (FSC), le volume sanguin cérébral (VSC), le rapport FSC/VSC — un indice de la réserve hémodynamique — le taux du métabolisme de l'oxygène ($CMRO_2$) et l'extraction fractionnaire d'oxygène (OEF) par le cerveau au moyen de la tomographie par émission de positrons (PET scan) dans le territoire cortical des deux carotides internes chez 15 cas de maladie carotidienne athérosclérotique extracrânienne dont la symptômatologie était transitoire ou progressive. Aucun des patients n'avait subi d'accident cérébrovasculaire majeur et ne présentait de déficit neurologique significatif, sauf un dont les données sur l'hémisphère endommagé sont exclues de l'étude. Tous étaient asymptomatiques au moment du PET scan. Nous avons recueilli des données dans le territoire de l'artère cérébrale moyenne (ACM) et dans les régions avoisinantes antérieures et postérieures. Huit cas avaient une sténose carotidienne unilatérale de 80% ou plus et 7 avaient une occlusion unilatérale ou bilatérale de l'origine de la carotide interne. Nous avons utilisé le test de "t" de Student pour comparer les résultats obtenus chez les patients et ceux obtenus chez des volontaires âgés normaux au point de vue neurologique. Les patients porteurs d'une sténose carotidienne avaient un FSC significativement réduit ($p <0.025$) et un rapport FSC/VSC également réduit de façon significative ($p <0.025$) sélectivement dans la région antérieure ipsilatérale avoisinante, ainsi qu'une tendance à l'élévation de l'OEF et à la diminution des valeurs du $CMRO_2$. Les patients avec occlusion carotidienne avaient une réduction significative du FSC ($p <.005$), du rapport FSC/VSC ($p <.005$) et du $CMRO_2$ ($p <.025$) dans la région antérieure ipsilatérale avoisinante et les territoires de l'ACM. Des changements similaires étaient présents dans l'hémisphère opposé chez les patients porteurs d'une maladie carotidienne bilatérale.

Ces résultats indiquent que la sténose carotidienne est associée à une hypoperfusion et à une diminution de la capacité de réserve hémodynamique dans la zone limitrophe antérieure, et que l'occlusion carotidienne provoque une hypoperfusion et une dépression métabolique plus étendues.

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Stenosis or occlusion of the internal carotid artery at its origin is a common condition that often produces transient cerebral ischemia or stroke.[1] Despite its prevalence and potentially devastating effects, the cerebral hemodynamic and metabolic consequences of atherosclerotic carotid disease in man are poorly understood and subject to controversy.

Atherosclerotic stenosis or occlusion of an internal carotid artery (ICA) can produce symptoms by creating a pressure gradient resulting in diminished blood flow and perfusion pressure distal to the lesion. This can be compensated for by the development of collateral channels that divert blood to the ischemic hemisphere through the circle of Willis from the contralateral carotid or ipsilateral vertebro-basilar systems, via leptomeningeal anastomoses between major cerebral vascular territories, or by spontaneous extra- to intracranial (EC-IC) anastomoses, usually through the ophthalmic artery. These collateral

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channels are not always successful in meeting the metabolic demands of the hemisphere ipsilateral to the diseased carotid.[2-4] According to current thinking, the neurological dysfunction then produced is reversible if the hemodynamic changes impede electrical activity but are not severe enough to interfere with mitochondrial function. However, if blood flow and perfusion pressure are below the threshold of mitochondrial viability infarction ensues, producing permanent neurological deficit or death. It is commonly assumed that a stenosis of 80% or greater is severe enough to alter cerebral blood flow (CBF) and potentially diminish cerebral perfusion pressure (CPP). Such lesions are felt, therefore, to be "hemodynamically significant".[5] Recently, the assumption that so-called hemodynamically significant carotid disease has universally deleterious effects on cerebral hemodynamic function has been challenged.[6]

The CBF, as an isolated measurement, is often unreliable in reflecting the hemodynamic and metabolic status of the brain. It can be elevated above metabolic demands in areas of cerebral infarction (the so-called "luxury perfusion syndrome") and diminished in areas where the $CMRO_2$ values are maintained in the normal range by a rising OEF (the so-called "misery perfusion syndrome").[17,18] The cerebral blood volume (CBV) is often a useful indicator of the hemodynamic status of the brain. A rise in CBV is associated, in ischemia, with a fall in CPP as resistance vessels dilate to maximize the area available for nutrient exchange.[19] When combined with CBF, the resultant CBF/CBV ratio is considered an indicator of cerebral hemodynamic reserve capacity.[8] The CBF/CBV ratio may be a better indicator of the adequacy of cerebral perfusion than either of its constituent parameters considered alone.[7] Below values of approximately 5.5-6, the CBF/CBV ratio can be correlated with a rise in OEF.[9] The OEF rises during acute cerebral ischemia to compensate for the effects of hypoperfusion in an attempt to maintain the $CMRO_2$ in the normal range.[10] As such, the OEF is considered an index of the cerebral metabolic reserve capacity.[8] The reciprocal of the CBF/CBV ratio, the CBV/CBF ratio, is mathematically equivalent to the cerebrovascular transit time. This parameter rises in ischemia to indicate a prolonged – or delayed – cerebral circulation.

These parameters can be measured, and their relationships derived, by Positron Emission Tomography (PET). Using PET, therefore, it is possible to assess cerebral perfusion, oxygen metabolism and the recruitment of hemodynamic and metabolic reserve mechanisms in any vascular territory of the brain. We have utilized PET in 15 cases of severe extracranial carotid stenosis (ICS) or carotid occlusion (ICO) that have not produced a major stroke to ascertain how these conditions affect cerebral perfusion and metabolism.

Patient Population and Radiological Findings

Twelve males and 2 females, aged 51 to 73 years (mean age: 62.3 years) with transiently symptomatic or progressive ICS of 80% or greater (8 cases), or with unilateral or bilateral ICO (7 cases), were studied with PET. One patient was studied twice, initially when she had an asymptomatic ICS (Case 8i) and 3 years later when she had a silent ICO (Case 15ii). Positron Emission Tomography was performed in patients that had not sustained a major stroke and who were to undergo carotid endarterectomy or EC-IC bypass if they consented to the examination and if PET could be carried out without undue delay in treatment. These patients do not, therefore, represent all patients with these conditions seen at our institution during the study period. Post-operative studies could not always be obtained and are not considered. Patients had ipsilateral TIAs (10 cases), amaurosis fugax (6 cases), progressing stenosis confirmed by serial angiography (3 cases), and completed stroke with good recovery (2 cases). All patients with ICS had a normal neurological examination except one with mild hemiparesis from a lacune in the internal capsule. One patient with bilateral ICOs was hemiplegic from a 2 year old stroke contralateral to his present TIAs, and 4 had mild neurological deficits (Table 1). Computed tomography (CT) scanning demonstrated a lacune in the ipsilateral internal capsule of one patient with ICS. Two patients with ICO had contralateral and bilateral lacunae, one had an ipsilateral capsular lacune, and one had a small ipsilateral cortical infarct. The patient with a remote stroke had a large infarct in the hemisphere opposite to the presently symptomatic one and the infarcted hemisphere was excluded from PET study. The remaining CT scans were normal (Table 2). None of the CT scans demonstrating lacunae or cortical infarction had associated findings suggestive of an acute, recent event. Angiography was performed at the same admission as the PET scans and the CT scans were performed approximately one week before PET scanning.

There were 3 cases of 80% and 5 of 95% ICS; there were 4 cases of unilateral and 3 of bilateral ICO. Two unilateral ICO patients also had significant contralateral carotid disease (Table 2). The degree of ICS was assessed by comparing the residual inner diameter across the maximal area of stenosis to the inner diameter of the common carotid artery in a disease-free segment nearest to the area of stenosis. All middle cerebral arteries (MCA) were free of atherosclerotic disease. Three patients with ICS had aplasia or hypoplasia of the first segment of the anterior cerebral artery (ACA) ipsilateral to the carotid lesion. Nine patients without bilateral ICO had extensive collateral supply to the symptomatic hemisphere across the anterior communicating artery. Vertebral angiography was not always performed in patients with ICS. The vertebro-basilar system supplied some of the territory of the occluded ICA in most patients with ICO (Table 2).

Positron Emission Tomography

PET images were obtained on the Therascan-31128 as previously described.[11,12] The patient's head was held fixed by a molded plastic neck support and a reference position was established by aligning a wall mounted laser with the patient's orbito-meatal line. PET images were obtained at 6 scan positions between 42 mm and 98 mm above the orbito-meatal (OM) line to cover the territories of the ACA, MCA and the posterior cerebral artery (PCA) above the tentorium cerebelli. ^{15}O-O_2, ^{15}O-CO_2 and ^{15}O-CO were administered sequentially in one session to provide functional maps of CBF (^{15}O-CO_2), CBV (^{15}O-CO) and of OEF and $CMRO_2$ (^{15}O-O_2); and the OEF and $CMRO_2$ images were corrected for CBV. During all of the studies, arterial samples were repeatedly collected for measurement of blood gases and pH, hematocrit, and radio-activity concentration. All physiological parameters were within normal limits at the time of PET scanning.

Each image was examined by placing circular regions of interest 9 mm in diameter over 13-19 cortical grey matter areas bilaterally. All 6 tomographic images were examined in the entire territories of the ACA and MCA; and in the borderzone

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regions between the ACA and MCA (anterior borderzone) and between the MCA and the PCA (posterior borderzone). The anterior borderzone is located in the upper mid-frontal region and corresponds anatomically to the site of the fine anastomotic pial vessels between the anterior internal frontal branches of the ACA and the pre-frontal branches of the MCA.[13,14] The posterior borderzone is located in the parieto-occipital and temporo-occipital areas. It corresponds anatomically to the zone of pial anastomosis between the angular or posterior temporal branches of the MCA and the parieto-occipital branch of the PCA[13].

Table 1*

Case No.	Age/Sex	Other Conditions	Signs and Symptoms
1	66,M	None	AF, Normal examination
2	68,M	CAD	AF (x1), TIA (x1) Normal examination
3	51,F	Asthma, CAD, HBP	TIA (Frequent) Normal examination
4	56,M	HBP	AF (Occasional) Normal examination
5	58,M	HBP	AF (x2), TIA (Frequent) CVA with minimal hemiparesis
6	56,M	CAD,DM,HBP	Progressive, asymptomatic ICS Normal examination
7	61,M	HBP	TIA (x1,1 year before PET Study) Progressive asymptomatic ICS Normal examination
8(i)	70,F	CRF,HBP	Progressive asymptomatic ICS Normal examination
9	59,M	HBP,PVD	AF (Frequent),TIA (Occasional)
10	68,M	CAD,PVD	CVA with mild hemiparesis
11	52,M	HBP	TIA (x4) Normal examination
12	64,M	HBP	TIA (x3) Hemiplegia from contralateral CVA
13	67,M	CAD	AF (Frequent), TIA (Frequent)
14	65,M	HBP	TIA (Occasional)
15(ii)	73,F	CRF,HBP	Contralateral TIA (x1) Normal examination

*AF: Amaurosis Fugax; CAD: Coronary artery disease; CRF: Chronic renal failure; CVA: Stroke; DM: Diabetes mellitus; HBP: Arterial hypertension; ICS: Internal carotid stenosis; PET: Positron Emission Tomography; PVD: Peripheral vascular disease; TIA: Transient cerebral ischemia; M: male; F: Female.

Table 2*

		ICA System			Collaterals	
Case No.	CT	Ipsilateral	Contralateral	V-B System	OA	ACoA
1	Normal	80% ICS with ulceration, A-1 hypoplasia	Normal	75% ipsilateral VAS	?	+
2	Normal	80% ICS with ulceration	ICA ulceration	Not studied	?	+
3	Normal	80% ICS	ICA ulceration	Normal	–	+
4	Normal	95% ICS	Normal	Not studied	+	+
5	Ipsilateral Lacune	95% ICS, Absent A-1	Normal	Normal	–	+
6	Normal	95% ICS, Hypoplastic A-1	Normal	Normal	+	+
7	Normal	95% ICS 50% Syphon stenosis	50% ICS 50% Syphon stenosis	Not studied	?	+
8(i)	Not done	95% ICS	40% ICS with ulceration	Normal	–	–
9	Normal	ICO	Normal	Normal	?	+
10	Small Cortical Infarct	ICO	Normal	Normal	?	+
11	Contralateral Lacunae	ICO	50% ICS with ulceration	Ipsilateral VAO	+	–
12	Contralateral Infarct	ICO	ICO	Contralateral VAO	+	–
13	Normal	ICO	ICO	Normal	–	–
14	Bilateral Lacunae	ICO	ICO	Ipsilateral VAO	+	–
15(ii)	Ipsilateral Lacunae	ICO	95% ICS	Normal	–	–

*A-1: First segment of anterior cerebral artery; ACoA: anterior communicating artery; CT: computed tomography; ICA: internal carotid artery; ICS: internal carotid artery stenosis at its origin; ICO: internal carotid artery occlusion at its origin; OA: ophthalmic artery; VAS: vertebral artery stenosis; VAO: vertebral artery occlusion; V-B: vertebro-basilar system; (+): present; (-): absent; (?): can't be assessed because of technical limitations.

Subcortical structures and the cerebellum were not studied for the purposes of this report. Borderzone areas were identified on the PET image by correlation with the CT scan image produced with similar OM alignment. $_{15}$Positron Emission Tomography was performed within two weeks of the most recent event in 2 patients and at 2 months or greater in the others, including the patients with lacunes or small cortical strokes. One patient was studied twice, initially when she had an asymptomatic right ICS and subsequently when she had a silent right ICO. All patients were asymptomatic at the time of the study. Thus, since all patients were studied while asymptomatic, many at a time far removed from the most recent ischemic event, and since CT scans were normal or showed only minor areas of focal atrophy (the one hemisphere with a large infarct being excluded from the study), our study addresses not the effect of acute focal ischemia but the chronic effects of severe carotid disease on normal or near normal brain within the limits of CT scanning. Results obtained in the patient group, in each vascular territory, were compared using Student's t-test to those obtained in 6 elderly (mean age: 64.8) volunteers with unremarkable medical histories and normal general physical and neurological examinations. Individual patient values are considered significantly different from the control values if they fall beyond 2 standard deviations of the control mean.

Results

Carotid Stenosis Group

The mean CBF and CBF/CBV values were significantly diminished ($p<.025$) in the anterior borderzone region ipsilateral to the carotid stenosis (Figure 1). Individual CBF/CBV values in the anterior borderzone of the 3 patients with 80% ICS ranged from 8.9 to 14.4 (mean ± SD = 10.8 ± 3.2) while those of the 5 patients with 95% ICS ranged from 8.2 to 9.6 (mean ± SD = 8.9 ± 0.6). The mean OEF value was elevated and the mean $CMRO_2$ was low in the anterior borderzone but these changes, compared to control values, failed to achieve statistical significance. Similar changes were observed in the contralateral anterior borderzone. There was no significant difference between any of the other parameters measured in this patient group, in other vascular territories, when compared to the control values.

Carotid Occlusion Group

a) Symptomatic side

The mean CBF and CBF/CBV values were significantly decreased ($p<.005$) in the anterior borderzone and MCA territory ipsilateral to the symptomatic carotid occlusion. The CBV was also significantly elevated ($p<.025$) in the MCA territory. These changes were matched by significant oxygen hypometabolism ($p<.025$) (Figure 2). Comparisons between the 2 patients with unilateral ICO and the 5 patients with bilateral ICOs or ICO and contralateral ICS are difficult because of the small number of patients in the former group. Nonetheless, patients with bilateral carotid disease had more pronounced decreases in $CMRO_2$ in the symptomatic MCA distribution than those with unilateral ICO (mean ± SD = 109 ± 13 µmol/100g/min versus 125 ± 18) with similar CBF/CBV ratios (6.2 ± 1.5 versus 6.4 ± 1.4). The $CMRO_2$ values were more severely depressed in the symptomatic anterior borderzone in patients with bilateral disease (88 ± 24 µmol/100g/min) than in patients with unilateral ICO (96 ± 32).

b) Asymptomatic side

The mean CBF/CBV value was significantly lower ($p<.025$) in the contralateral anterior borderzone where, although it did

Table 3: Hemodynamic and Metabolic Values in Patients with Severe Carotid Disease*

	Control Group	Carotid Stenosis		Carotid Occlusion	
		Stenotic Side	Contralateral Side	Symptomatic Side	Contralateral Side
Anterior Borderzone					
CBF	37.0 ± 7.0	26.0 ± 6.0[b]	28.0 ± 6.0[c]	25.0 ± 5.0[a]	31.0 ± 5.0
CBV	2.9 ± 0.4	2.8 ± 0.5	2.6 ± 0.4	4.0 ± 1.3	3.2 ± 1.1
CBF/CBV	12.9 ± 2.0	9.6 ± 2.0[b]	10.3 ± 1.7[c]	6.7 ± 2.0[a]	9.5 ± 1.9[b]
$CMRO_2$	152 ± 42	131.0 ± 36.0	121.0 ± 38.0	90.0 ± 23.0[c]	117.0 ± 27.0
OEF	0.45 ± 0.08	0.54 ± 0.09	0.51 ± 0.09	0.5 ± 0.11	0.47 ± 0.07
MCA Distribution					
CBF	39.0 ± 5.0	38.0 ± 9.0	41.0 ± 10.0	31.0 ± 6.0[c]	37.0 ± 7.0
CBV	3.9 ± 0.4	3.7 ± 0.6	3.7 ± 0.5	5.0 ± 1.2[b]	3.7 ± 0.9
CBF/CBV	10.0 ± 2.0	10.6 ± 3.4	10.2 ± 3.5	6.2 ± 1.3[a]	10.5 ± 1.8
$CMRO_2$	159.0 ± 13.0	167.0 ± 51.0	154.0 ± 32.0	113.0 ± 15.0[a]	138.0 ± 21.0
OEF	0.47 ± 0.07	0.46 ± 0.08	0.43 ± 0.07	0.49 ± 0.11	0.33 ± 0.03
Posterior Borderzone					
CBF	40.0 ± 6.0	36.0 ± 9.0	38.0 ± 11.0	33.0 ± 9.0	35.0 ± 7.0
CBV	3.3 ± 0.2	3.1 ± 0.8	1.9 ± 0.6	4.0 ± 1.1	2.7 ± 0.9
CBF/CBV	12.0 ± 2.0	11.9 ± 2.7	12.6 ± 2.7	8.3 ± 3.9	9.7 ± 3.1
$CMRO_2$	158.0 ± 19.0	167.0 ± 53.0	160.0 ± 32.0	116.0 ± 41.0	137.0 ± 36.0
OEF	0.44 ± 0.06	0.50 ± 0.07	0.51 ± 0.06	0.54 ± 0.11	0.49 ± 0.07

*Units: CBF = ml/100g/min.; CBV = ml/100g; CBF/CBV = 1/min; OEF = %; $CMRO_2$ = µmol/100g/min.
a: $p<.005$; b: $p<.025$; c: $p<.05$

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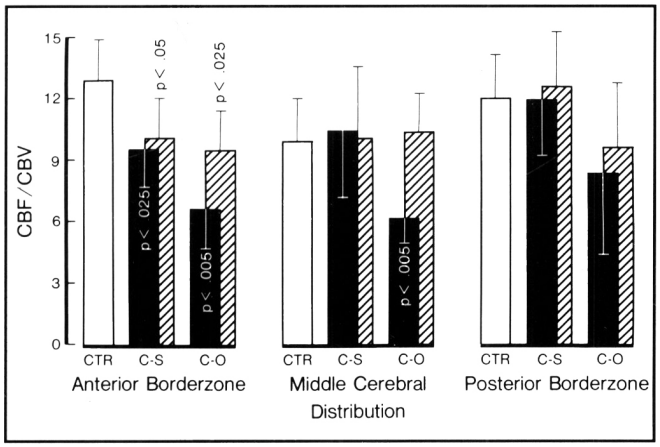

Figure 1 — Hemodynamic values (mean and standard deviation) in patients with carotid stenosis (C-S) and carotid occlusion (C-O) compared to the control group (CTR). Black bars correspond to the side ipsilateral to the stenosis or occlusion and striped bars to the contralateral side. The CBF/CBV ratio is significantly diminished, bilaterally, in the anterior borderzone in patients with carotid stenosis or carotid occlusion; and in the ipsilateral middle cerebral artery distribution in the group with carotid occlusion.

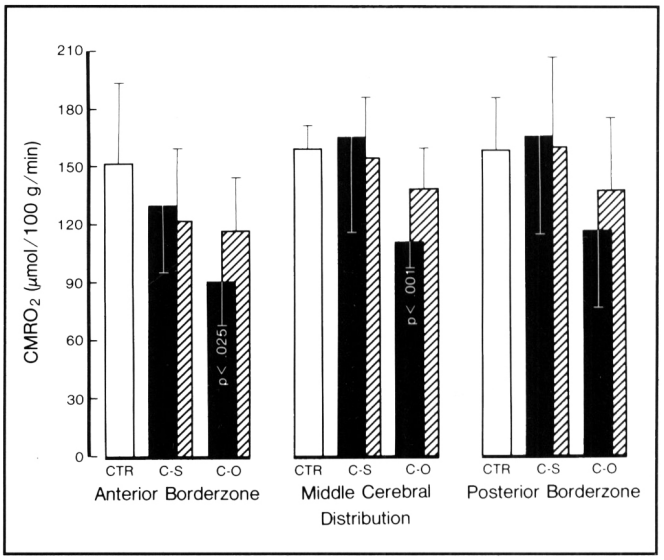

Figure 2 — Oxygen metabolic values (mean and standard deviation) in patients with carotid stenosis (C-S) and carotid occlusion (C-O) compared to the control group (CTR). Black bars indicate the side ipsilateral to the stenosis or occlusion and striped bars indicate the contralateral one. The cerebral metabolic rate of oxygen ($CMRO_2$) is significantly decreased in the ipsilateral anterior borderzone and middle cerebral artery distribution in the group of patients with carotid occlusion.

not achieve statistical significance, the mean $CMRO_2$ was the lowest of the 3 vascular territories studied. The CBF/CBV value (mean ± SD) of the 2 patients with unilateral ICO was 10.7 ± 0.6 in the anterior borderzone, while the corresponding value for patients with bilateral disease was 8.9 ± 2.1. Hemodynamic and metabolic parameters in other vascular territories were not significantly different from the control group.

Angiographic and PET Correlation

There was good correlation between the presence of ICS and changes in hemodynamic function in the anterior borderzone. When compared to the normal range of values in our laboratory, the CBF and CBF/CBV ratios were decreased in the anterior borderzone ipsilateral to the ICS in 6 and 7 patients, respectively. Although there was overlap between the values of patients with 80% and 95% ICS, there was greater variability in the former group, perhaps indicating a more variable effect of the lesser degree of stenosis. These changes were associated with diminished CBF and CBF/CBV values in the contralateral anterior borderzone in 5 patients. The contralateral hemodynamic changes may reflect diversion of blood from the opposite internal carotid artery system to the one supplied by the stenotic carotid artery via the anterior communicating complex, as was observed angiographically in all our patients with ICS.

Transiently symptomatic ICO was associated with widespread hemodynamic changes reflected by a diminished ipsilateral CBF/CBV ratio in all our patients. Changes in $CMRO_2$ paralleled those of the CBF/CBV ratio. Contrary to the correlation between the CBF/CBV ratio and $CMRO_2$ values, the OEF remained normal in all territories except for the occasional patient. The $CMRO_2$ was more severely depressed in patients with bilateral carotid disease than in those with unilateral ICO, indicating diminished collateral supply from the opposite ICA system. These metabolic changes were worse in the anterior borderzone, attesting to the vulnerability of this region to cerebral ischemia.

In the contralateral, asymptomatic hemisphere the mean CBF/CBV ratio was significantly decreased in the anterior borderzone where the mean $CMRO_2$ was the lowest of the three territories studied. Analysis of individual CBF/CBV values in this region reveals overlap between patients with unilateral ICO and those with bilateral carotid disease but nonetheless a lower value was obtained in the latter group.

Analysis of the patient whose stenotic carotid progressed to occlusion is especially informative. The initial CBF/CBV values in the anterior borderzone ipsilateral to the ICS was 8.2 and the $CMRO_2$ value was 96 μmol/100g/min. With ICO, her $CMRO_2$ value fell to 60 μmol/100g/min in the anterior borderzone and the mean hemispheric $CMRO_2$ value (average of the borderzone regions and MCA territory) fell from 101 ± 5 μmol/100g/min to 82 ± 19. During the same period of time the contralateral ICA went from a normal calibre to a stenosis of 90%. The corresponding mean hemispheric $CMRO_2$ values fell from 109 ± 10 μmol/100g/min to 84 ± 17, with a corresponding $CMRO_2$ value in the anterior borderzone of 78 μmol/100g/min.

It is noteworthy that hemodynamic and metabolic values stayed within the normal range, bilaterally, in the posterior borderzone regions in patients with ICO. This underscores the importance of vertebro-basilar collateral supply to the ICA distribution in patients with carotid occlusion.

Discussion

It is widely held that 80% or greater atherosclerotic narrowing of an internal carotid artery at its origin, or narrowing producing a residual lumen smaller than 2 mm, is of hemodynamic significance, producing diminished cerebral perfusion distal to

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the area of stenosis.[5] For this reason carotid endarterectomy is often performed in patients with carotid stenosis of this magnitude to prevent an eventual stroke. This assumption and course of action have recently been questioned because of the absence of epidemiological studies demonstrating a beneficial effect of carotid endarterectomy in this patient population.[16] Furthermore, a recent PET study has failed to demonstrate a correlation between the severity of carotid disease and cerebral hemodynamic status measured in the MCA territory.[6]

Positron Emission Tomography is well suited to study cerebral hemodynamic and metabolic functions in patients with severe carotid disease. It is a non-invasive technique that measures the activity of positron emitting isotopes as a function of their perfusion and metabolism within the brain in a tomographic fashion that allows measurements in all vascular territories. Using ^{15}O-labelled compounds it is possible to directly measure the CBF, CBV and OEF. From these measurements the CBF/CBV ratio and the $CMRO_2$ can be derived. PET, therefore, has been used to assess cerebral perfusion and metabolism and the activation of hemodynamic and metabolic compensatory mechanisms in patients with obstructive cerebrovascular disease, to study the effects of acute ischemia, to define hemodynamic and metabolic criteria for ischemia and tissue viability, and to assess the effects of cerebral revascularization.[6,7,9-12,18,20-25] Wise and co-workers first drew attention to the importance of a rising OEF, in the earliest phase of acute cerebral ischemia, as a possible indicator of preserved but threatened oxygen metabolism, and suggested that this tissue at risk might be rescued from eventual infarction by revascularization.[10] Baron and colleagues subsequently reported a fall in the OEF of 1 patient following extracranial to intracranial (EC-IC) bypass.[18] The same group, however, reported in a later study that the response of the OEF to EC-IC bypass is complex and variable.[11] Most groups studying the effects of ICO by PET have observed that the commonest finding is a low CBF/CBV ratio that is often matched by a low $CMRO_2$ value, but that an elevated OEF is an unusual occurrence.[9,20] Our data is therefore in keeping with that of others, indicating that ICO produces a rising CBV, lowered CBF/CBV ratio, a fall in $CMRO_2$ and a normal OEF. Four groups have assessed the effects of EC-IC bypass using PET scanning.[11,21,23,25] The overwhelming findings are of a post-operative fall in CBV (62% of cases) and rise in the CBF/CBV ration (94% of cases). These hemodynamic changes are only occasionally associated with an elevated post-operative $CMRO_2$ (11% of cases) which is more likely to fall or to remain unchanged post-operatively. These data indicate that once ICO occurs, even without an overt, clinically apparent stroke, a situation of irreversible oxygen hypometabolism prevails, one refractory to revascularization.

Recently, in a PET study limited to hemodynamic function in the MCA territory, Powers et al studied 11 patients with ICO and 8 patients with ICS greater than 66%.[6] Only 2 of the latter, however, had a stenosis of 80% or greater. They observed diminished CBF in 4 patients and reduced CPP in 8. They concluded that the presence of a "hemodynamically significant" carotid lesion, as demonstrated angiographically, is a poor indicator of the cerebral hemodynamic status. Their study, however, did not assess hemodynamic function in the anterior borderzone. Our data indicate that the anterior borderzone is a hemodynamically vulnerable region, and that severe ICS is associated with significantly decreased perfusion and hemodynamic reserve capacity in this area.[12] These hemodynamic changes are matched by a trend towards activation of metabolic compensatory mechanisms, as manifested by rising OEF, to maintain $CMRO_2$ in the low normal range. The borderzone, or watershed, regions between major cerebral arteries are susceptible to ischemia and infarction.[26] Cortical borderzone regions are located between the areas supplied by the ACA and MCA (the anterior borderzone), between the MCA and PCA (the posterior borderzone), and between the superior cerebellar and posterior inferior cerebellar arteries.[13,14,26] Deep, subcortical watershed regions exist between the lenticulostriate arteries and the superficial branches of the MCA in the region of the basal ganglia.[26] Bilateral anterior watershed infarction is common after profound systemic hypotension resulting from cardiac arrest and unilateral infarction occurs with ICS or ICO.[15,26-32] In a post-mortem study of borderzone infarction from atherosclerotic carotid disease, Romanul and Abramowicz observed patchy, older infarcts within the cortex of the anterior borderzone and more recent infarcts within the distribution of the ACA and MCA.[28] They concluded that infarction occurred first in the area where the most distal branches of these two arteries meet. Rodda observed that anterior borderzone infarction is associated with unilateral ICS and disease of the anterior circle of Willis or with bilateral ICA lesions.[29] These findings are similar to those observed in our ICS patients, 3 of whom had hypoplasia or aplasia of the first segment of the ipsilateral ACA and another who had stenosis of both carotid siphons. Similarly the anterior borderzones were more severely affected both hemodynamically and metabolically in patients with ICO than other vascular territories, and the more so in patients with bilateral carotid disease. Powers et al also observed an elevated CBV in the ipsilateral MCA territory of 7 of 9 patients with ICO.[6] We observed similar findings in the MCA territory in 6 of our 7 patients and also found a diminished CBF/CBV ratio in all. We further observed that these hemodynamic changes were associated with oxygen hypometabolism in all cases and that hemodynamic and metabolic changes are present beyond the MCA territory.

Carotid occlusion, even if it does not acutely produce a stroke, nonetheless has diffuse adverse effects on cerebral perfusion and metabolism. In this regard PET may be useful in identifying patients with altered hemodynamic function, especially in the anterior borderzone, who may be at risk for further ischemic events should stenosis progress to occlusion.

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