CEREBRAL HAEMODYNAMIC AND METABOLIC CHANGES IN CAROTID ARTERY OCCLUSION : A PET STUDY

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Introduction : The development of Regional Cerebral Blood Flow (CBF) and oxygen metabolism ($CMRO_2$) measurement by positron emission tomography has improved our understanding of the processes leading to cerebral ischemia in patients with internal carotid artery (ICA) occlusion. For example, a specific pattern of focal functional anomalies indicating persistant haemodynamic ischemia and reversible by extra-intracranial arterial by pass (EIAB) was demonstrated earlier (1-2). We report here our results in 37 patients with ICA occlusion studied by the quantitative oxygen 15 steady state technique.

Patients : The 37 patients (mean age 56,8 ± 10 years) were possible candidates for EIAB. In all patients ICA occlusion was proved by angiography. Contralateral angiography was available in 35 patients. Four patients had bilateral carotid occlusion, while the contralateral ICA showed haemodynamic stenosis (> 50% in diameter), mild stenosis, or a normal appearance in 11,5, and 15 patients, respectively. A stroke had occurred in 28 patients, related to the occluded territory, to the opposite carotid territory, and to both sides in 23,4, and 1 patients, respectively. In those patients, PET studies were done at least 3 weeks after the last neurological event (range 3 weeks - 9 years). The remaining 9 patients had isolated transient ischaemic attacks (TIA) related either to the occluded side (n=5) or to the opposite side (n=2), transient global amnesia (n=1) or a central retina artery thrombosis (n=1). One of the stroke patients had clinical features of a "haemodynamic dementia", 18 had various focal neurological signs and 18 had very mild or no deficit. In 8 patients, spontaneous neurological events occurred distal to the previously occluded carotid.

Methods : All patients were studied with the ^{15}O steady-state technique (3), eyes closed, at rest, with the ECAT II device. Two slices were studied 4 and 6 cm above the orbito-meatal plane (thickness slice is 19 mm and transverse resolution 16 mm). Published equations (4) were used to compute rCBF, regional oxygen extraction fraction (rOEF) and $rCMRO_2$ values from the $C^{15}O_2$ and $^{15}O_2$ scans. In two patients OEF and $CMRO_2$ data were not available.

Data analysis : Regional values were obtained from a set of 28 circular cortical 4 cm^2 regions of interest (ROI). After exclusion of the infarcted areas (based on CT scan data), 6 regional values were defined in each hemisphere, according to the brain arterial supply : two sylvian areas, MCA_1 from the lower slice and MCA_2 from the upper slice ; by pooling ROIs from both slices, values were obtained in the territories of the anterior cerebral artery (ACA) and the posterior cerebral artery (PCA), as well as in anterior (AW) and posterior (PW) watershed areas.

Two different analysis were performed : 1) Individual relative asymmetries related to the unoccluded side were compared to 95 % confidence limits from 27 control studies, 2) Mean regional absolute values of CBF, OEF and $CMRO_2$ were compared to normal values from 15 age-matched control subjects (56,1 ± 10 years), by analysis of variance combined to the Bonferroni method.

Results :

1) Asymmetries : three differents pattern were found in the sylvian areas distal to a occluded carotid : 1) a relative increase of OEF (i.e. the so-called "misery-perfusion syndrome" (1), 2) Matched CBF and $CMRO_2$ relative decrease; and 3) No asymmetry.

A relative increase of OEF was found in 15 of the 35 patients (43 %), always associated with a CBF decrease that was significant in 10/15 patients. In 7 of these 15 patients, a significant asymmetry of $CMRO_2$ was found. In 3 of those 7 patients, a marked relative (range 27%-53%) as well as absolute (range

0.62-0.90) OEF increase was found ; two of them had postocclusive events and the last one a progressive apragmatic state. In contrast, the 8 patients without significant $CMRO_2$ assymetry had only mild OEF increases (range 9-20%) and none of them had postocclusive ischaemic events.

A matched decrease in CBF and $CMRO_2$ was found in 5 patients (14%), while 11 patients (31 %) had no significant asymmetry in any parameter. The remaining 4 patients had either a OEF relative decrease (2 patients) or a pattern clearly indicating contralateral ischaemia.

Patients with post-occlusive events had no specific pattern of CBF or OEF, but had a significant higher incidence of $CMRO_2$ asymmetry ($p<0.01$). In the 27 patients where 4 axis angiography allowed assessment of the collateral supply of the territory distal to the occluded carotid, OEF increase was correlated with either "ophthalmic supply" or "Willisi supply" from a stenosed artery ($p<0.05$). Conversely, in "symmetrical" patients, supply was usually achieved through the circle of Willis from a patent artery. However, no relationship was found between extension of occlusive disease to both carotid arteries and asymmetry.

2) Absolute values (Table 1) : Compared to the control groups, a significant decrease of rCBF was found in all areas distal to the occluded ICA, except the ACA region. A similar trend was found with the $CMRO_2$ regional values. In the PCA area and in the unoccluded hemisphere no significant changes were found, although the regional values were slightly lower than controls.

As seen in Fig. 1, the decrease of CBF and $CMRO_2$ in the occluded hemisphere, did not depend on the prior occurrence of a stroke.

When patients with strictly unilateral carotid disease (n=15) where compared with the 15 patients with significant occlusive disease of contralateral ICA, a significantly lower OEF value was found in the former group, over the occluded hemisphere, despite similar CBF values. When compared to control values, the $CMRO_2$ decrease was significant only in the patients with extensive occlusive disease (see Fig. 2)

Discussion : Two differents types of pathophysiological informations were obtained from the present study. First, the study of asymmetries (an analysis which increases the sensitivity of the method in the detection of focal abnormalities) disclosed a high frequency (43 %) of misery-perfusion syndrome (i.e. relative decrease of CBF, with a relative increase of OEF) in the occluded side, while a truly matched focal decrease of CBF and $CMRO_2$ was rarely observed (14%). Second, as compared to controls, an absolute decrease of mean CBF and $CMRO_2$ values was found in the occluded territory (Table 1) which, on the basis of subgroups analysis, seemed to depend, in part, on extension of occlusive disease, but not on the presence of clinical stroke (fig. 1 and 2).

Asymmetries : A focal misery-perfusion syndrome is commonly interpreted as indicating a failure of CBF autoregulation (1, 5). In our population, this pattern was correlated with collateral supply through the ophthalmic artery or from a diseased contralateral ICA or vertebral artery. Thus, these types of collateral supply may have poor haemodynamic efficiency as also suggested previously (6). Interestingly, the patients showing marked misery-perfusion with simultaneous $CMRO_2$ decrease all had clinical evidence of haemodynamic ischemia. In one of these patients, an EIAB was performed and resulted in a complete reversal of these changes. In this patient, the $CMRO_2$ decrease was therefore truly ischemic, suggesting a state of "chronic ischemic penumbra".

On the other hand, a matched relative decrease of CBF and $CMRO_2$ distal to occlusion was found in five stroke patients. This lack of OEF increase indicates that the blood supply was not decreased with respect to the metabolic needs of the tissue. Since this pattern is usually unchanged after EIAB (7), partial neuronal loss leading to a primary decrease of $CMRO_2$ can been implicated (8), although a functional deafferentation of morphologically intact tissue cannot be excluded in these stroke patients (9).

Absolute values : We found a global decrease of CBF and $CMRO_2$ distal to the ICA occlusion. Again, this could reflect a partial neuronal loss or deactivation. However, our results do not support this view because this decrease in CBF and $CMRO_2$ was also observed in the patients without history of stroke (fig. 1). In addition, our study of EIAB patients showed a marked post-operative impro-

vement of CBF and $CMRO_2$, involving both cerebral hemispheres (7). This would be a strong argument against neuronal loss as the sole cause of this metabolic depression. Together with these facts, we observed that the $CMRO_2$ decrease was more prominent in patients with contralateral carotid obstructive disease (fig. 2), a population presumably having a very low cerebral perfusion pressure (10); thus, it would appear that chronic haemodynamic failure may by itself induce such metabolic depression.

There is no clear explanation for this phenomenon. However, it clearly was not concommitant with the usual pattern of ischemia, since the OEF in this group was not elevated. In fact, the OEF was unexpectedly lower in this group than in unilateral ICA disease patients, while the CBF was similar in both groups (Fig. 2). Lack of increase (actually a mild decrease) in the cerebral oxygen arteriovenous difference ($DA-VO_2$), was reported earlier in baboons with chronic fourvessel occlusion (11), and low $DAVO_2$ was found in some patients with ICA occlusion (12). Whatever the precise mechanisms by which haemodynamic failure leads to a decrease in $CMRO_2$ either involving the neuronal metabolism itself or the intrinsic process of oxygen diffusion, complex alterations in the flow - metabolism - pressure interrelationships must occurs. The clinical correlations of such mild but widespread metabolic depression are not immediately apparent, perhaps because they involve subtle neuropsychological changes.

It remains that, superimposed on this type of metabolic depression, a mild focal misery-perfusion (as defined by asymmetry analysis) was observed in 6 of the 15 patients with bilateral ICA occlusive disease. This suggests that those patients remain at risk for further haemodynamic cerebral ischemia.

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CBF ml/mn/100 ml	CONTROL n=15	52 ± 17	43 ± 11	41 ± 9	40 ± 9	41 ± 10	48 ± 13
	OCCLUDED n=39	36 ± 11**	31 ± 9**	35 ± 13	29 ± 9*	32 ± 9*	44 ± 13
	NON OCCLUDED n=33	45 ± 17	38 ± 11	39 ± 12	36 ± 13	37 ± 12	47 ± 15
OEF (0-1)	CONTROL n=15	.50 ± .10	.49 ± .10	.50 ± .10	.49 ± .08	.52 ± .10	.55 ± .11
	OCCLUDED n=39	.50 ± .11	.51 ± .10	.50 ± .11	.51 ± .12	.54 ± .11	.52 ± .10
	NON OCCLUDED n=31	.49 ± .09	.49 ± .08	.49 ± .09	.50 ± .10	.53 ± .10	.53 ± .09
$CMRO_2$ ml/mn/100 ml	CONTROL n=15	4.3 ± 1.2	3.5 ± .8	3.4 ± .8	3.2 ± .8	3.5 ± .9	4.4 ± 1.2
	OCCLUDED n=39	3.2 ± 1.0*	2.8 ± .9	3.1 ± 1.2	2.7 ± 1.0	3.0 ± .9	4.2 ± 1.4
	NON OCCLUDED n=31	3.9 ± 1.6	3.3 ± 1.1	3.3 ± 1.1	3.0 ± 1.0	3.5 ± 1.5	4.5 ± 1.7

TABLE 1 : Regional values in control subjects and in occluded and unoccluded hemispheres of patients. (mean ± sd) MCA1 : Lower sylvian area - MCA2 : Upper sylvian area - ACA : Anterior cerebral artery area - AW : Anterior watershed area - PW : Posterior watershed area - PCA : Posterior cerebral artery area.

** $p<.01$ (With respect to control group).

* $p<.05$

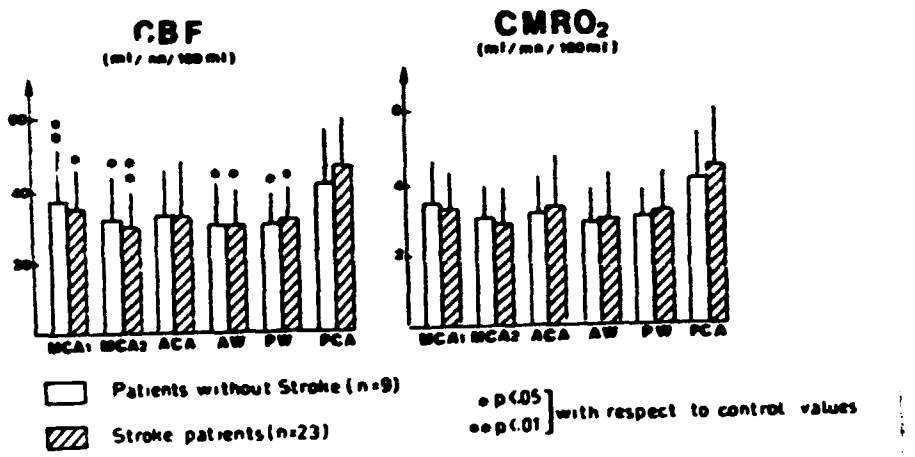

Fig. 1 : Regional values (mean ± sd) in the occluded hemisphere in patients with or without history of ipsilateral stroke (excluding the 5 patients with contralateral Stroke) - See table 1 for abbreviations -

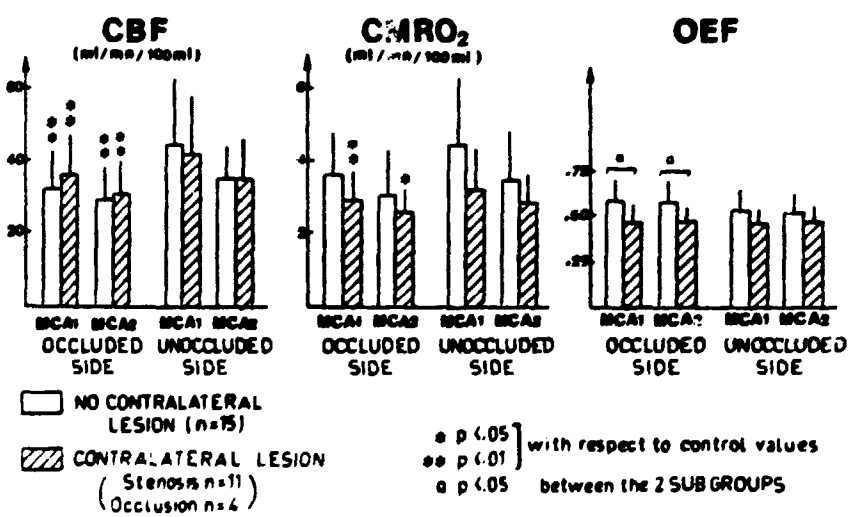

Fig. 2 : Effects of haemodynamic contralateral carotid lesions on regional values (mean ± sd) in MCA areas

ABSTRACT

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Using the positron emission tomography, we studied, with the O^{15} inhalation technique, the cerebral blood flow (CBF), the oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen ($CMRO_2$) in 37 patients with internal carotid artery (ICA) occlusion. In the territory of the occluded ICA, two pattern of focal anomaly have been observed : a CBF decrease with a "compensatory" OEF increase or a matched CBF and $CMRO_2$ decrease. On the other hand , as compared to age matched control values, $CMRO_2$ is significantly decreased in the territory of the occludedcarotid only in patients with extensive neck vessels obstructive disease.

Soumis à : "International Salzburg Conference on Cerebro vascular disease".

RESUME

CEREBRAL HAEMODYNAMIC AND METABOLIC CHANGES IN CAROTID ARTERY OCCLUSION : A PET STUDY

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Nous avons étudié en tomographie à émission de positons par la méthode à l'oxygène 15, le débit sanguin cérébral (DSC), le taux d'extraction de l'oxygène (EO_2) et la consommation d'oxygène cérébrale ($CMRO_2$) chez 37 patients atteints d'occlusion carotidienne. Dans le territoire de l'occlusion artérielle, deux types d'anomalies focales sont fréquemment observés : une diminution de DSC, avec augmentation "compensatrice" d'EO_2 et une diminution couplée de DSC et de $CMRO_2$. Par ailleurs, comparativement aux valeurs de témoins d'âge similaire, la $CMRO_2$ apparaît sélectivement diminuée en aval du territoire de l'occlusion, chez les patients dont les lésions obstructives artérielles sont bilatérales.

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