Non-invasive regional study of chronic cerebrovascular disorders using the oxygen-15 inhalation technique

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SUMMARY The regional cerebral metabolism-to-perfusion imbalance has been studied in the three main categories of cerebrovascular disorders in a chronic phase of the disease, using the non-invasive oxygen-15 inhalation technique. In patients presenting with a history of transient ischaemic attacks, regional defects in cerebral perfusion were greater than for the corresponding oxygen uptakes. Areas of relative ischaemia within which there was an enforced increase in the oxygen extraction ratio were highlighted. The reverse pattern was observed frequently in patients with brain infarcts arising from strokes, so indicating areas of relative luxury perfusion as is inferred from the reduction in the oxygen extraction ratio. In the multi-infarct dementia group of patients, there were parallel focal reductions in both flow and metabolism. The oxygen-15 inhalation technique is shown to be a unique tool in investigating cerebrovascular disorders because of its non-invasiveness and its ability to define regional metabolism-to-perfusion imbalance within the brain.

The clinical relevance of the acute phase of cerebrovascular disorders has led to extensive investigations into the modifications of cerebral blood flow (CBF), oxygen consumption (CMRO₂), intracranial pressure, and so on. A regional evaluation of these has been performed in some neurological centres. Patients with chronic cerebrovascular insufficiency have rarely been investigated in this way except when the disease has led to dementia (Simard *et al.*, 1971; Hachinski *et al.*, 1975). There exists, therefore, a large area of relatively unexplored pathophysiological events in the natural history of cerebrovascular insufficiency.

Metabolic studies in the chronic phase of cerebrovascular insufficiency have to date been confined to experimental models or to extreme clinical situations (Lassen *et al.*, 1957; Malmund *et al.*, 1971). The present report is concerned with illustrating the relationships between regional metabolic demand and blood supply in the chronic phase of cerebrovascular disorders. This has been

possible by making use of a non-invasive technique that provides a regional assessment of the brain's extraction of oxygen from the blood which is directly related to the cerebral tissues' aerobic glycolytic metabolism. The aim of this study was to determine whether, in the different phases of cerebrovascular insufficiency, the circulatory and metabolic defects are equally affected.

Patients and methods

The theory of the oxygen-15 inhalation technique (OIT) used for these investigations has been fully described by Jones *et al.* (1976), and its general application in the study of neurological disorders demonstrated by Lenzi *et al.* (1978). The OIT is a completely non-invasive approach that provides two brain scintigram images. The first image, obtained during the inhalation of oxygen-15, represents the distribution of the production of metabolic water within the brain—that is, the hemisphere nearest to the gamma-camera. The second image, obtained during the inhalation of oxygen-15 labelled carbon dioxide, represents the distribution of circulating water within the same cerebral regions. The two distributions can be

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obtained as numerical matrices, an analysis of which provides (a) a regional index of the glycolytic metabolic activity, called the Metabolic Ratio (MR), and (b) a regional index of the cerebral blood flow, called the Perfusion Ratio (PR). The ratio of MR to PR for the same cerebral region is an expression of the Oxygen Extraction Ratio (OER) of that region.

Thirty-one patients were investigated, each presenting with clinical evidence of cerebral ischaemia for a period of more than two months before the study. The patients were subdivided into three groups in accordance with their symptoms and with an accepted classification of cerebrovascular disorders (Marshall, 1976) *group 1*—transient ischaemic attacks (TIAs), without abnormal findings at the neurological examination

(*n*=11); *group 2*—brain infarcts (BIs), with abnormal findings at the neurological examination, but without dementia (*n*=11); and *group 3*—multi-infarct dementias (MIDs), with abnormal findings at the neurological examination, plus a multi-infarct dementia, that is, a dementia due to “the occurrence of multiple small or large cerebral infarcts”, as defined by Hachinski *et al.* (1974), (*n*=9).

Details of the individual patients are presented in Tables 1, 2, and 3. The severity of symptoms found at the neurological examination, the objective findings in the angiography and CAT scan are expressed in the Tables with an arbitrary, descriptive score comprising three levels: —=normal; ±=borderline; +=abnormal findings.

Table 1 Patients presenting with transient ischaemic attacks

Case	Sex	Age (yr)	Duration of disease (months)	Neurological examination	Cerebral territory affected	Angiography	CAT	OER	MR	PR
1	M	58	4	—	C	—	n	1.01	82	81
2	F	34	60	±	C	+	n	1.21	74	64
3	M	71	7	±	C	n	n	1.07	79	74
4	M	67	3	—	C	—	n	1.10	82	72
5	M	61	3	±	C	—	n	1.17	77	60
6	M	53	2	—	C	—	n	1.14	78	72
7	M	65	3	—	C	—	n	1.23	74	62
8	M	52	2	±	VB	—	—	1.18	87	78
9	M	72	12	—	C	n	n	1.10	79	73
10	F	46	12	±	C	+	n	1.01	72	71
11	F	46	2	—	VB	—	n	1.13	80	72
Mean values		56.8	10.0					1.12 ± 0.07	78.6 ± 4.1	70.8 ± 6.5

Examination score: —=normal; ±=borderline; +=abnormal findings (see methods); n=examination not performed; C=Carotid artery territory; VB=Vertebral artery territory.

Patient 2 presented a moya-moya syndrome, patient 10 a stenosis of the internal carotid artery.

Table 2 Patients presenting with brain infarcts (all in the carotid artery territory)

Case	Sex	Age (yr)	Duration of disease (months)	Neurological examination	Angiography	CAT	OER	MR	PR
1	F	60	6	+	—	n	0.73	63	83
2	M	60	2	+	n	+	0.85	56	63
3	M	62	24	+	+	n	0.68	57	70
4	F	44	2	+	+	+	0.86	64	73
5	M	70	48	+	+	n	0.90	69	77
6	F	48	18	+	—	—	0.93	68	77
7	M	56	2	+	—	n	0.93	77	83
8	M	56	48	+	n	n	0.94	71	73
9	M	65	36	+	+	n	0.95	77	78
10	F	69	6	+	—	n	0.87	69	81
11	M	52	2	+	—	n	0.87	69	81
Mean values		58.4	17.6				0.86 ± 0.09	67.3 ± 6.9	76.3 ± 6.1

Examination score as in Table 1.

Table 3 Patients presenting with multi-infarct dementia

Case	Sex	Age (yr)	Duration of disease (months)	Neurological examination	Angiography	CAT	OER	MR	PR
1	F	70	10	+	n	n	0.98	75	74
2	F	68	8	+	+	+	0.90	65	76
3	M	61	24	+	+	±	0.93	79	73
4	M	73	24	+	+	+	1.00	75	73
5	M	73	12	+	n	+	1.02	59	57
6	M	64	12	+	+	+	1.02	69	66
7*	F	32	48	+	+	n	0.90	68	75
				+	+	n	0.89	70	76
8	M	67	12	+	n	±	1.07	78	79
9	M	62	36	+	+	n	0.95	64	68
Mean values		63.3	20.7				0.97 ± 0.06	70.2 ± 6.5	71.7 ± 6.6

Examination score as in Table 1.
*Case 7 had both hemispheres studied.

Results

GROUP 1

The general finding in the TIA group was that there were larger regional defects in the circulating water distribution than in the corresponding metabolic water distribution. Figure 1 illustrates the typical example of a patient presenting with a seven month history of short attacks of motor aphasia. Neurological examination showed a

slight left parietal lobe impairment. The ^{99m}Tc brain scan was normal, as was the EEG. No other neuroradiological examinations were performed. The perfusion defect seen in Fig. 1 ($H_2^{15}O$ circ.) indicated relative ischaemia in the frontotemporal region which was not causing any neurological defect. The minimal size of the metabolic defect ($H_2^{15}O$ met.) was in good agreement with the present clinical condition of this patient. This imbalance between the metabolic and circulatory

Fig. 1 Left lateral views of the cerebral distributions of oxygen uptake ($H_2^{15}O$ met.) and circulation ($H_2^{15}O$ circ.) in a TIA patient. Metabolic, perfusion, and oxygen extraction ratios are shown for the identified frontotemporal lesion.

distributions was a constant finding throughout the TIA group (Table 1). The Metabolic and Perfusion Ratios of the lesions were obtained by expressing the average signal per unit area recorded within it as a ratio of the corresponding value contained in the cerebral region exhibiting maximal uptake. The rOER for the lesion was in turn obtained by dividing the MR by PR. For a normal population of 10 subjects with a mean age of 55 years, the values of these ratios when averaged between six anatomically definable regions of the brain (frontal, motor, parietal, occipital, temporal, and pontomesencephalic) were: $PR=85.1\pm1.6$; $MR=84.0\pm1.9$; $OER=1.00\pm0.03$.

Table 1 shows that only four patients had on OER within normal limits. In all others a relative reduction of circulatory activity was detected, leading to an increase of the OER. Statistical analysis (Table 4) proved that increase to be significant.

Table 4 Student's *t* test probability levels for the comparison between the four groups

	Normal	TIA	BI
TIA	< 0.1%		
BI	< 1%	< 0.1%	
MID	ns	< 0.1%	< 5%

GROUP 2

The brain infarct group showed all the patients to have large defects in the metabolic images which correlated well with the clinical findings except for those cases in which the "silent areas" of the brain were affected. In general, the degree of impairment of the oxygen uptake correlated with the severity of the clinical disability. The circulation within these areas was not so severely decreased, and in some instances a normal pattern was observed. Figure 2 shows an example of this imbalance in a patient who had experienced a sudden loss of vision in her right eye, with left hemiparesis and hypaesthesia six months before the OIT was performed. While vision had recovered completely within a few days, the other neurological defects showed only a slight improvement. Angiography had been carried out, and was reported to be normal. Table 2 shows quantitative data from this group of patients. Seven patients showed large metabolic defects, but only in four was a decrease in circulatory distribution detected and in these it was less severe than the metabolic defect. In only one patient (case 9) was the OER within normal limits. The mean OER for the lesions was significantly decreased, thus indicating an imbalance between metabolic demand and blood supply. Such a decrease in the distribution of metabolic activity when coupled with a normal

Fig. 2 Right lateral views of the cerebral distributions of oxygen uptake and circulation in a brain infarct patient. Metabolic, perfusion, and oxygen extraction ratios are shown for the identified lesion in the region of the middle cerebral artery.

or less impaired circulation indicates relative luxury perfusion.

GROUP 3

The patients with multi-infarct dementia showed, in general, the largest lesions in both metabolic and circulatory distributions.

Figure 3 represents an example of a patient with multi-infarct dementia. Although significant decreases in both MR and PR can be observed, the average OER was within normal limits. This indicates that the pathology tends to affect equally the neuronal metabolism and the tissue perfusion.

Figure 4 shows histograms of the average metabolic, perfusion, and oxygen extraction ratios ($\pm$ SE of the mean) as recorded within the detected lesion. Also shown are the values obtained in normal subjects when averaged over six cerebral regions. A statistical analysis of the OER within the three groups is presented in Table 4. In addition the analysis was performed on a normal population of similar age. This analysis confirmed that there were significant differences in the OER between the four populations. The exception was the multi-infarct dementia group which did not show an OER significantly different from the normal group.

Discussion

In the previous publications using the OIT (Jones *et al.*, 1976; Lenzi *et al.*, 1978) it has been demonstrated that, by matching the cerebral distributions of oxygen uptake (H_2^{15}O met.) and that of the circulating labelled water (H_2^{15}O circ.), it is possible to obtain a distribution of the cerebral OER. This ratio expresses the metabolism-to-blood flow relationships within the brain. The results presented in this study on chronic cerebrovascular insufficiency were largely in agreement with the corresponding clinical and neuroradiological data. In fact, the symptoms presented by the patients showed particularly close agreement with the regional defects demonstrated in the oxygen uptake distributions (H_2^{15}O met.)

In one-third of the patients, a computerised axial tomographic (CAT) investigation was performed, and this confirmed that the low H_2^{15}O metabolic uptake was associated with a loss of nervous tissue.

It may be relevant to underline that patients in the TIA group did not show any major metabolic defect. In contrast, the circulatory distribution was often severely affected, resulting in an increase in rOER. Only one patient in this group had a CAT

Fig. 3 Right lateral views of the cerebral distribution of oxygen uptake and circulation in a multi-infarct dementia patient. Metabolic, perfusion, and oxygen extraction ratios are shown for a common occipital lesion.

Fig. 4 Regional metabolic, perfusion, and oxygen extraction ratios (SE of the mean) shown for (a) the mean value for six cerebral areas as averaged within a normal population, and (b) the average value obtained in lesions identified within the brains of patients presenting with transient ischaemic attacks (TIA), brain infarct (BI), and multi-infarct dementia (MID).

examination, and this was reported as normal. Nine of the 11 patients had an angiographic study, and only two of these were reported as being abnormal—one had a stenosis of the internal carotid artery, with an otherwise intact intracranial circulation, and the other a *moya-moya* syndrome.

It is, therefore, possible to conclude that in this group there was a chronic reduction in rCBF without any consistently demonstrable anatomical defect of the cerebral arteries. This suggestion is in contrast to previous data which have indicated that in TIAs the focal abnormalities of rCBF disappear within four days (Skinhøj *et al.*, 1970). However, as Lassen and Skinhøj (1975) pointed out, the rCBF measurements may underestimate the relative frequency and extent of ischaemic foci. The clinical observation of repetitive similar TIAs in patients (as in the case presented in Fig. 1) contrasts with a complete restitution of normal

physiological conditions within the chronically "critical" cerebral region. Our data agree with the report of Rees *et al.* (1971) on the focal disturbances in CBF observed in patients with TIA studied eight to 90 days after the last clinical episode.

Patients in the brain infarct group showed the opposite situation to the TIAs, with clear-cut metabolic lesions that were closely related to the neurological impairment. Four of the eight cases had angiography and these were reported to be normal. Normal angiographic appearances have frequently been described in brain infarcts (Paulson *et al.*, 1970). This association between a preserved blood flow and a metabolic defect constitutes a chronic luxury perfusion syndrome. This condition of relative luxury perfusion must be distinguished from that of an absolute increase in blood flow which results from the acute metabolic acidosis after the stroke (Lassen, 1966). In agreement with Fieschi and Des Rosiers (1976), we observed "more pronounced focal abnormalities in cases where an occlusion of the middle cerebral artery or its branches could be demonstrated angiographically".

In only the multi-infarct dementia group was there a close association between the defects in the metabolic and circulatory distributions, and this was substantiated by the neuroradiological examination. In many patients of this group the areas showing defect were larger than those of defective circulation; and some ischaemic regions were also detected in patients belonging to this group.

In conclusion, a constant finding in our study was that the clinical picture of patients with chronic cerebrovascular disease showed a better correlation with the distribution of the metabolic than with the circulatory defects. The possibility of obtaining with a non-invasive, repeatable examination a sharp definition of the metabolic or circulatory defects in patients with chronic disease is relevant for the assessment of the evolution of the disease, and for the therapeutic approach.

The value of the rCBF assessment in chronic cerebrovascular disease, apart from TIAs, may be challenged on the basis of its apparently poor correlation with the actual pathology. This is supported by the results of other workers who have concentrated on neuronal metabolic activity (Paulson *et al.*, 1970).

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