Assessment of cerebral haemodynamic reserve: correlation between PET parameters and CO₂ reactivity measured by the intravenous ¹³³xenon injection technique

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SUMMARY Regional cerebral blood flow (CBF), oxygen utilisation, fractional oxygen extraction (OER) and cerebral blood volume (CBV) were measured by positron emission tomography (PET) in 21 patients with occlusive carotid artery disease. In the same patients, measurements of cerebral CO₂ reactivity were performed using the intravenous xenon-133 technique. A significant correlation was found in symptomatic hemispheres between the CBF/CBV ratio and CO₂ reactivity. Four patients had significant increases in OER and this was associated with a reduction in CBF/CBV ratio implying exhaustion of haemodynamic reserve. CO₂ reactivity was reduced below 1.5% mm Hg in all four cases with raised OER but only in two cases with normal OER. In patients with CO₂ reactivities above 1.5% mm Hg, OER was normal in all cases. It is concluded that measurements of CO₂ reactivity provide a satisfactory method for assessing cerebral haemodynamic reserve.

The international EC-IC bypass study recently showed that EC-IC bypass does not reduce the subsequent risk of stroke in patients with carotid artery occlusion.¹ The results of this well designed and conducted trial appear to provide convincing evidence against the further use of this procedure. Patients were selected for the study on the basis of clinical criteria and a description of the anatomy of the carotid arteries obtained by angiography.² However, some commentators have pointed out that there remains a possibility that the operation might be successful in preventing stroke if a subgroup of patients with impaired cerebral haemodynamics could be identified.^{3,4}

A quantitative assessment of the haemodynamic compensatory responses to a fall in perfusion pressure can be obtained by the combined measurement of regional cerebral blood flow (CBF), cerebral blood volume (CBV) and fractional oxygen extraction

(OER) with positron emission tomography (PET).^{5,6} There is an increase in CBV (as autoregulatory vasodilatation occurs) and a subsequent decline in CBF (when the limit of autoregulation is reached), consequently the relationship between the two physiological parameters expressed by the CBF/CBV ratio is a sensitive index of haemodynamic reserve. This reasoning is supported by observations on the relationship between the CBF/CBV ratio and the OER. The latter increases when the CBF/CBV ratio falls below a critical threshold value which appears to indicate the limit of autoregulation and haemodynamic reserve. These measurements allow quantification of the degree of haemodynamic compromise in patients with occlusive carotid artery disease but their routine application is limited by the scarcity and expense of PET facilities.

An alternative approach to assessing the degree of compensatory vasodilatation demonstrated as a low CBF/CBV ratio with PET rests on the observation that some patients with carotid occlusion have a reduced capacity to increase CBF in response to hypercapnia.⁷⁻⁹ This reduced CO₂ reactivity is explained by maximal or near maximal resting or base-

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line vasodilatation in response to reduced perfusion pressure. CBF can be measured by more readily available single photon techniques, particularly the xenon-133 clearance method. Because of the fast elimination of xenon-133 from the tissues, the method easily allows the sequential measurements of CBF during normocapnia and hypercapnia necessary for the determination of CO_2 reactivity.

We have compared these two ways of assessing haemodynamic reserve by performing both PET studies and measurements of CO_2 reactivity with the xenon-133 clearance method on the same day in a group of patients with occlusive carotid artery disease. Our aim was to establish whether a readily available clinical test could be calibrated and validated against direct measurements of haemodynamic reserve with PET.

Patients and methods

Patients

Twenty-one patients with arteriosclerotic carotid artery disease were studied. Mean age was 61.9 years (SD 11.0 years). The extent of carotid artery disease was demonstrated by angiography in 19 patients. Two patients underwent Doppler examination only. Sixteen patients had unilateral occlusion of the internal or common carotid artery, six with significant contralateral stenosis (> 50%). Three subjects had bilateral occlusion of the internal carotid artery; of those three, two had previously undergone EC-IC bypass surgery on one side. One patient had unilateral and one bilateral high grade stenosis of the internal carotid artery. Clinically, six patients presented with a history of previous stroke and two patients with a history of previous transient ischaemic attacks (TIAs) but all had not had any symptoms for at least 2 months. Six patients who had had TIAs with symptoms appropriate to the carotid circulation on the side of the occlusion within 2 months prior to the study were classified as having continuing symptoms. Three patients had experienced symptoms consistent with ischaemia in the vertebrobasilar territory. Four patients were asymptomatic. In these patients, carotid artery disease had been established during the course of investigations for cardiac or peripheral vascular disease. One patient with continuing symptoms showed a clinical feature suggesting reduced perfusion pressure. He suffered from focal seizures associated with change of posture.

The study was approved by the Research Ethics Committee of the Royal Postgraduate Medical School, Hammersmith Hospital and the National Hospital, Queen Square. Permission for the use of radioisotopes was given by the UK Administration of Radioactive Substances Advisory Committee. Patients' informed consent was obtained prior to each study.

Methods

(1) *Positron emission tomography* Regional cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilisation (CMRO_2) and cerebral blood volume (CBV) were measured by positron emission tomography, using the

oxygen-15 steady state inhalation technique¹⁰ and the carbon-11 carboxy-haemoglobin technique.^{11 12} Two separate emission scans were carried out during continuous inhalation of oxygen-15 labelled carbon dioxide and molecular oxygen respectively for the measurement of CBF and OER. A third emission scan was performed after bolus inhalation of carbon-11 labelled carbon monoxide for the measurement of CBV. During the scans, serial blood samples were taken via a fine gauge radial artery cannula to measure arterial isotope activity, arterial oxygen content (O_2C) and arterial pCO_2 . Oxygen utilisation was calculated from the relationship $\text{CMRO}_2 = \text{CBF} \times \text{OER} \times \text{O}_2\text{C}$. The CBV provided physiological information and was also used to correct the OER measurement for the signal arising from non-extracted haemoglobin-bound oxygen-15.¹³ The scans were performed using an ECAT-II (EG & G Ortec) PET scanner with a spatial resolution of $16.7 \times 16.7 \times 16$ mm at full width half maximum.¹⁴ Emission scans were corrected for the effects of tissue attenuation by corresponding transmission scans obtained with an external $^{68}\text{Ge}/^{68}\text{Ga}$ ring source.¹⁰ Data were collected from two transaxial planes 4.5 and 6.5 cm above and parallel to the orbitomeatal line in which apart from the posterior regions the cortical blood supply arises from the carotid arteries.

Data analysis from the physiological images was performed using an objective cortical plot technique previously described for the analysis of data from patients with acute and chronic cerebrovascular disease.^{5 15} Values were obtained from a strip of 12 contiguous rectangular blocks of tissue of size 7.5×15 mm, corresponding to the superficial distribution of the middle cerebral artery in each hemisphere. The reported values were obtained by calculating the mean from both tomographic planes in each patient. Areas of grossly infarcted tissue, clearly delineated on PET-images and CT-scans, were present in 11 of the patients and were excluded from the regions of analysis.

(2) *Measurement of CO_2 reactivity* CBF measurements for the determination of CO_2 reactivity were performed using a noninvasive intravenous xenon-133 clearance technique.¹⁶ A bolus of approximately 7 mCi of xenon-133 dissolved in saline was injected intravenously and the clearance of the isotope from the brain monitored by six external 25 mm diameter scintillation detectors. The concentration of xenon-133 in the expired air was monitored with a seventh detector and the end-tidal levels were used to estimate recirculating arterial xenon-133 concentrations. Regional CBF values for each detector were derived from a one minute initial slope analysis of the clearance curves. Arterial pCO_2 was estimated from the mean end tidal concentration of CO_2 in expired air, monitored throughout the procedure by a Datex CD300 infrared capnograph.

Each patient had two CBF measurements within 2 hours. Measurements were separated by at least 45 minutes to allow for complete elimination of the first dose of xenon-133. The first CBF measurement was performed with the patient breathing room air (normocapnia), the second with the patient breathing 5% CO_2 in air (hypercapnia). Inhalation of CO_2 was started at least 2 minutes prior to the beginning of the second CBF measurement to allow for equilibration and it was continued at the same concentration throughout the measurement. This led to an average increase in pCO_2 of 11, SD 2 mm Hg (range 9–16 mm Hg) between the two mea-

surements.

Hemispheric CBF values were calculated as the mean of the initial flow values from the three detectors on each side placed over frontal, fronto-parietal and temporo-parietal regions. Hemispheric CO₂ reactivity was calculated as the percentage rise in CBF above normocapnic values per mm Hg increase in pCO₂.

PET studies and measurements of CO₂ reactivity were usually performed on the same day except in two patients where technical failures delayed the second investigation for 1 and 2 days. There was no significant difference in blood pressure between the two studies (paired *t* tests). Arterial pCO₂ levels during the baseline xenon measurement (37.5 SD 2.6 mm Hg) were significantly lower than during the PET study (39.5, SD 3.3 mm Hg; *p* < 0.01).

Because the two cerebral hemispheres are not haemodynamically independent, statistical analysis (using Student's *t* test) was confined to the hemisphere from which the patients' clinical symptoms had arisen or, in the case of the asymptomatic patients and the patients with symptoms of vertebrobasilar ischaemia, to the hemisphere with the greater degree of occlusive disease.

Results

Figure 1 shows the relationship between CBF/CBV ratio (measured with PET) and CO₂ reactivity (measured with the xenon-133 intravenous injection method) for the symptomatic hemispheres of the 21 patients. There is a significant linear relationship between the two variables (*r* = 0.573; *p* < 0.01).

Figure 2 gives a plot of the CBF/CBV ratio against the oxygen extraction ratio and fig 3 shows the corresponding plot of CO₂ reactivity against OER. These

Fig 2 Relation between CBF/CBV ratio and oxygen extraction ratio in the symptomatic middle cerebral artery territories of 21 patients. Normal range of OER is 0.29–0.48.

data can be looked at in two different ways. Linear relationships are apparent to the eye and are statistically significant (*r* = 0.575, *p* < 0.01 in fig 2; *r* = 0.573, *p* < 0.01 in fig 3). However, there also seems to be a stepwise response, CBF/CBV ratios and CO₂ reactivities below a critical value being associated with abnormal OERs (age-matched normal OER range in patients' age group in our laboratory 0.29–0.48). Four of the 21 patients had mildly raised OERs between 0.50 and 0.56 which suggests an exhausted hae-

Fig 1 Relationship between CBF/CBV ratio measured by PET and CO₂ reactivity determined with the xenon-133 injection technique in 21 patients with carotid occlusive disease (*r* = 0.573; *p* < 0.01). CBF = cerebral blood flow; CBV = cerebral blood volume.

Fig 3 Relation between CO₂ reactivity and oxygen extraction ratio in the symptomatic hemisphere of 21 patients with occlusive carotid artery disease. Normal range of OER is 0.29–0.48.

mododynamic reserve and a decreased oxygen carriage reserve. CBF/CBV values in these four cases were below 7.0 (range 2.9–6.9). A stepwise increase in OER with diminishing CBF/CBV ratio was more strikingly demonstrated in a previous study from our laboratory which also included normal controls⁵ though recalculation of the data also shows a significant linear relationship ($r = 0.559$, $p < 0.001$). The apparent linearity results from the relatively small number of patients with elevated OERs in both the current and the previous data set. Also, increases in OER are only slight to moderate, since major rises mainly occur in situations of acute ischaemia.¹⁵

For CO₂ reactivity, a cut-off point of 1.5%/mm Hg appeared to separate the severely compromised cases: of the six patients with CO₂ reactivities below 1.5%/mm Hg, four had elevated OERs. All patients with CO₂ reactivities above 1.5%/mm Hg had normal OERs. Error estimation using the “leaving-one-out method”¹⁷ gives a misclassification rate of 14% for this threshold value in relation to definitely abnormal OERs. The point furthest on the left (CO₂ reactivity –0.7%/mm Hg) represents a patient with a difference in OER of 0.04 between the two hemispheres (0.48 on occluded side, 0.44 on contralateral stenosed side). Such an asymmetry is very suggestive of impairment of oxygen carriage reserve on the occluded side, although the absolute value of OER still lay in the range found in normal subjects.

The six patients with CO₂ reactivities below 1.5%/mm Hg were amongst those with the most severe occlusive disease demonstrated angiographically; four had unilateral occlusion with a contralateral stenosis of more than 50%, one was the patient with bilateral occlusions and no previous EC-IC bypass surgery. None of the six patients was asymptomatic. Three had had previous stroke or TIA, two belonged to the group of patients with continuing symptoms and one had presented with symptoms of vertebrobasilar ischaemia. One of the patients with continuing symptoms and reduced CO₂ reactivity was the patient with clinical features of a critical haemodynamic state.

Discussion

Previous studies of cerebral haemodynamics and oxygen metabolism using PET have shown that only a proportion of patients with occlusive carotid artery disease is haemodynamically compromised; in the majority of patients, cerebral blood flow is adequate for the tissue's metabolic demands though it may be reduced in absolute terms.^{5 18} In this study, almost 20% of patients had increased cerebral oxygen extraction fractions compensating for an inappropriately reduced blood supply. In agreement with a previous

study,⁵ low CBF/CBV ratios in these patients suggested an exhausted cerebral circulatory reserve. Theoretically, patients with haemodynamic compromise who cannot be reliably distinguished clinically, should be identifiable. They may constitute a pathophysiological homogeneous group of patients in which the effects of revascularising surgery could be assessed.

The measurement of regional OER can only be achieved by PET and hence is restricted to small numbers of patients. CBF/CBV ratios can be determined with single photon emitting isotopes and gamma scanning but quantification of these methods is difficult. The studies published to date have reported hemispheric ratios of radioactivity rather than absolute values of the physiological variables^{19 20} an approach which will overlook bilaterally compromised hemispheres.

Assessment of the capacity to increase cerebral blood flow in response to vasodilators such as carbon dioxide or acetazolamide is an alternative way of measuring cerebral circulatory reserve.^{7–9 21} Such a “physiological stress test” has several advantages. The two separate measurements are made with one technique. The relevant information is a change of flow following an intervention, thus patients serve as their own controls. Problems inherent in the regional quantification of resting flow levels, such as “cross-talk” from the opposite hemisphere and “look through” of low flow areas, with the xenon washout methods, have relatively little effect on the measurement of CO₂ reactivity.

Another approach for assessing cerebral vascular reserve uses transcranial Doppler to measure middle cerebral artery blood flow velocity and its response to hypercapnia.²² CO₂ reactivity was found to be significantly lower in middle cerebral arteries above a carotid occlusion than in those above a patent carotid artery. A good correlation between CO₂ reactivity measured by xenon-133 flow measurements and doppler middle cerebral artery flow velocity changes was shown.²³

Our study validates and confirms the usefulness of measuring CO₂ reactivity to assess cerebral haemodynamic reserve. As expected from basic pathophysiological considerations, the capacity to vasodilate in response to inhaled CO₂ decreased as blood volume rose in relation to the prevailing cerebral blood flow and a significant correlation was obtained between CO₂ reactivity and CBF/CBV ratio. The scatter around the line can be attributed to the use of three tracer techniques (C¹⁵O₂, ¹¹CO and ¹³³Xe), four measurements and two different ways of analysis. However, more important seems the demonstration of a clear association between reduced CO₂ reactivity and raised OER. All patients with impaired oxygen

carriage reserve had a CO₂ reactivity below a threshold value of 1.5%/mm Hg. Only one patient with clearly normal OER had a CO₂ reactivity below this threshold and all those with values above had appropriately normal OER. This is consistent with the finding of a previous study that the majority of patients with apparently haemodynamic transient ischaemic attacks had reactivity values of less than 1.5%/mm Hg.⁹

PET studies following extracranial-intracranial bypass surgery have demonstrated an increase in blood flow and a fall of preoperatively raised oxygen extraction ratios to normal levels in a small number of patients.^{18,24–26} In one of these studies, the more frequent finding was that of a postoperative reduction in CBV and a rise in the CBF/CBV ratio²⁶ suggesting improvement of haemodynamic reserve. Analogously, the CBF response to CO₂^{27,28} and acetazolamide²¹ has also been found to increase after bypass surgery although resting flow levels changed very little.

It now seems that adequate techniques for assessing cerebral haemodynamic reserve are available. In our study, as in others, the most haemodynamically compromised patients had the most severe angiographic findings, usually with bilateral pathology.²⁹ According to the international EC-IC bypass study, these patients may also carry the highest risk of peri-operative stroke.¹ Such patients should therefore only be subjected to surgery if a clear indication exists. The presence of impaired haemodynamic reserve may be such an indication. Whether improvements in circulatory reserve do indeed reduce the risk of subsequent stroke needs to be assessed by a controlled trial to which patients are recruited on the basis of physiological measurements.

References

- 1 The EC/IC bypass study group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischaemic stroke: results of an international randomised trial. *N Engl J Med* 1985;313:1191–200.
- 2 The EC/IC bypass study group. The International Cooperative Study of Extracranial/Intracranial Arterial Anastomosis (EC/IC bypass study): methodology and entry characteristics. *Stroke* 1985;16:397–406.
- 3 Plum F. Extracranial-intracranial arterial bypass and cerebral vascular disease. *N Engl J Med* 1985;313:1211–23.
- 4 Editorial: Extracranial to intracranial bypass and the prevention of stroke. *Lancet* 1985;ii:1401–2.
- 5 Gibbs JM, Wise RJS, Leenders KL, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. *Lancet* 1984;i:310–4.
- 6 Gibbs JM, Wise RJ, Leenders KL, Herold S, Frackowiak RJS, Jones T. Cerebral haemodynamics in occlusive carotid-artery disease. *Lancet* 1985;i:933–4.
- 7 Norrving B, Nilsson B, Risberg J. rCBF in patients with carotid occlusion. Resting and hypercapnic flow related to collateral pattern. *Stroke* 1982;13:155–62.
- 8 Bullock R, Mendelow AD, Bone I, Patterson J, Macleod WN, Allardice G. Cerebral blood flow and CO₂ responsiveness as an indicator of collateral reserve capacity in patients with carotid arterial disease. *Br J Surg* 1985;72:348–51.
- 9 Brown MM, Wade JPH, Bishop CCR, Ross Russell RW. Reactivity of the cerebral circulation in patients with carotid occlusion. *J Neurol Neurosurg Psychiatry* 1986;79:899–901.
- 10 Frackowiak RJS, Lenzi GL, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ¹⁵O and positron emission tomography: theory, procedure and normal values. *J Comput Assist Tomogr* 1980;4:427–36.
- 11 Phelps ME, Huang SC, Hoffman EJ, Kuhl DE. Validation of tomographic measurement of cerebral blood volume with C-11 labelled carboxyhaemoglobin. *J Nucl Med* 1979;20:328–34.
- 12 Lammertsma AA, Jones T. Correction for the presence of intravascular oxygen-15 in the steady state technique for measuring regional oxygen extraction ratio in the brain: 1. Description of the method. *J Cereb Blood Flow Metabol* 1983;3:416–24.
- 13 Lammertsma AA, Wise RJS, Heather JD *et al.* Correction for the presence of intravascular oxygen-15 in the steady-state technique for measuring regional oxygen extraction ratio in the brain: 2. Results in normal subjects and brain tumour and stroke patients. *J Cereb Blood Flow Metabol* 1983;3:425–31.
- 14 Williams CW, Crabtree ML, Burgiss SG. Design and performance characteristics of a positron emission computed axial tomograph—ECAT II. *IEEE Trans Nucl Sci NS* 1979;26:619–27.
- 15 Wise RJS, Bernardi S, Frackowiak RJS, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke: the transition from ischaemia to infarction as reflected in regional oxygen extraction. *Brain* 1983;106:197–222.
- 16 Thomas DJ, Zilkha E, Redmond S, *et al.* An intravenous ¹³³Xenon clearance technique for measuring cerebral blood flow. *J Neurol Sci* 1979;40:53–63.
- 17 Hand DJ. Recent advances in error rate estimation. *Pattern Recognition Letters* 1986;4:335–46.
- 18 Powers WJ, Martin WRW, Herscovitch P, Raichle ME, Grubb RL. Extracranial-intracranial bypass surgery: hemodynamic and metabolic effects. *Neurology* 1984;34:1168–74.
- 19 Knapp WH, von Kummer R, Kübler W. Imaging of cerebral blood flow-to-volume distribution using SPECT. *J Nucl Med* 1986;27:465–70.
- 20 Derlon JM, Bonvard G, Lechevalier B *et al.* Haemodynamic study of internal carotid artery stenosis and occlusions: value of coupled measurements of regional cerebral blood flow and regional cerebral blood volume. In: Meyer JS, Lechner H, Reivich M, Ott EO (eds). *Cerebral Vascular Disease 5. Proceedings of the World Federation of Neurology 12th International Salzburg Conference*. Amsterdam: Excerpta Medica 1985;170–176.
- 21 Vorstrup S, Brun B, Lassen NA. Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke* 1986;17:1291–8.
- 22 Bishop CCR, Powell S, Insall M, Rutt D, Browse NL. The effect of internal carotid artery occlusion on middle cerebral artery blood flow at rest and in response to hypercapnia. *Lancet* 1986;i:710–2.
- 23 Bishop CCR, Powell S, Rutt D, Browse NL. Transaxial doppler measurement of middle cerebral artery blood flow velocity: a validation study. *Stroke* 1986;17:913–5.
- 24 Baron JC, Boussier MG, Guillard A, Comar D, Castaigne P. Reversal of focal “misery-perfusion syndrome” by extra intracranial bypass in haemodynamic cerebral ischemia. *Stroke* 1981;12:454–9.

- 25 Samson Y, Baron JC, Bousser MG *et al.* Effects of extra-intracranial arterial bypass on cerebral blood flow and oxygen metabolism in humans. *Stroke* 1985;**16**:609-16.
- 26 Gibbs JM, Wise RJS, Thomas DJ, Mansfield AO, Ross Russell RW. Cerebral haemodynamic changes after extracranial-intracranial bypass surgery. *J Neurol Neurosurg Psychiatry* 1987;**50**:140-50.
- 27 Halsey JH, Morawetz RB, Blauenstein UW. The haemodynamic effect of STA-MCA bypass. *Stroke* 1982;**13**:163-7.
- 28 Bishop CCR, Burnand KG, Brown MM, Ross Russell R, Browne NL. Reduced response of cerebral blood flow to hypercapnia is restored by EC-IC bypass. *Br J Surg* 1987;**74**:802-4.
- 29 Powers WJ, Press GA, Grubb RL, Gado M, Raichle ME. The effect of hemodynamically significant carotid artery disease on the hemodynamic status of the cerebral circulation. *Ann Intern Med* 1987;**106**:27-35.