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The clinical role of PET in cerebrovascular disease

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Abstract

In normal subjects cerebral oxygen metabolism and blood flow are closely coupled, both grey and white matter extracting about 40% of their arterial oxygen supply. During acute ischaemia blood flow falls and oxygen extraction rises to 100% so that cerebral metabolism becomes totally blood flow dependent. Once acute infarction has occurred both cerebral oxygen metabolism and arterial oxygen extraction fall to low levels, while blood flow often paradoxically rises – the state of luxury perfusion. Once luxury perfusion becomes established the use of pharmacological or surgical methods to increase cerebral blood flow is inappropriate. PET will measure regional cerebral metabolism and blood flow non-invasively in man. Using PET ischaemic tissue can be distinguished from infarcted tissue, and the presence of luxury perfusion can be confirmed. In this way strokes in evolution can be detected, and the use of revascularisation procedures rationalised.

Not only are regional cerebral metabolism and blood flow closely coupled, but blood volume is also coupled to blood flow. When > 60% stenosis of extracranial arteries occurs, reactive vasodilatation of the distal circulation with an increase in rCBV results in order to reduce vascular resistance. By monitoring rCBV with PET, haemodynamically compromised regions of brain can be detected. It has been shown that patients with local areas of raised rCBV due to carotid artery stenosis are at a higher risk of infarction. PET will identify such patients and follow the haemodynamic effects of endarterectomy or EC-IC bypass.

Finally PET can look at the distant functional effects of lacunar infarction. In this way more information about the functional anatomy of the brain can be obtained, and mechanisms of functional recovery from stroke can be monitored.

Keywords: Cerebravascular disease, PET.

1 The physiology of ischaemia

The blood supply assigned to the brain in order to provide for its metabolic requirements constitutes about 20% of the total cardiac output. Regional cerebral metabolism and blood flow are closely coupled under normal resting conditions, being high in peripheral cortical and central grey matter and lower in white matter. A consequence of this coupling is that the fraction of the arterial oxygen supply extracted regionally is uniform throughout the brain, being roughly 40% of the total supply for both grey and white matter [10]. There is, thus, a considerable oxygen reserve in the arterial supply to the brain. If cerebral perfusion falls due to a drop in cardiac output, or stenosis of carotid or vertebral arteries, then the fraction of the arterial oxygen supply extracted (rOER) can rise from its normal level of 40% up to a maximum level of 100% in order to preserve cerebral metabolism [22]. When the rOER reaches 100% the level of regional cerebral oxygen utilisation ($rCMRO_2$) becomes blood flow (rCBF) dependent, and a state of ischaemia exists.

Not only are regional cerebral metabolism and blood flow closely coupled under resting conditions in normal brain, but regional cerebral blood flow and blood volume are also coupled. The rCBF : rCBV ratio is roughly 10 min^{-1} in both grey and white matter, this ratio representing the "transit rate" of the cerebral blood supply and reflecting the resistance of the cerebral microvasculature. If a fall in cerebral perfusion occurs, cerebral blood flow is maintained initially by dilatation of the cerebral vasculature which reduces resistance. As a result rCBV rises and the rCBF : rCBV ratio falls. If the rCBV : rCBV ratio falls from its normal value of 10 min^{-1} to a level of 6 min^{-1}, vasodilatation of the microvasculature becomes maximal [5]. In this situation cerebral blood flow can no longer be maintained by further vasodilatation when cerebral perfusion pressure falls to lower levels.

It can be seen, therefore, that there are two homeostatic mechanisms for preserving levels of re-

gional cerebral metabolism in the presence of falls in cerebral perfusion pressure. Initially the brain uses up its vascular reserve to maintain cerebral blood flow by dilating its microvasculature and increasing the rCBV. Secondly, if the rCBF : rCBV ratio drops below a level of 6 min^{-1} and rCBF begins to fall, the brain uses up its oxygen reserve to compensate for the falling rCBF, arterial extraction rising from 40% towards 100% to preserve the level of $rCMRO_2$.

When brain tissue becomes ischaemic due to a focal or general fall in perfusion, oxidative phosphorylation fails. There is a far larger arterial glucose than oxygen reserve in the normal brain tissue, cerebral glucose extraction being only 10% of the arterial supply under resting conditions [2]. As a consequence ischaemic brain utilises the less efficient glycolytic pathway to generate ATP via lactic acid formation. This results in a local fall in pH [7]. Once ischaemia is established, failure to re-establish cerebral perfusion leads to irreversible infarction and cerebral oxygen metabolism and arterial oxygen extraction fall towards zero [22]. Initially the cerebral blood flow remains low, but within hours the circulation tends to re-establish spontaneously and "luxury perfusion" results, the rCBF far exceeding the metabolic requirements of the infarcted tissue [10]. At this point the pH of the infarcted tissue becomes alkaline [21]. After some weeks the state of luxury perfusion subsides, and the infarcted area becomes a gliotic scar with a low coupled $rCMRO_2$ and rCBF.

2 Measurements of regional cerebral function with PET

Positron emission tomography (PET) can be used to measure regional oxygen and glucose metabolism, blood flow, blood volume, pH, microvascular haematocrit, and brain barrier permeability in patients. The technique is relatively non-invasive, a suitable tracer tagged with a positron emitter being administered by inhalation or intravenously, and tomographic scans of regional cerebral activity being acquired [15]. By employing suitable mathematical models to describe tracer uptake kinetics quantitative images of regional cerebral function can be computed, current commercial scanners having a resolution of 3–8 mm. Table I details PET isotopes and tracers, and the cerebral functions for which they are appropriate.

Apart from ^{68}Ga, which can be obtained from a generator, the short-lived PET isotopes ^{15}O, ^{11}C, and ^{18}F all need to be prepared on-site from a cyclotron. This makes PET an expensive technique, and limits its general availability.

3 Assessment of pre-ischaemic extracranial artery disease with PET

A 60% or greater stenosis of a carotid artery is generally haemodynamically significant, resulting in a distal fall in cerebral perfusion pressure and the opening up of collateral circulations. Using PET, POWERS et al. [18] have shown that falls in

Table I. PET tracers and their application

Isotopes	Half-life	Tracer	Cerebral function
^{15}O	2 mins	$C^{15}O_2$, $H_2{}^{15}O$	Blood flow
		$C^{15}O$	Blood volume
^{11}C	20 mins	^{11}CO,	Blood volume and
		^{11}C-methylalbumin	haematocrit
		$^{11}CO_2$	pH
		^{11}C-dimethyloxazolidenedione	pH
		^{11}C-2-deoxyglucose	Glucose metabolism
^{18}F	110 mins	^{18}F-2-fluro-2-deoxyglucose	Glucose metabolism
		^{18}F-methane	Blood flow
^{68}Ga	68 mins	^{68}Ga-EDTA	Blood volume and
		^{68}Ga-transferrin	blood-brain barrier integrity

the rCBF : rCBV ratio, reflecting dilatation of the cerebral microcirculation in affected carotid territory, correlate well with both the degree of occlusive carotid disease and the presence of angiographically-demonstrated collateral circulations. Gibbs et al. [5] showed that subjects with unilaterally occluded carotid arteries had impaired vascular reserves but normal oxygen reserves, as evidenced by low rCBF : rCBV ratios and normal rOER's in territory distal to the affected carotid artery. Subjects with bilaterally occluded carotid arteries were in a far more dangerous situation, as both their vascular and oxygen reserves were impaired.

It would appear logical, on haemodynamic grounds, to revascularise patients with occlusive carotid artery disease and impaired vascular oxygen reserves. It has been shown, in a two year prospective study, that subjects with PET evidence of impaired vascular reserves have a higher stroke incidence than similar subjects with carotid artery disease, but normal rCBF : rCBV ratios [16]. There is little doubt that both carotid endarterectomies and extracranial-intracranial (EC-IC) bypass procedures, when performed on patients with critically stenosed or occlused carotid arteries, result in a satisfactory improvement in their cerebral haemodynamics [4, 6, 17, 20] (Figure 1). Anecdotally there is also an improvement in the patients' TIA frequency. Unfortunately those patients with an impaired oxygen reserve, who have most to gain from revascularisation, are most at risk of developing a peri-operative cerebral infarct [6]. There is clearly still a need for a controlled trial to examine whether revascularisation is beneficial clinically for patients with extracranial artery disease and impaired vascular reserves on functional imaging. A preliminary, non-controlled study, did not find any benefit from EC-IC bypass on stroke incidence in a group of 23 patients with impaired vascular and oxygen reserves [16].

4 PET and the ischaemic state

PET has been used to follow the evolution of cerebral ischaemia through to frank infarction [7, 11, 22] (Figures 2a, 2b). The rOER may be raised above its normal 40% level for weeks after the onset of ischaemia, but generally it falls to low levels within 48 hours of the ictus, indicating infarction has occurred. During the ischaemic phase rCBF is very low, and there is a coupled fall in

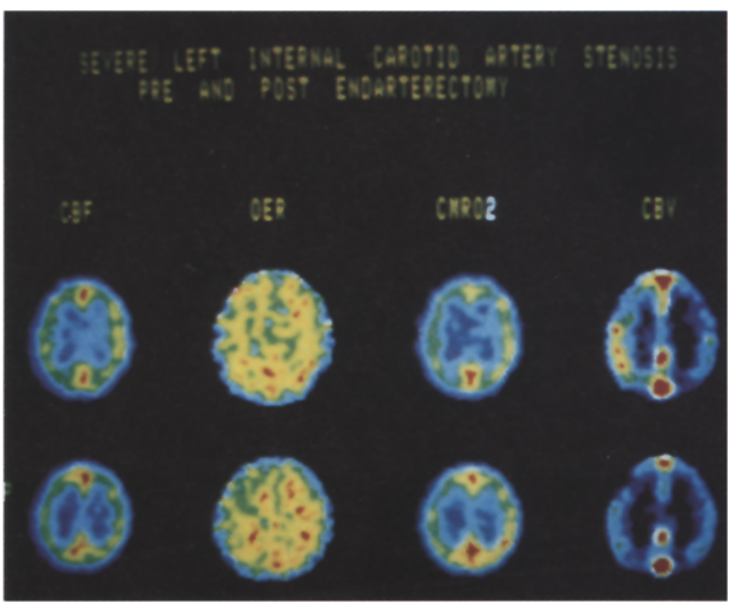
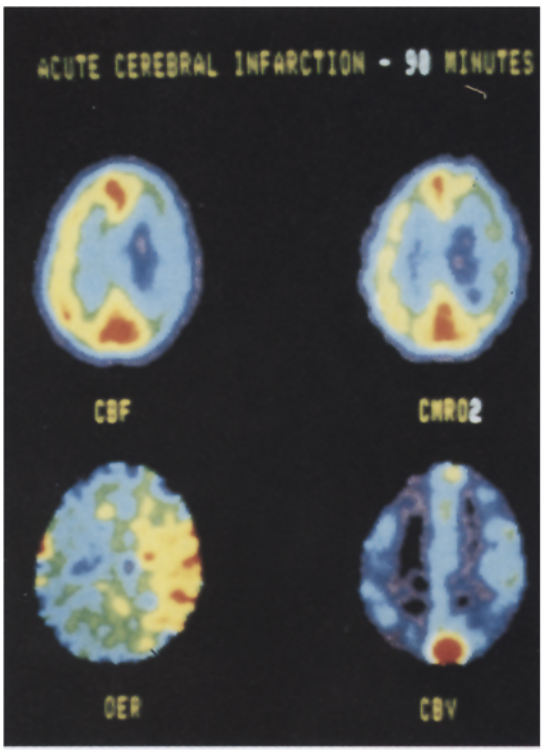


Figure 1. PET scans of regional cerebral blood flow, oxygen extraction fraction, oxygen utilisation, and blood volume in a patient with 90% stenosis of the left internal carotid, before and after endarterectomy. The pre-operative scans show focal vasodilatation in left carotid territory in the CBV image, which resolves post-operatively.



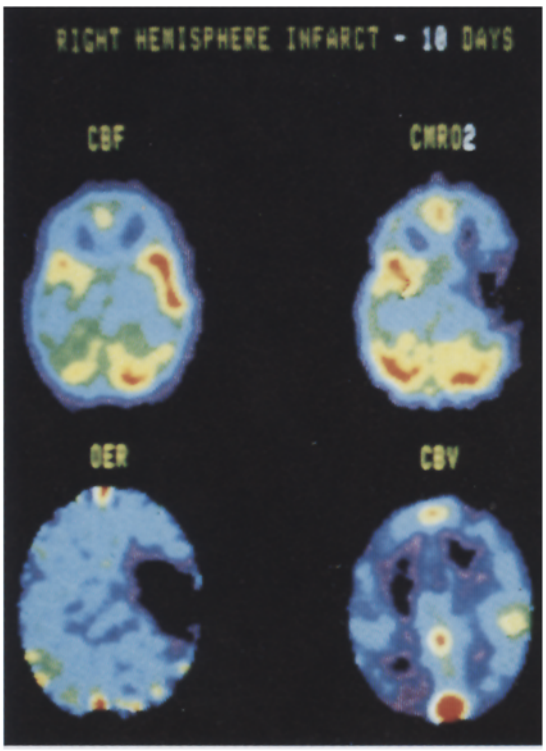


Figure 2a/2b. PET scans of a subject performed 90 minutes, and ten days, after a stroke in right middle cerebral artery territory. At 90 minutes ischaemia is present with a low rCBF and high rOER. By ten days frank infarction has occurred with luxury perfusion, rOER and $rCMRO_2$ being negligible while rCBF is high.

both regional cerebral oxygen and glucose metabolism, with accompanying acidosis [7]. Following infarction rCBF, pH, and rCMRGlu all tend to rise, and there is a state of luxury perfusion, the blood flow exceeding the metabolic demands of the infarcted tissue [7, 11]. For this reason it is inappropriate to follow rCBF alone when monitoring stroke recovery. It is also inappropriate to treat many stroke patients with vasodilators or haemodilution as luxury perfusion will already be present. Interestingly a recent controlled study has failed to find any benefit from haemodilution in stroke [13]. An important clinical application of PET is the study of stroke in evolution. If progressive infarction is occurring PET can determine whether rOER is focally elevated, that is on-going ischaemia is present. In such a situation acute revascularisation, either surgical or via thrombolysis, would be theoretically justified. To date surgical revascularisation and pharmacological procedures to increase perfusion in infarcts where a raised rOER is present have failed to improve cerebral metabolism, although rCBF has increased satisfactorily [4, 8, 22]. There have been no trials, however, on the effects of thrombolysis in such a situation.

5 The local and distant effects of infarction, and mechanism of stroke recovery

PET is a far more sensitive technique than CT for detecting both the presence and extent of infarction [9]. Levels of glucose metabolism in infarcts correlate well with the patients eventual outcome. Lacunar infarcts, and microvascular disease associated with hypertension and diabetes, can produce wide-ranging reductions in cerebral oxygen and glucose metabolism, explaining the frequent occurrence of dementia in such patients [19, 23]. Hemispheric infarcts produce a coupled fall in metabolism and blood flow in both cerebellar hemispheres, the contralateral cerebellar cortex being most affected [1, 11, 12]. This phenomenon has been termed "crossed cerebellar diaschisis",

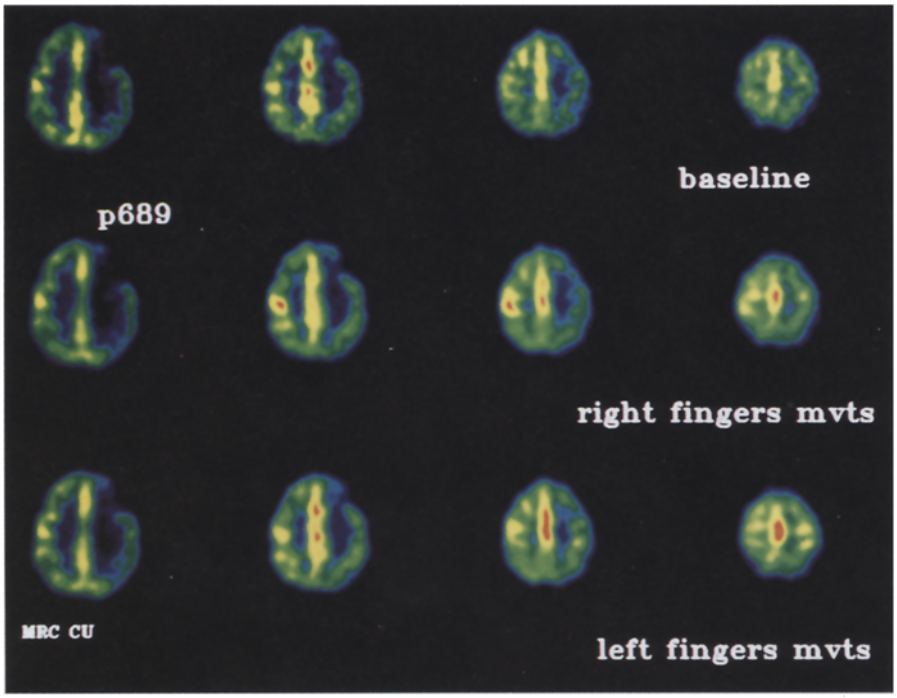


Figure 3. rCBF activation scans of a patient recovering from a right middle cerebral artery stroke. Right finger movement causes normal activation of the left contralateral sensorimotor cortex. Left finger movement causes abnormal activation of the left ipsilateral sensorimotor cortex.

and is likely to result from decreasing activity in the corticopontocerebellar efferent tracts. By studying the distant metabolic effects of localised lacunar infarcts, PET provides a means of examining the functional connections of the brain.

PET also provides a means of monitoring mechanisms of recovery from infarction. It is a frequently observed phenomenon that subjects with a pure motor hemiparesis, or hemisensory deficit, due to an internal capsule or thalamic lacunar infarct, make a full clinical recovery inspite of lack of resolution of the causative lesion on CT or MRI. Similarly patients with aphasia may recover inspite of residual structural damage to the dominant hemisphere. Simple motor actions of the arm and hand result in increases in rCBF in the contralateral sensorimotor cortex and supplementary motor area which can be detected with PET [14]. Such cerebral activation paradigms can be used to monitor mechanisms of stroke recovery. Preliminary data from our unit suggest that in patients who have made a clinical recovery from hemiparesis and aphasia the ipsilateral sensorimotor and speech cortex is taking over the normal role of the damaged pathways form the contralateral cortex [3] (Figure 3).

6 Conclusion

PET provides a non-invasive means of assessing the regional cerebral vascular and oxygen reserve where extracranial artery stenosis is present, and provides a rationale on haemodynamic grounds for revascularisation procedures such as endarterectomy or EC-IC bypass procedures. It is a more sensitive technique than CT for detecting lacunar CVA's, and can also show the distant effects of such strokes on regional cerebral function. Using cerebral activation paradigms, PET can also show that the brain recruits ipsilateral cortical structures to aid in recovery from strokes affecting cortical pathways contralateral to affected limbs. Finally PET enables the effects of controversial treatments, such as haemodilution and cerebrovasodilators, on the cerebral function of stroke patients to be monitored.

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