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PET in Cerebrovascular Disease

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SYNOPSIS

Investigation of the interplay between the cerebral circulation and brain cellular function is fundamental to understanding both the pathophysiology and treatment of stroke. Currently, PET is the only technique that provides accurate, quantitative in vivo regional measurements of both cerebral circulation and cellular metabolism in human subjects. We review normal human cerebral blood flow and metabolism and human PET studies of ischemic stroke, carotid artery disease, vascular dementia, intracerebral hemorrhage and aneurysmal subarachnoid hemorrhage and discuss how these studies have added to our understanding of the pathophysiology of human cerebrovascular disease.

Keywords

positron emission tomography; cerebrovascular disease; vascular dementia; cerebral blood flow; cerebral metabolism; cerebral hemodynamics

INTRODUCTION

Cerebrovascular disease results from a derangement of the normal relationship between the cerebral vasculature and the brain parenchyma. Thus, investigation of the interplay between the cerebral circulation and brain cellular function is fundamental to understanding both the pathophysiology and treatment of stroke. Currently, PET is the only technique that provides accurate, quantitative in vivo regional measurements of both cerebral circulation and cellular metabolism in human subjects. It is therefore well-suited for the study of human cerebrovascular disease, but its application to this end is not easy. An on-site cyclotron and radiochemistry facility is necessary due to the short half-lives of the commonly used radionuclides ¹⁵O (2 minutes) and ¹¹C (20 minutes). Quantitative physiological measurements require complex postprocessing and multiple arterial blood samples, although for some specific applications simple count-based images can be used.(1;2) Patients with acute stroke may be medically unstable, requiring a nurse or physician in attendance. For these reasons, PET is still a research tool for cerebrovascular disease. It has provided us with valuable new knowledge and insight into both ischemic and hemorrhagic stroke regarding pathophysiology, therapy and

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NOTE: None of the PET radiopharmaceuticals mentioned in this article is FDA-approved for use in patients with cerebrovascular disease.

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prognosis but has not entered the mainstream of clinical practice. In the future, the results of the Carotid Occlusion Surgery Study (www.cosstrial.org), an ongoing clinical trial in which PET is being used to determine eligibility, may demonstrate the clinical value of PET for the routine management of cerebrovascular disease.

NORMAL CEREBRAL HEMODYNAMICS AND ENERGY METABOLISM

Energy in the brain is used for the maintenance of membrane potentials, for the biosynthesis and transport of neurotransmitters, and for the biosynthesis and transport of cellular elements. Under normal circumstances, the brain relies on a continuous supply of oxygen and glucose from the blood for its functional and structural integrity.(3) Since storage of substrates for energy metabolism in the brain is minimal, it is exquisitely sensitive to even brief disturbances in this supply. Complete interruption of the cerebral circulation in cardiac arrest causes loss of consciousness within 10 seconds.(4)

Healthy young adults have an average whole brain cerebral blood flow (CBF) of approximately 46 mL 100g⁻¹ min⁻¹, cerebral metabolic rate of oxygen (CMRO₂) of 3.0 mL 100g⁻¹ min⁻¹ (134 μmol 100g⁻¹ min⁻¹), and cerebral metabolic rate of glucose (CMRglc) of 25 μmol 100g⁻¹ min⁻¹.(5–8) The CMRO₂/CMRglc molar ratio calculated from arterio-jugular venous differences is 5.4 rather than 6.0 as expected for complete oxidation because of the production of a small amount of lactate by glycolysis.(5;7;9) CBF in gray matter (80 mL 100g⁻¹ min⁻¹) is approximately four times higher than in white matter (20 mL 100g⁻¹ min⁻¹), but differences of this magnitude are not seen with PET due to partial volume effects.(10) Under normal physiological conditions, regional CBF is closely matched to the resting regional metabolic rate of the tissue.(11;12) As with CBF, CMRO₂ and CMRglc are higher in gray than white matter. Because of this relationship between regional flow and metabolism, the fraction of available glucose and oxygen extracted by the brain from the blood is uniform throughout the brain (Figure 1). The oxygen extraction fraction (OEF) is normally 30–40%, indicating that oxygen supply is 2–3 times greater than oxygen demand. The glucose extraction fraction (GEF) is normally about 10%.(12;13)

Many studies report that CBF declines from the third decade onward.(14–17) The change in metabolic rate for oxygen and glucose with age is less clear, with several studies showing a decrease(14;16;18–20) and others showing no change.(21–23) Studies that have corrected for brain atrophy show lesser or absent changes in CBF, CMRO₂ and CMRglc with increasing age. (19;24–26) Our own PET data corrected for brain atrophy from 23 normal subjects, ages 23–71 years, shows no significant change in CBF or CMRO₂, but a decline in CMRglc of 4–5% per decade.

CEREBROVASCULAR CONTROL

Regional CBF is determined by the local cerebral perfusion pressure (CPP) and the local cerebrovascular resistance (CVR).

$$CBF = \frac{CPP}{CVR}$$

CPP is equal to the difference between the mean arterial pressure (MAP) driving blood into the brain and the venous backpressure. Venous backpressure is negligible unless there is elevated intracranial pressure (ICP) or obstruction of venous outflow, such as cerebral venous thrombosis. Under normal conditions of constant MAP and CPP, any local changes in CBF must occur as a result of changes in CVR. CVR is determined by blood viscosity, vessel length,

and vessel radius. Of these factors, changes in the radius of resistance vessels (primarily arterioles) are the primary determinants of CBF in most situations with normal CPP.

The cerebrovascular bed is not a static system. Resistance vessels dilate and constrict in response to a variety of stimuli. When there is a primary reduction in the metabolic rate of brain cells (e.g. by hypothermia or barbiturates), vessels constrict to produce a comparable decline in CBF and thus little or no change in OEF or GEF.(27–29) With increased neuronal activity, vessels dilate producing an increase in regional CBF that is accompanied by a similar in magnitude increase in regional CMR_{glc} and little or no increase in regional CMRO₂.(30–32) Acute changes in arterial pCO₂ cause proportional changes in CBF. A decrease in arterial pCO₂ from hyperventilation leads to a decrease in CBF (30–35% at 25 mm Hg) and an increase in arterial pCO₂ leads to an increase in CBF (about 75% at 50 mm Hg).(33–37) The mechanism for the change in CBF is a change in CVR produced by vasodilation with increased pCO₂ and vasoconstriction with decreased pCO₂.(34) When the perturbation in arterial pCO₂ is maintained for a prolonged time, CBF gradually returns toward normal values.(37) With passive hyperventilation, no reduction in CMRO₂ or high energy phosphate levels accompanies the reduction in CBF.(38;39) However, with active hyperventilation, a slight increase in CMRO₂ has been reported.(33;34). The effects of arterial pO₂ on the cerebral circulation are different from those of pCO₂. CBF does not increase until arterial pO₂ is reduced below about 30–50 mm Hg,(40;41) indicating that variations in pO₂ are unlikely to constitute an important mechanism for regulating CBF at physiological levels of pO₂. Because of the sigmoid shape of the oxygen dissociation curve, a significant reduction in hemoglobin saturation and hence in arterial oxygen content (CaO₂) does not occur until arterial pO₂ falls to about 50–60 mm Hg.(40;42) The similarity between this number and the threshold for hypoxia-induced reduction in CBF suggests that it is primarily CaO₂ and not pO₂ that determines CBF. Reductions in CaO₂ due to hypoxemia or anemia cause vasodilation and compensatory increases in CBF.(5;34;40;43) Likewise, the increase in CaO₂ with polycythemia is associated with a decrease in CBF.(44) In neither of these cases does cerebral metabolism change.(40; 44) With chronic changes in CaO₂, there is a significant reciprocal inverse relationship between CaO₂ and CBF throughout the range of oxygen content levels such that oxygen delivery (CBF x CaO₂) remains constant.(43) Acute changes in CaO₂ due to reduction in hemoglobin or pO₂ produce less of an increase in CBF than do chronic changes.(45;46) Hematocrit is an important determinant of viscosity and thus viscosity often varies with CaO₂. Although an inverse relationship between viscosity and CBF has also been reported,(43;47) it is unlikely that viscosity is an independent determinant of CBF under most circumstances. In anemic, paraproteinemic subjects in whom reduced CaO₂ is dissociated from changes in viscosity, there is no correlation between viscosity and CBF, but there is a highly significant inverse relationship between CaO₂ and CBF.(48) In hematologically normal subjects, reduction of viscosity by plasma exchange without a concomitant change in hemoglobin concentration or CaO₂ does not increase CBF.(49) Finally, reducing CaO₂ via carbon monoxide inhalation without changing arterial pO₂ or viscosity has been shown to increase CBF.(50) From these findings, it can be concluded that increases in blood viscosity induce compensatory vasodilation to maintain cerebral oxygen delivery. Thus, increases in CBF brought about by hemodilution, if they are simply reciprocal responses to changes in arterial oxygen content, will not increase cerebral oxygen delivery and may even decrease it.(51) This compensatory mechanism may be exhausted when pre-existing vasodilation impairs the ability of vessels to dilate further to changes in viscosity.(52) All of these responses of the cerebral vasculature have been determined at normal CPP. When CPP varies, a different set of cerebrovascular and brain metabolic responses occur.

Changes in CPP over a wide range from 70 to 150 mm Hg have little effect on CBF. Known as autoregulation, this compensatory mechanism is mediated by changes in CVR. When CPP decreases, vasodilation of the small arteries or arterioles reduces CVR. When CPP increases,

vasoconstriction of the small arteries or arterioles increases CVR (53;54) This mechanism is effective at maintaining CBF in normal human subjects until MAP falls below the lower autoregulatory limit.(55;56) Chronic hypertension shifts both the lower and upper limits of autoregulation to higher levels. In chronically hypertensive subjects, the lower autoregulatory limit is 100–120 mm Hg MAP.(55;57) This limit is variably and unpredictably affected by chronic antihypertensive drug treatment. Thus, acute reductions in MAP or CPP that would be safe in normotensive subjects may precipitate cerebral ischemia in patients with chronic hypertension. As CPP falls below the autoregulatory limit and the maximal vasodilatory capacity of the cerebral circulation has been exceeded, there is a steep decline in CBF. A progressive increase in the amount of oxygen extracted from the blood by the brain by a factor of two or more to levels sometimes approaching 100% now maintains oxygen metabolism (Figure 2). (58;59) When maximally increased OEF is no longer adequate to supply the energy needs of the brain, further reductions in CBF disrupt normal cellular metabolism and produce clinical evidence of brain dysfunction.

When the cerebral blood vessels are already dilated in response to some other stimulus, they are less responsive to further vasodilation induced by reduced CPP. Therefore, the autoregulatory response is attenuated or lost in the setting of pre-existing hypercapnia, anemia, or severe hypoxemia.(60;61)

The cerebral blood volume (CBV) is the amount of blood circulating in the brain vessels at any time. CBV is composed of arterial, capillary, and venous segments. Veins account for some 80–85% of CBV, arteries 10–15%, and capillaries less than 5%.(62;63) Of these, arteries are the most responsive to autoregulatory changes in CPP. Veins respond less and capillaries even less.(64;65) Although reductions in CPP produce visible dilation of pial vessels, data regarding the response of CBV to reduced CPP are conflicting.(53;66–68) (Figure 1.) With experimental reductions in CPP, it is sometimes possible to measure an increase in CBV that is presumed to be due to autoregulatory vasodilation.(69–71) However, this increase in CBV to reduced CPP is not always evident.(59) Failure to demonstrate increased CBV in the setting of reduced CPP has been ascribed to various possible mechanisms in various situations, including differential vasodilatory capacity of different vascular beds, passive collapse of vessels due to low intraluminal pressures, small vessel vasospasm, and re-setting of vascular tone in response to a compensatory down-regulation of CMRO₂.(72) The CBF/CBV ratio (or its reciprocal, the mean vascular transit time, MVT) has been proposed to be a more sensitive indicator of reduced CPP than CBV alone.(59;73) Although it may be more sensitive, it is not reliable because it may decrease in low flow conditions with normal perfusion pressure, such as hypocapnia.(74;75)

HEMODYNAMIC EFFECTS OF ARTERIAL OCCLUSIVE DISEASE

Carotid endarterectomy is empirically proven by randomized clinical trials to reduce subsequent stroke risk in patients with high-grade extracranial carotid stenosis; therefore differentiating the relative importance of hemodynamic versus embolic mechanisms in these patients has little clinical value.(76;77) The same cannot be said for symptomatic carotid occlusion, for which no surgical treatment has proven to be effective in reducing the 5–10% annual risk of subsequent ipsilateral ischemic stroke on medical therapy.(2;78–80) A substantial amount of PET research has been devoted to assessing the hemodynamic effect of arterial occlusive disease with the goal of defining a subgroup of patients with hemodynamic compromise who might benefit from revascularization procedures.

The hemodynamic effect of carotid artery occlusion on the cerebral circulation depends on the adequacy of the collateral circulation. Vascular imaging techniques such as angiography or

Doppler ultrasonography can identify the presence of these collateral vessels, but not necessarily the adequacy of the blood supply they provide.(81)

Measurement of CBF alone also is inadequate for this purpose. Normal CBF may be found when CPP is reduced but flow is maintained by autoregulatory vasodilation of distal resistance vessels. Second, CBF may be low when perfusion pressure is normal, such as when the metabolic demands of the tissue are reduced due to pre-existing ischemic damage or the destruction of normal afferent or efferent fibers by a remote lesion.(58;82–84) Current methods for assessment of local cerebral hemodynamics depend on the compensatory responses observed during global reductions in CPP due to systemic hypotension and increased ICP, as described above. Similar responses are assumed to occur with local reductions in CPP due to focal arterial stenosis.

Three strategies are commonly used with PET to determine the hemodynamic effect of carotid artery occlusion on the cerebral circulation. The first relies on measurement of CBF at baseline and after application of a vasodilatory stimulus, such as CO₂ inhalation, acetazolamide administration, or physiological increase in neuronal activity (e.g., hand movement). Impairment of the normal increase in regional CBF to vasodilatory stimuli is assumed to reflect existing autoregulatory vasodilation due to reduced CPP. The second strategy entails the quantitative measurement of regional CBV either alone or in combination with measurement of CBF at rest to detect the presence of autoregulatory vasodilation. Increases in CBV or the CBV/CBF ratio relative to the range observed in normal control subjects is assumed to indicate hemodynamic compromise, but, as noted above, the changes in CBV that can be measured with experimental reductions in CPP are variable and inconsistent. As a result, the sensitivity and specificity of these measurements in detecting reduced CPP is unknown. The third strategy involves direct measurement of regional OEF as an indicator of local autoregulatory failure.

Based on the known physiological responses of CBF, CBV, and OEF to reductions in global CPP, a three-stage sequential classification system for local cerebral hemodynamic status due to chronic carotid occlusion has been proposed.(85) Stage 0 is the condition of normal CPP due to collateral circulation that completely compensates for the occluded artery. CBF and CMRO₂ are closely matched such that OEF is normal. CBV is not elevated and the CBF response to vasodilatory stimuli is normal. Stage I hemodynamic compromise reflects a condition of reduced CPP where CBF is maintained by autoregulatory vasodilation of arterioles. Consequently, CBV is increased and the CBF response to vasodilatory stimuli is decreased, but OEF remains normal. In Stage II hemodynamic failure, CPP is reduced below the lower limit of autoregulation. There is increased OEF since CBF has declined with respect to CMRO₂. CMRO₂ is preserved at a level that reflects the underlying energy demands of the tissue, but may be lower than normal due to the effects of previous ischemic damage.(58;82; 83) This stage has also been termed “miser perfusion” by Baron et al. (Figure 3) (86;87)

Two independent PET studies have demonstrated that Stage II hemodynamic failure is a powerful independent predictor of subsequent ipsilateral ischemic stroke. Yamauchi et al (88) found a significantly higher 1-year incidence of ipsilateral stroke in patients with symptomatic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusive disease having increased OEF (4/7) than in those having normal OEF (2/33). In 3 of 4 patients with increased OEF and subsequent stroke, infarction occurred in a watershed territory corresponding to the area of increased OEF.(89) In the St. Louis Carotid Occlusion Study (STLCOS), a blinded prospective study of 81 patients with symptomatic carotid occlusion, Grubb et al similarly found that increased OEF distal to the occlusion was an independent predictor of subsequent ipsilateral ischemic stroke. Ipsilateral stroke occurred in 11/39 patients with increased OEF and in 2/42 patients with normal OEF, respectively. When other factors were controlled for, patients with symptomatic carotid artery occlusion with increased OEF

had a risk of ipsilateral ischemic stroke seven times greater than those with normal OEF. (90) These investigations establish the prognostic value of OEF in patients with symptomatic carotid occlusion but not its role in choosing therapy. Even though previous PET studies demonstrated improvement in OEF following extracranial-intracranial (EC-IC) bypass, the benefit of this surgery in reducing the risk of stroke remains to be determined by a properly designed clinical trial (Figure 3).(91–93) The Carotid Occlusion Surgery Study is currently underway to assess the efficacy of EC-IC bypass in reducing the risk of subsequent stroke in patients with symptomatic carotid occlusion who have increased OEF measured by PET (94).

A PET study of patients with never-symptomatic carotid occlusion reported a lower incidence of elevated OEF (4 of 30) than is seen in symptomatic patients (39 of 81). Since no ipsilateral strokes occurred in any of the 30 subjects, no conclusions could be drawn with regard to the ability of increased OEF to predict ipsilateral stroke risk in this population.(95)

Although the three-stage classification scheme is conceptually useful, it is too simplistic. As discussed above, increases in CBV are not reliable indices of reduced CPP. CBF responses to different vasodilatory agents may be impaired or normal in the same patient.(96–98) A normal vasodilatory response may occur in the setting of increased CBV.(99;100) Finally, according to the three-stage system, all patients with increased OEF should have increased CBV and poor response to vasoactive stimuli. However, this increase in CBV is not always evident nor is the impaired response to vasodilatory stimuli.(72;101)

In the original descriptions of the three-stage classification of cerebral hemodynamics, the effects of further reductions in CPP and CBF when OEF is maximal (beyond Stage II) were described, but acknowledged to be based on inadequate data: CMRO₂ will decrease, normal cellular function and metabolism will be disrupted and cell death may occur. In this proposed scheme, OEF remained maximal as CBF and CMRO₂ both declined.(58;85) Nemoto and colleagues have postulated that patients who initially have CPP below the autoregulatory limit with increased OEF (Stage II hemodynamic failure) may suffer subsequent ischemic neuronal damage that reduces CMRO₂ and normalizes OEF, but without any improvement in CPP. They refer to this as Stage III.(102)The plausibility of this scenario is supported by PET studies that show evidence for selective neuronal necrosis in brain regions with low CMRO₂ and normal OEF and the progressive development of selective neuronal necrosis in areas with initially high OEF.(82;103). Nemoto and colleagues propose that, while these patients would look like Stage I hemodynamic compromise (impaired response to vasodilatory stimuli, normal OEF), their stroke risk would in fact be similar to that of stage II patients due to the persistently low CPP. (102) Thus, according to this construct, there should be a group of patients with normal OEF and impaired vasoreactivity who are at high risk for stroke. This does not appear to be the case. In the STLCOS, none of the 13 ipsilateral strokes that occurred in follow-up of 3.1 years occurred in patients with increased CBV and normal OEF.(72) The two patients with normal OEF who had ipsilateral strokes were among the 8 patients with the highest OEF values in the normal OEF group of 41 subjects. Furthermore, in this cohort of patients, OEF was predictive of subsequent ipsilateral stroke as a continuous variable, indicating that the higher the OEF the higher the risk of stroke.(104)

EVOLUTION OF ACUTE INFARCTION

The evolution of changes in flow and metabolism early after acute ischemic stroke has been established from PET studies of MCA occlusion in large mammals. Approximately one hour after occlusion, CBF was decreased and OEF was increased in the territory of the occluded MCA. CMRO₂ was reduced somewhat initially in the deep regions of the territory, but fell further over the subsequent 2–3 hours. CBF remained relatively stable during this time period, falling only slightly.(105–109) Reflecting the stably reduced CBF and further declining

CMRO₂, the initially markedly increased OEF progressively decreased. By 24 hours, CBF in the center of the MCA territory reached its nadir at less than 20% of baseline values and CMRO₂ reached 25% of baseline values (Figure 4). Also at this time point, increased OEF was seen to develop outside the area of primary perfusion disturbance in the tissue adjacent to the infarct core.(109) The volume of severely hypometabolic tissue remained stable between 1 and 7 hours post-occlusion, but increased by 24 hours and increased even further an average of 17 days after occlusion.(110) The fate of high OEF regions in the core and surrounding regions is variable; some portions may go on to infarct and other portions may survive.(105)

Human data obtained at 2 to 24 hours after ictus show an area of reduced CBF, reduced CMRO₂, and high OEF.(111;112) Over the subsequent days, CBF usually increases. Spontaneous reperfusion will occur in about three-quarters of patients. It may take place within a few hours of infarction,(113) but peaks at day 14.(114) This rise in CBF occurs without a concomitant rise in CMRO₂; rather, CMRO₂ generally falls further. Consequently, a decrease in regional OEF below normal values mirrors the rise in CBF. This state, termed “luxury perfusion,”(115) indicates that the normal coupling of CBF to oxygen metabolism in the resting brain is deranged (Figure 5). Luxury perfusion may be absolute with CBF values greater than normal. Alternatively, luxury perfusion may be relative with low or normal CBF that is still in excess of that required to produce a normal OEF for the reduced CMRO₂.(116) Luxury perfusion is evident by 48 hours in one-third of patients(117;118) and peaks at 1 to 2 weeks, paralleling the time course of spontaneous reperfusion.(116) Following this subacute period, CBF progressively declines and OEF normalizes such that the chronic stable infarct demonstrates flow and metabolism that are close to zero with OEF at or below baseline values (Figure 6).(119) In the rim of tissue surrounding the infarct core, areas demonstrating reduced CBF and increased OEF with variable CMRO₂ can often be identified within hours after ictus and may persist for up to 16 hours. As with the animal data, the fate of high OEF regions in the core and surrounding regions is variable; some will infarct and some will not.(120;121)

The peripheral benzodiazepine receptor ligand ¹¹C-PK 11195 primarily binds to cerebral microglia/macrophages.(122;123) It can be used to image the inflammatory responses that occur following acute cerebral infarction.(124) In studies of human ischemic stroke, increased ¹¹C-PK 11195 uptake begins after 3 days and persists for months. It is seen in the region of the primary lesion and later spreads to distant sites in the brain.(125;126)

IDENTIFICATION OF PREVENTABLE INFARCTION

Studies in experimental animals have elucidated the capacity of neurons to tolerate transient cerebral ischemia. At CBF below 20 mL 100g⁻¹ min⁻¹, neuronal electrical activity is at first impaired and then abolished. Neurological deficits appear. If CBF remains below 20 mL 100g⁻¹ min⁻¹ the cells may go on to die. The ability of brain cells to tolerate CBF below 20 mL 100g⁻¹ min⁻¹ depends on both the magnitude and duration of the CBF reduction. CBF of 5–10 mL 100g⁻¹ min⁻¹ may be tolerated for a period of less than one hour whereas CBF of 10–15 mL 100g⁻¹ min⁻¹ may not produce cell death for 2–3 hours. Some neurons may tolerate the same reduction in CBF for a period of time that is lethal to other cells. White matter is more tolerant than gray matter.(127–133) In a baboon model of transient MCA occlusion, evidence of reversibility as manifested by immediate improvement of hemiparesis was observed in 14/14 with occlusion less than one hour, 8/11 with occlusion of 2–4 hours, 1/3 with occlusion of eight hours and 1/6 with occlusion of 16–24 hours.(132;134–136)

The demonstration of improved recovery from stroke with early intravenous thrombolytic therapy provided the human counterpart for these experimental studies.(137;138) Although currently limited in practice to a time window of 4.5 hours, the variability observed in both animal experiments and clinical practice has led to a great deal of interest in developing a PET

method to identify those patients with preventable infarction, i.e. vulnerable brain cells that are still alive, but whose natural history is to go on and die. A simple construct to test the ability of PET to accurately identify preventable infarction has recently been proposed (Table 1). (139) It requires three PET signals that spatially match the three pathophysiological tissue types in the brain with acute cerebral ischemia – already dead or irreversibly damaged (signal A), preventable infarction (signal B), and not at risk (signal C). Three distinct approaches based on three different PET radiopharmaceuticals have been investigated: ^{18}F -fluoromisonidazole, ^{11}C -flumazenil, and combined measurements of CBF and CMRO_2 .

^{18}F -fluoromisonidazole (^{18}F -FMISO) is a nitroimidazole compound that is selectively trapped within hypoxic but living cells. (140) Synthesis takes at least an hour and scanning cannot be performed until 2 hours after injection to provide adequate time for washout of unbound tracer. (140;141) Uptake of ^{18}F -FMISO PET was detected in the periphery and surrounding tissue of infarcts in 69% of patients studied within 48 hours and in no patient studied 6 to 11 days after stroke onset, including those who had positive early studies (142). Uptake of ^{18}F -FMISO has been demonstrated to shift from the eventual infarct core (in patients studied <6 hours after stroke onset) to the periphery and surrounding tissue (in patients studied 6 to 48 hours after stroke onset). Over time, the amount of hypoxic tissue declines. When imaged within 6 hours of stroke onset, about 90% of the region of ^{18}F -FMISO is included in the eventual infarct whereas this percentage falls to 50% by 16 hours. (141;143) Clinical correlations exist between the volume of initially affected tissue and initial severity of the neurological deficit and between the proportion of initially affected tissue progressing to infarction and neurological deterioration during the first week after stroke. (143) During 2 hour transient MCA occlusion in the rat, the area of ^{18}F -FMISO uptake is much larger than the area of subsequent infarction, but a small area of infarction equal to 10–15% of the area of uptake still occurs. (144) Since a variable portion of the tissue detected by ^{18}F -FMISO uptake does not go on to infarct if untreated (over 50% more than 16 hours after stroke onset), ^{18}F -FMISO does not accurately identify preventable infarction. The best interpretation for these data is that the degree of hypoxia necessary for ^{18}F -FMISO binding is less than the degree that leads to cell death.

^{11}C -flumazenil (^{11}C -FMZ) is a central benzodiazepine receptor radioligand that binds to gamma-aminobutyric acid (GABA) receptors on synapses of cortical neurons. (145) Since GABA receptors are sensitive to ischemia (146), reduction of ^{11}C -FMZ uptake has been used to provide an early indication of neuronal damage. (146) A major limitation of the ^{11}C -FMZ technique is that the low or negligible densities of central benzodiazepine receptors in subcortical gray and white matter restrict its ability to detect tissue destruction in these regions. (147) Synthesis takes at least one hour and scanning takes one hour. In clinical ^{11}C -FMZ PET studies performed within 16 hours of stroke onset, decreased ^{11}C -FMZ binding was seen in areas of markedly decreased CMRO_2 despite a wide range of OEF values. ^{11}C -FMZ binding predicted final tissue status on late CT with a sensitivity of 84% and a specificity of 85%. (148) However, acute studies in the cat demonstrated that decreased ^{11}C -FMZ binding consistently underestimated the volume of subsequent tissue infarction. (149) In both tPA-treated and untreated patients, ^{11}C -FMZ binding > 5.5 times contralateral white matter (CWM) is 95% predictive of late tissue survival, ^{11}C -FMZ binding < 3.4 times CWM is 95% predictive of late tissue death and 3.4 – 5.5 times CWM is indeterminate. Combining with CBF measurements to improve the predictive value shows that ^{11}C -FMZ binding > 3.4 times CWM and CBF < 50% of contralateral hemisphere identifies tissue all of which will survive with thrombolysis < 3 hrs, but that 80% will also survive if untreated. (2;148;150). Thus, ^{11}C -FMZ performs better than ^{18}F -FMISO, but still falls short at accurately identifying preventable infarction. Thresholds for 95% prediction of tissue death and survival can be derived as can accurate predictions of tissue survival with treatment. However, the fate of tissue with ^{11}C -FMZ binding between 3.4 – 5.5 times CWM is indeterminate. Most of the tissue with low CBF and high ^{11}C -FMZ binding that survives if treated will also survive when untreated.

Defining cells that are already dead or irreversibly damaged involves determination of thresholds for CBF and/or CMRO₂ below which spontaneous tissue survivability does not occur. Measurements of CBF alone perform poorly because of the importance of both magnitude and duration in determining cell death, the variable response of different cells and the occurrence of high CBF in dead tissue (see above). (121;151;152) Thresholds for cell death based on early measurement of CMRO₂ have been shown to be more reliable. CMRO₂ thresholds for infarction have been reported from 0.87–1.7 mL 100g⁻¹ min⁻¹. (110;151;153; 154) Identification of areas of preventable infarction by measurements of CBF and metabolism is much more difficult. Because tissue regions demonstrating increased OEF represent areas with reduced blood supply relative to oxygen demand but still with metabolically active cells, OEF has received much attention as the factor capable of predicting tissue viability, but it has been shown to be a poor predictor of tissue outcome. (105;121;152;155) The combination of CMRO₂ > 40–60% of normal and CBF < 40–60% of normal has been shown to accurately identify areas of the brain that will go on to infarct if untreated and live if successfully reperfused. Usually, when both CBF and CMRO₂ are above these levels the tissue survives and when both are below these levels the tissue dies. (105–107;110;151;152;154–156) These data represent a mix from humans and non-human primates with minimal human reperfusion data. All these attempts to determine thresholds suffer from a variety of technical problems including small numbers of subjects, poor spatial resolution, lack of co-registration to CT, and poor counting statistics. Further human reperfusion studies are needed to demonstrate reliability of these criteria for identifying preventable infarction based on combined CBF and CMRO₂ in clinically heterogeneous patient populations.

CAROTID ARTERY ATHEROSCLEROSIS

Imaging of carotid atherosclerosis with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) has demonstrated that plaques show varying levels of ¹⁸F-FDG uptake. (157;158) The degree of uptake corresponds to pathological evidence of active inflammation by macrophage infiltration. (159–161) The clinical relevance of these findings is still under investigation. (159;160;162)

REMOTE METABOLIC EFFECTS OF CEREBRAL INFARCTION

A common finding from PET studies of stroke is the presence of reduced blood flow and metabolism in brain regions distant from the site of infarction that appear normal on CT or MRI. Remote hypometabolism has been demonstrated for both oxygen consumption (116; 163–165) and glucose utilization. (166;167) Metabolic values at these distant sites always remain greater than those within the ischemic core. (112;166;167) CBF is reduced slightly more than metabolism, resulting in a slight increase in OEF. (168;169) Distinguished from “misery perfusion,” this situation has been interpreted to represent primary metabolic depression with secondary reduction in perfusion.

The best-described remote metabolic effect of ischemia is contralateral cerebellar hypometabolism (“crossed cerebellar diaschisis”), which occurs in about 50% of patients with hemispheric lesions (Figure 7). (165;170) Several factors have been reported to influence its occurrence, though data are not consistent across studies. Such hypometabolism may be more profound with greater volumes of hemispheric hypoperfusion, (171) deep MCA infarcts, (165) those involving the frontal (164) or parietal lobes, (116) and those encompassing more than one lobe. (165;167;172) Although Lenzi et al (116) found that “crossed cerebellar diaschisis was not evident in cases in which the dimensions of the infarct were small,” Martin and Raichle (164) reported no relationship to infarct size. Cerebellar hypometabolism has been shown to correlate with the presence of, (119) but likely not the severity of, hemiparesis. (164) It also occurs in some patients having no motor deficit. (165;167) Reduction of CMRglc

is greater than that of CMRO₂ in chronic stroke (4 to 46 months), indicating an uncoupling of oxygen consumption and glucose utilization.(173)

Reduction in blood flow and metabolism in the hemisphere contralateral to cerebral infarction has also been described for both the homologous cortical area and for the whole hemisphere. (116;174;175) Wise et al(176) found that while patients with recent infarction had lower contralateral CMRO₂ compared to normal control subjects, this difference vanished when the comparison group consisted of subjects with extracranial cerebrovascular disease but without previous cerebral infarction. Non-human primate models of cerebral ischemia have not revealed evidence for contralateral hemispheric hypometabolism either acutely(108) or at delayed measurement (> 2 weeks).(155)

Ipsilateral cerebral hypometabolism has been observed in the cortex overlying subcortical stroke and in the basal ganglia, thalamus, and distant sites in the cortex after cortical stroke, (166;174;177;178) likely occurring in a delayed fashion (beyond 18 hours after clinical onset). (179) This “intrahemispheric remote hypometabolism” is most frequently described with thalamic lesions.(166;180;181)

These areas of remote hypometabolism are typically ascribed to a decrease in neuronal activity caused by interruption of afferent or efferent fiber pathways by the ischemic lesion, a phenomenon often termed *diaschisis*.(163) This term is not strictly accurate though, because diaschisis refers to an acute and reversible functional depression at sites distant from but connected with the site of injury,(182) whereas the remote effects of ischemia are often stable for months(164;183) and may be permanent. Trans-synaptic neuronal degeneration has been proposed as an alternate explanation for the remote hypometabolism(165) and is supported by the fact that contralateral CMRO₂ often declines between acute and chronic studies,(184) but this is unlikely to account for all cases since hypometabolism can be seen within hours of stroke.(170;171) In the hemispheres distal to occluded carotid arteries, regions of reduced metabolism show evidence of reduced central benzodiazepine receptors consistent with selective neuronal damage.(82;185)

The clinical correlate of these remote changes is unclear. Single case reports have suggested an association with focal neurological deficits, including ataxia,(186;187) aphasia,(188;189) neglect,(190) and hemianopia,(174) but larger series of infarcts at various locations have revealed no such relationships.(84;165) In one study, stepwise regression analysis revealed that language performance mainly depended on parieto-temporal metabolism irrespective of infarct location.(191) Similarly, the relationship between remote metabolic effects seen acutely after stroke and eventual clinical outcome is uncertain. Widespread metabolic disruption was a poor indicator of neurological outcome (disability at 2 weeks to 3 months) regardless of CT findings in one study.(192) In another, metabolism in structurally normal ipsilateral mesial-prefrontal tissue at 5 to 18 hours after MCA stroke was predictive of neurological status at 3 weeks.(179) Furthermore, glucose metabolism in the left hemisphere 2 to 3 weeks after left MCA stroke predicted both short-term (4 months) and long-term (2 year) recovery from aphasia.(193;194) The degree of acute crossed cerebellar hypometabolism did not correlate with the degree of later recovery in one study whereas in another it did.(170;171)

VASCULAR DEMENTIA

Vascular dementia remains an elusive entity. There are no agreed upon clinical diagnostic criteria and the correspondence between the clinical diagnosis and pathology is poor. (195–197). The situation is further complicated by the common pathological occurrence of both Alzheimer’s disease and cerebrovascular disease and their synergy in producing clinical dementia.(198) These cautions must be born in mind in interpreting PET studies of vascular dementia, none of which have been based on pathological diagnoses. These studies have

primarily evaluated changes in CBF and CMRO₂ and, in some cases, used OEF to distinguish between ongoing active ischemia (high OEF) and permanent ischemic damage (normal or low OEF). Frackowiak and colleagues reported reduced CBF and CMRO₂ and normal OEF in nine subjects with vascular dementia and concluded that there was no evidence to support the existence of a chronic ischemic brain syndrome.(199) Similar findings were reported for patients with dementia associated with large cerebral infarcts.(200) Most of the other PET studies of vascular dementia have concentrated on patients with leukoaraiosis, the deep white matter abnormalities seen as hyperintensities on T2-MRI and hypodensities on CT.(201;202) These abnormalities are associated with age-related cognitive decline.(202;203) Patients with leukoaraiosis have decreases CBF and CMRO₂ in both abnormal white matter and overlying gray matter with the degree of reduction paralleling the severity of the white matter abnormalities and the degree of dementia. Both increased and normal OEF have been reported, leaving the issue of chronic ischemia unresolved.(200;204–207) Ihara and colleagues have reported decreased cortical binding of ¹¹C-FMZ in patients with leukoaraiosis and dementia suggesting that the white matter damage causes cortical neuronal injury.(207)

INTRACEREBRAL HEMORRHAGE

Investigations of CBF and metabolic rate in intracerebral hemorrhage (ICH) have been less extensive than those in ischemic stroke. These have focused on the zone of tissue immediately surrounding the clot. Reduced CBF, determined by autoradiography or SPECT, has been demonstrated in this area in experimental models of ICH(208;209) and in patients with ICH, (210) but not always.(211;212) This reduction in CBF is often attributed to cerebral ischemia due to mechanical compression of the microvasculature surrounding the clot.(208;213) As in ischemic stroke, PET and SPECT studies of ICH suffer from the effect of partial volume averaging, which may cause regions of normal flow to appear reduced depending upon image resolution and the proximity to non-perfused tissue.(214;215) Unlike in ischemic stroke, a validated method exists permitting the correction for partial volume effects in ICH.(216) Using this method, a zone of hypoperfusion is still evident surrounding acute ICH.(216;217) In 19 patients studied 5 to 22 hours after symptom onset, Zazulia et al found that peri-clot CMRO₂ was reduced to a greater degree than CBF, resulting in decreased OEF rather than the increased OEF that occurs in ischemia (Figure 8). (217) This pattern was suggestive of a primary metabolic depression, consistent with a subsequent report of peri-hematoma mitochondrial dysfunction. (218). In 14 hypertensive patients with small to medium sized acute hemorrhages studied within 24 hours of onset, lowering mean arterial pressure by 17% from 143 ± 10 to 119 ± 11 mm Hg did not produce any significant change in CBF in the peri-hematoma region or in the brain as a whole.(219)

Transient focal increases in glucose metabolism in the peri-hematoma region that occur 2–4 days after ICH have been described in 6 of 13 patients studied in the first week following ICH. These were resolving or had returned to baseline on repeat scans at 5–8 days (Figure 9). (220) These focal increases are strikingly similar to foci of hyperglycolysis observed following traumatic brain injury.(221;222) While the pathophysiological basis for these metabolic changes remains to be determined, they may be indicative of ongoing injury that is amenable to intervention that will improve outcome.(223) Remote hypometabolism in structurally intact brain regions, similar to that found with cerebral infarcts, is also seen in patients with ICH. (224;225)

ANEURYSMAL SUBARACHNOID HEMORRHAGE

Several PET studies performed within the first few days after aneurysm rupture have investigated the effects of subarachnoid hemorrhage (SAH) before vasospasm occurs. In one series of patients who had not undergone surgery and who did not have evidence for vasospasm,

hydrocephalus, or ICH, there was a significant reduction in global CMRO₂ and CBF with normal OEF that did not correlate to the use of sedative drugs when they were studied 1 to 4 days after aneurysmal SAH.(226) This was interpreted by the authors as indicating that the initial aneurysm rupture produced a primary reduction in metabolism at this stage and the reduction in CBF occurred secondary to reduced metabolic demands. Another case series of 7 unsedated patients studied within the first 48 hours showed non-significant trends for a reduction in CBF and CMRO₂ and an increase in OEF. The authors did not posit a causal relationship. (227)

Vasospasm, defined as segmental or diffuse narrowing of the large arteries at the base of the brain, can be detected angiographically in up to 70% of patients beginning at 4–12 days after aneurysm rupture.(228–230) Depression of CBF and CMRO₂ has been reported by several investigators with OEF variably described as normal or elevated.(231–237) Reduced metabolism with normal OEF has been interpreted as evidence for non-ischemic primary metabolic depression with vasospasm as a secondary response to reduced metabolic demand. However, since OEF returns to normal within several hours or at most a few days after cerebral infarction, the findings of normal OEF with reduced CBF and CMRO₂ cannot be used to discard ischemic infarction as a cause for reduced metabolism in SAH-induced vasospasm. Consistent with subacute cerebral infarction in which OEF had returned to normal, some investigators who have demonstrated reduced CBF and CMRO₂ with no change in OEF report subsequent cerebral infarction or moderate to severe disability in the majority of the patients. (234;235) To investigate whether large artery vasospasm causes ischemia without the confounding effects of subacute infarction, Carpenter and colleagues studied a group of patients with vasospasm who did not develop subsequent infarction.(226) CBF was decreased, CMRO₂ was normal, and OEF was increased, consistent with ischemia (Figure 10).(226) With resolution of vasospasm, CBF increased.(236)

Studies of CBV in patients with SAH likewise have yielded conflicting results. In a non-PET study using oxygen-15 radiotracers, Grubb and co-workers(233) reported a statistically significant increase in CBV in Hunt and Hess grade III–IV patients with angiographic vasospasm when compared to normal volunteers. OEF values were not reported, but examination of the CBF and CMRO₂ data indicates that OEF was probably not increased in the patients with vasospasm as compared to those without. In a PET study of SAH, Hino and associates reported a significant increase in CBV in regions of symptomatic angiographic vasospasm.(234) They did not, however, observe an elevation in regional OEF. In another PET study, patients with carotid artery occlusion were compared to those with SAH.(238) Regional OEF was higher both during vasospasm and distal to carotid occlusion than in SAH without vasospasm or in normal volunteers. Regional CBV was reduced compared to normal in regions with and without spasm, whereas it was increased ipsilateral to carotid occlusion. These findings of reduced CBV during vasospasm under similar conditions of tissue ischemia (increased OEF) that produce increased CBV in patients with carotid occlusion were interpreted as evidence that parenchymal vessels distal to arteries with angiographic spasm following SAH do not demonstrate normal autoregulatory vasodilation. The reason for the discrepancies among these studies in the measurement of CBV during vasospasm is not clear but it may reflect the variability of CBV changes during reduced CPP noted earlier.(72)

Surgical retraction may have profound effects on cerebral metabolism. A small PET study before and after right fronto-temporal craniotomies for clipping of ruptured anterior circulation aneurysms showed a 45% reduction in regional CMRO₂ and 32% reduction in regional OEF without significant change in CBF in the region of retraction, but no change in the opposite hemisphere.(239) These changes indicate a primary reduction in metabolism and uncoupling of flow and metabolism (luxury perfusion). They are not suggestive of vasospasm since vasospasm produces diffuse changes respecting large vascular territories whereas these

changes were focal in the area of retractor blade placement. Another study showed similar reductions in CMRglc in the area of retraction.(240)

CONCLUSIONS

Measurements of CBF and CMR in ischemia and infarction have provided valuable insight into the pathophysiology of cerebrovascular disease. Much has been learned about the compensatory responses of the brain to reductions in perfusion pressure and in the evolution of changes in blood flow and metabolism that occur when these mechanisms fail. Knowledge of these changes can help guide therapy when multiple factors such as ischemia, hypoxemia, hypocarbia, or hypotension may be affecting cerebral blood flow. Understanding the hemodynamic effects of arterial stenosis or occlusion on the downstream perfusion pressure has been instrumental in designing new trials for treatment.(94) In acute ischemic stroke, measurements of CBF and metabolism have been used to define the “ischemic penumbra” and to predict both tissue and clinical outcome, although the clinical utility of these markers of ischemia in distinguishing viable from irreversibly damaged tissue in the acute period still requires further study.

Blood flow and metabolic studies in ICH have documented the integrity of autoregulation and suggested that hematomas exert a primary depression of metabolism rather than inducing ischemia in the surrounding tissue. This has important implications for future consideration of therapeutic interventions in this disease. Studies in SAH have differentiated the primary effects of the hemorrhage on cerebral hemodynamics and metabolism from those of vasospasm and surgical retraction. In addition, vasospasm-induced ischemia has been demonstrated to be reversible.

In summary, defining the pathophysiological changes in CBF and metabolism in human cerebrovascular disease has provided and will continue to provide the basic foundation for development and testing of new treatment strategies.

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Figure 1.

Normal cerebral blood flow and metabolism. PET scans from a normal 70 year old woman. Cerebral blood flow (CBF, mL 100g⁻¹ min⁻¹), cerebral metabolic rate of oxygen (CMRO₂, mL 100g⁻¹ min⁻¹) and cerebral metabolic rate of glucose (CMR_{glc}; micromol 100g⁻¹ min⁻¹) all show higher values in cortex than in white matter. Oxygen extraction fraction (OEF) and glucose extraction fraction (GEF) are relatively uniform throughout the brain. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 2.

Compensatory responses to reduced cerebral perfusion pressure (CPP). As CPP falls, cerebral blood flow (CBF) is initially maintained at almost baseline levels by arteriolar dilation. When vasodilatory capacity has been exceeded, cerebral autoregulation fails and CBF begins to decrease rapidly. A progressive increase in oxygen extraction fraction (OEF) preserves (CMRO₂). The response of cerebral blood volume (CBV) to reduced CPP is variable, ranging from a steady rise (of as much as 150%) to only a modest increase beginning at the point of autoregulatory failure. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 3.

Improvement of oxygen extraction fraction (OEF) after extracranial-intracranial (EC-IC) bypass surgery in a 69-year-old man with symptomatic occlusion of the right carotid artery. The baseline PET images (top row) demonstrate reduced cerebral blood flow (CBF, mL $100\text{g}^{-1}\text{min}^{-1}$), and increased OEF in the right hemisphere. A second study performed 35 days after EC-IC bypass shows that ipsilateral CBF has improved and OEF has normalized (bottom row). In all images, the right side of the brain is on the reader's right. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 4.

Pathophysiological changes in cerebral infarction. At the onset of ischemia, the initial fall in regional cerebral blood flow (CBF) is mirrored by a rise in regional oxygen extraction fraction (OEF). Since the increase in OEF is not sufficient to supply the energy needs of the brain, the regional cerebral metabolic rate of oxygen (CMRO₂) falls to the level of oxygen delivery. With time, CMRO₂ falls further even though there is only a slight further decrease in CBF, resulting in a decrease in OEF. Reperfusion via recanalization of the occluded artery or recruitment of collateral pathways results in an increase in CBF ("luxury perfusion") and a concomitant fall in OEF below baseline with no change in CMRO₂. With evolution to the stage of chronic infarction, CBF progressively declines and OEF increases, but often remains below baseline values. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 5.

Luxury perfusion seven days after a hemispheric infarction. Cerebral blood flow (CBF, mL $100\text{g}^{-1}\text{ min}^{-1}$) is elevated in combination with reduced cerebral metabolic rate of oxygen (CMRO₂, mL $100\text{g}^{-1}\text{ min}^{-1}$) and OEF. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 6. PET five months after hemispheric infarction. Cerebral blood flow (CBF, $\text{mL } 100\text{g}^{-1} \text{min}^{-1}$) and cerebral metabolic rate of oxygen (CMRO₂, $\text{mL } 100\text{g}^{-1} \text{min}^{-1}$) are severely reduced and oxygen extraction fraction (OEF) is below normal.

Figure 7.

Crossed cerebellar diaschisis 5 months after a left frontal infarct. Tomographic slices through the posterior fossa demonstrate reduced cerebral blood flow (CBF, mL 100g⁻¹ min⁻¹) and cerebral metabolic rate of oxygen (CMRO₂, mL 100g⁻¹ min⁻¹) in the right cerebellum. Oxygen extraction fraction (OEF) looks relatively uniform although it is usually found to be slightly elevated. In all images, the right side of the brain is on the reader's right.

Figure 8.

PET images corrected for partial volume effects from a 44-year old man with a putaminal hemorrhage studied 21 hours after onset. Peri-hematoma cerebral blood flow (CBF, mL 100g⁻¹ min⁻¹), cerebral metabolic rate of oxygen (CMRO₂, mL 100g⁻¹ min⁻¹) and oxygen extraction fraction (OEF) are all reduced compared to the contralateral hemisphere, indicating primary metabolic depression. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Figure 9. ^{18}F -fluorodeoxyglucose PET images from a 72-year-old woman with left putaminal hemorrhage studied 26 hours (top left), 2.2 days (top center), and 4.9 days (top right) after onset. Images are normalized to mean activity in the initial scan. Bottom row shows initial CT (left) and the subtraction image of the first two PET studies superimposed on the CT, demonstrating the region of increased glucose metabolism adjacent to the hematoma.

Figure 10.

PET study of a 54-year old woman who developed left hemiparesis due to vasospasm 9 days after subarachnoid hemorrhage. Right hemispheric cerebral blood flow (CBF, mL 100g⁻¹ min⁻¹) is reduced more than the cerebral metabolic rate of oxygen (CMRO₂, mL 100g⁻¹ min⁻¹) and oxygen extraction fraction (OEF) is increased, indicative of ischemia. In all images, the right side of the brain is on the reader's right. Adapted from Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. *Neuroimaging Clin N Am* 2003; 13: 741–758.

Table 1

Criteria to Establish Accurate PET Imaging of Preventable Infarction

	Imaging Signal A	Imaging Signal B	Imaging Signal C
Untreated Tissue	All Dies	All Dies	All Survives
Treated Tissue	All Dies	All Survives	All Survives