PET Scanning: Can It Help Resolve Management Issues In Cerebral Ischemic Disease?

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THIS EDITORIAL ATTEMPTS to critically evaluate how PET may affect the care of patients with ischemic cerebrovascular disease and to identify directions in which future studies might be directed. PET scanning studies of patients with cerebral ischemic disease have been reported in the open literature from 1978. Since then PET scanning has advanced technically and new methods for measuring a variety of physiological variables have been described or refined. It seems opportune to review the capabilities of modern PET technology and well established methods of physiological measurement pertinent to the investigation and management of cerebral vascular disease.

Physiological Measurement with PET

There are now established and widely used PET methods for measuring regional cerebral energy metabolism and hemodynamics. Cerebral function can be assessed with oxygen or glucose consumption measured in micromoles per volume of brain per minute. Measurement of oxygen consumption depends on the role of oxygen as an acceptor of reducing equivalents (hydrogen) from the electron transport chain. This results in the production of metabolic water in amounts proportional to the ATP generated. As a corollary, if electron transport is uncoupled from phosphorylation the measurement of functional activity will be in error. Glucose consumption is measured using the analogue tracer deoxyglucose as a function of the steady-state activity of hexokinase; the first step in the glycolytic pathway. Under ischemic conditions, the behaviour of the analogue may deviate from normal. In addition, glyceraldehyde may persist despite impaired citric acid cycle metabolism or failure of oxidative phosphorylation, with the resultant production of lactate and other intermediate metabolites but little useful energy.

An important aspect of the study of ischemia is an appreciation of the relationship between the supply of the essential energy substrates, glucose and oxygen and demand for them by the cerebral tissues. This can be done regionally with PET by reference to the fractional arterio-venous extraction of the substrate into the tissue from the perfusing blood. The extraction of glucose is normally about 10% and that of oxygen 40%. There is therefore a greater reserve of glucose than oxygen in the blood stream, hence oxygen becomes the first limiting substrate when perfusion fails. The appearance of maximal extraction of oxygen and hence perfusion-limited metabolism (and function) constitutes the onset of ischemia.

Physiology can be assessed with reference to regional cerebral blood volume and blood flow. These are readily measured by a number of techniques. The measurement of blood volume (in ml per volume of brain) with a red cell or a plasma tracer requires knowledge of the cerebral to peripheral haematocrit ratio, which can itself be measured in addition to regional cerebral haematocrit, by the combined use of the two tracers. Regional blood flow measurements (in ml per volume of brain per minute) are made using inert, freely diffusible tracers, most frequently oxygen-15 labelled water. In the latter case the accumulation of the tracer in tissue is a non-linear function of blood flow. Hence, the mean regional flow recorded from heterogeneous mixtures of tissue may be underestimated. This problem can be overcome to some extent by appropriate modelling strategies. Techniques are also available for the measurement of cerebral pH and blood brain barrier function. However, these are somewhat less well established and so far not so extensively applied to cerebrovascular problems. It is clear that the clinician who requires a detailed knowledge of the pathophysiological mechanisms responsible for his patient’s illness has at his disposal a wide, appropriate range of measurable variables and well established PET techniques by which they can be quantitatively assessed.

PET scanners have evolved from slow, relatively insensitive, single slice machines to fast, sensitive, multiple slice machines capable of rapid repeated measure-
ment of regional tissue tracer concentrations. These permit the construction of regional time activity curves with precision and a spatial resolution of approximately 0.2 cm. Improved temporal resolution implies that methods for making measurements of blood flow and energy metabolism should also become more rapid. For example, techniques are being developed which will now permit the measurement of both flow and oxygen extraction with one tracer simultaneously (rather than consecutively), which has not been possible to date. Such developments will permit repeated studies and therefore the acute assessment of the effects of therapeutic intervention.

**PET and Human Cerebral Ischemia**

Before making extravagant claims for the impact of PET, it is as well to ask what has been elucidated in human cerebral ischemic pathophysiology with PET so far. There have not been many studies in terms of numbers of patients, but most agree on the substance of the observations if not always their interpretation. What is the response of the cerebral tissues to ischemia? The characteristic pattern is of an acute and marked elevation of local oxygen extraction to maximal levels indicating perfusion limited metabolism. Clinical dysfunction is mirrored by an appropriate focal depression of oxygen metabolism. The ischemic phase is short lived in man. Tissues in the region of the basal ganglia and deep white matter show an early pattern of falling oxygen extraction, depressed metabolism, and heterogeneous flow. This is the pathophysiological characteristic of infarction and indicates a particular susceptibility of these tissues to ischemic insult. It is not clear whether this is because of an intrinsic sensitivity to ischemia of the neurones in these regions, or a result of the anatomical arrangement of anastomoses between deep and superficial perforating arterial systems. In the great majority of patients presenting with major strokes whose deficits become fixed and significant, the pattern of low oxygen extraction and low metabolism affects most of the tissue (both deep and cortical) that has been subjected to severe ischemia within 12 hours. The fall in oxygen extraction indicates the end of the phase of flow limited metabolism and function. Metabolism following a severe ischemic insult with infarction remains irreversibly depressed below normal levels indicating cellular death. Reperfusion is heterogeneous and can rise to values above normal, indicating revascularization or spontaneous dysubstilation of occluded vessels. The phase of relative hyperemia (flow high relative to metabolism), characterized by low oxygen extraction, persists for a number of days or even weeks depending on the size of infarction.

There are a number of preliminary observations which remain to be more precisely defined. The metabolic and perfusion thresholds for infarction in terms of depth and duration of ischemia remain imprecisely known though some preliminary, largely extrapolated data are available in the literature. The period of supranormal oxygen extraction may last hours, a considerable proportion of this at submaximal levels so that the actual ischemic episode may be very short. The time course of maximal oxygen extraction is still imprecisely understood, acute sequential studies in patients with very early ischemia are now needed, with clear documentation of subsequent functional outcome. Such studies may have a considerable impact on defining early prognostic features of ischemic disease.

The sequence of events in transient ischemic attacks is also largely unexplored. It is not clear whether patients with TIA have a completely reversible metabolic deficit, or whether the changes are so restricted in space or degree that no clinical deficit is clinically obvious, but limited neuronal death occurs. This latter scenario would have major implications on the therapeutic attitude to patients with TIA, and on the understanding of intellectual decline known to be associated with cerebral ischemic disease. There is also the question of cerebral functional recovery. Acute observations with sequential follow-up to assess if focally depressed metabolism is ever reversible are urgently required.

The modification of the response of human cerebral tissue to ischemia has hardly been investigated. Attempts at altering perfusion pressure in the phase of elevated oxygen extraction are limited; a case study in a patient with a stroke in whom increased perfusion pressure reduced an elevated OER has been published; a patient with TIA with persistently, though submaximally raised oxygen extraction which normalized on extracranial-intracranial arterial bypass surgery has been described; a few cases of reversion of elevated oxygen extraction to normal in patients with ischemic episodes and extensive extracranial occlusive disease have also been reported following endarterectomy or extra-intracranial bypass surgery. There have been no reported studies in patients with evolving infarction and the vexed question of emergency revascularization in the very earliest stages of evolving stroke, secondary to acute carotid occlusion have not been studied. Treatment of patients with drugs designed to suppress metabolism lend themselves to study as do objective monitoring both of the primary aim of therapy and the metabolic end result. The question of metabolic activity as a prognostic factor and its accuracy in indicating cell death, as well as the correlation of degrees of disability with residual metabolic levels and patterns of disturbance remain to be investigated. A correlating study between agonal metabolic rates and regional neuronal cell counts might help to answer these questions.

The frequent observation of the so called distant effects of acute ischemic infarction, especially effects in the contralateral cerebral and cerebellar hemispheres are entirely unexplained. Some studies suggest that these changes may be transient indicating diachisis or functional impairment. Others suggest that the changes may be permanent or even antedate the ischemic insult and thus represent previous subclinical ischemic events in patients with generalized atherosclerotic disease. One distant effect which appears to
be a genuine example of functional deactivation is "crossed cerebellar diaschisis." The intriguing aspect of this observation is that so far the phenomenon has no obvious, recognizable clinical correlate. This raises questions about the sensitivity and usefulness of the metabolic rate as a prognostic or functionally related factor.

**PET and Hemodynamic Failure**

Threatened stroke and incipient hemodynamic decompensation are potentially more amenable to therapy than established ischemic events and as problems lend themselves to physiological study. The aim would be to identify patients on physiological grounds who might benefit from treatments designed to improve regional perfusion. The recent EC-IC bypass trial recruited over 2400 patients in order to assess the efficacy of this surgical procedure. The results were disappointingly negative, the more so because the very patients who were most expected to benefit from an improvement in perfusion seemed to do least well. It is clear that the inclusion of so many patients was a direct result of the fact that patients with atheroma, extracranial vascular occlusions, transient ischemic attacks or mild to moderate ischemic deficits form a very heterogeneous group. Anatomically as much as clinically, no two patients are the same although there are common pathophysiological mechanisms leading to tissue destruction. However, there has been no reliable way of measuring in a comparable and readily interpretable manner these common factors, which are the metabolic activity of the cerebral tissue and its regional hemodynamic status. PET has changed this state of affairs. The degree of reduction of the oxygen carriage reserve can be assessed with the OER and the degree of preexisting, underlying metabolic damage can be assessed with the metabolic rate. Regional hemodynamic decompensation can be assessed by regional measurement of the CBF/CBV ratio. Patients with different vascular anatomy and lesions as well as different presentations can be grouped into homogeneous groups on the basis of pathophysiology. Indeed preliminary observations of the physiological effects of EC-IC bypass have appeared in the literature which can be compared to the clinical results of the EC-IC bypass study.

An outstanding question in relation to states of physiological compromise and decompensation is their temporal stability. The natural history of the impaired CBF/CBV ratio needs to be established by serial measurements. The state of incipient ischemia characterized by an elevated fractional oxygen extraction requires similar investigation. Clinical observations comparing the outcome in groups of patients in the three principle states of normal physiology, exhausted hemodynamic reserve and impaired oxygen carriage reserve are needed. If these homogeneous pathophysiological states have prognostic significance in terms of stroke risk, it would be legitimate to select patients on the grounds of demonstrated physiological decompensation. Half of these patients could be subjected to revascularization therapy and the outcome compared clinically with an unoperated, conventionally treated cohort. This type of study with physiological entry criteria and defined clinical end points could economically answer a question not posed and therefore left unanswered by the excellent EC-IC bypass study: can the operation be a useful prophylactic treatment in patients selected on pathophysiological rather than less discriminatory clinical grounds?

Other questions of management which would lend themselves to investigation with PET based physiological measurement include the problem of risk of stroke in patients with generalized atherosclerosis undergoing coronary artery bypass grafting or peripheral vascular surgery. Such patients frequently have carotid disease which may be symptomatic or asymptomatic. It is presently unclear which patients should have carotid before other surgery and which are at no risk of peri-operative cerebral infarction for hemodynamic reasons. On the other hand, the study of energy metabolism and hemodynamics seems to have little to offer in the management of patients who suffer ischemic events from acute embolii arising in the heart or cervical vessels. However, the underlying state of the hemodynamic and oxygen carriage reserves will indicate the susceptibility to severe ischemia and infarction from what could otherwise be a banal occlusive event if occurring in the context of a fully compensated circulation.

**PET and Other Physiological Variables**

There can be little doubt that there are many clinically relevant questions with major implications on management which might be usefully elucidated by measurement of regional energy metabolism and hemodynamics. The measurement of variables such as local hematocrit in acute ischemia and its modification with objective monitoring of effects could also go some way to settling the question of the efficacy of plasma expansion and the role of viscosity in the propagation of ischemic damage. There are preliminary data which suggest local increases in cerebral hematocrit in patients with acute focal ischemia and the spontaneous normalization of this change with time. Likewise, studies have already shown disturbances of oxygen and glucose stoichiometry in subacute infarcts, but there is little information on the changes in very acute ischemia and whether they have any bearing on eventual outcome. Similarly, local pH changes have been recorded from infarcted tissue with a suggestion that such tissue is alkaline compared to normal brain. On the other hand, pH has not been measured in early ischemia when the oxygen extraction is still elevated. Local tissue lactate acidosis may be buffered by residual blood flow above a critical threshold. It may be that this will also have an effect on the degree of eventual irreversible ischemic damage.

**PET and Future Advances in Cerebral Ischemia**

What are the factors retarding advances in the understanding of the pathophysiology of human cerebral
ischemia and preventing the more widespread application of PET in clinical practice? PET facilities are expensive in capital costs and personnel. The technological advances in scanner design and wide variety of physiological variables available for measurement have posed considerable intellectual problems of data reduction, correlation and presentation, many of them incompletely resolved. In any event it is also clearly no longer sufficient to measure a single variable in large, inhomogeneous groups of patients with the hope of discovering something of significance to the understanding or management of cerebral ischemic disease in all its diversity.

The costs of clinically dedicated scanners and cyclotrons capable of producing appropriate tracers are falling rapidly and it is possible to conceive in the future of PET-based investigations of individual clinical problems. Indeed it could be argued that patients with extensive, extracranial vascular occlusive disease already constitute a group in which individual clinical questions, with an immediate bearing on management, might be resolved with PET scanning. However, it is the author's view that for the time being the main impact of PET to the management of ischemic disease will reside in programs of good clinical research, which will produce knowledge which may alter or test the efficacy of clinical practice and which will point to clinical indications or simpler tests, which might suffice to make the necessary management decisions. For this reason further significant studies in ischemic disease depend on the formulation of strictly defined and well circumscribed questions, capable of answer by the techniques at hand and performed on rigorously selected and clinically documented patient populations.

A problem of clinical research with PET in cerebral ischemic disease which has not been adequately resolved is that of logistics. PET based techniques are demanding of time and require dedicated, immediately available tracer production facilities to be able to study acute and rapidly changing pathophysiological states and clinical conditions such as stroke. The logistics of combining a professional clinical workup with a multi-parametric PET study and perhaps radical operative or experimental medical treatment, all in an intensive care environment, has been tackled by very few of the existing PET facilities which are frequently sited away from main patient care areas. There are also problems with the recruitment of patients within short periods of the onset of acute disease. Strategic siting of PET facilities in high dependency clinical settings with good referral bases and efficient and competent clinical and ancillary investigations, including neuroradiology, must be a priority. Only then can many of the more interesting management questions be addressed by PET measurement of physiological variables of direct relevance to the assessment of acute therapy.

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