RELIANCE ON CLINICAL AND ANATOMICAL information alone has proven of limited value in the management of ischemic cerebrovascular disease (CVD). Heretofore, progress in understanding the pathophysiology of ischemic stroke in the clinical patient has been slow due to the lack of readily available, sensitive, accurate and above all non-invasive methods of measuring cerebral hemodynamics and metabolism. Methods that meet some of these required criteria have been developed in recent years and their incorporation into routine clinical investigation appears imminent. Thus it is timely to take stock of the relative merits of these techniques prefaced by a brief discourse on the importance of functional measures in the routine evaluation of stroke.

Although the causes of acute ischemic stroke are multiple, the common factor is reduction of cerebral blood flow (CBF) to levels that produce neurological deficit. If the extent and degree of reduction is within the limits of resolution of any of the available methods, then CBF measurement may have use in the diagnosis of ischemic stroke because accepted imaging modalities such as CT frequently reveal no abnormality in the acute stages. Perhaps more importantly and essential to the ideal management of acute stroke, is the knowledge of whether the jeopardized brain tissue is reversibly or irreversibly damaged. Backed by an expanding and persuasive volume of experimental literature the measurement of zero flow and the delineation of blood flow thresholds in a focus of ischemia may have value in this regard. 1

Metabolic measures are also essential. For example, a pattern of low cerebral metabolic rate for oxygen (CMRO₂) combined with either a reduced or increased oxygen extraction fraction (OEF) obtained by positron emission tomography (PET) can respectively differentiate between infarcted tissue or an ischemic area where viable tissue, though of impaired function, metabolizes proportional to the available perfusion. 2 The former condition renders the issue of CBF adequacy irrelevant for tissue viability, whereas CBF becomes a critical issue in the latter case. The experimental literature also underscores the importance of monitoring high energy phosphates, lactate, pH and redox state of the tissue in progressive ischemia. 3 This type of functional information is likely to be of value not only to those clinical stroke units where an aggressive therapeutic approach is taken but is also of prognostic importance.

Transient ischemic attacks (TIAs) often can herald an established stroke and accordingly must be expeditiously evaluated to define their cause, to predict the subsequent natural history and to take appropriate therapeutic action. Despite the transient nature of neurological deficit, a substantial number of these patients either have CT or MRI findings consistent with infarction (cerebral infarction with transient signs, CITS) 4 or show persistent hemodynamic and metabolic abnormality. 5 For example, it is possible to identify patients with a pattern of persistently decreased regional CBF and CMRO₂ with increased regional cerebral blood volume (CBV) and OEF that most likely categorizes a non-embolic hemodynamic pathogenesis for the TIA (fig. 1). Functional activation with CO₂ inhalation or intravenous (IV) Diamox to determine the effectiveness of collateral vasocapacitance in such patients could further support a hemodynamic pathogenesis (fig. 2).

The majority of strokes occur without warning although a number of well known risk factors can signal a potential problem. It is in the asymptomatic but high risk group that non-invasive functional studies may have the greatest use. Study of the hemodynamic consequence of extracranial arterial obstruction using the noninvasive methods of B-mode and Duplex doppler scanning in combination with ocular plethysmography has achieved great popularity although surprisingly there has been little or no attempt to combine and correlate results with direct measures of CBF. Nevertheless, the serial use of these techniques can potentially identify those patients at risk of stroke from progressive carotid occlusive disease. Again in the asymptomatic patient, occlusion of one internal carotid artery (ICA) is not an infrequent occurrence, may increase stroke risk and causes a heterogeneous spectrum of CBF and metabolic change distal to the occlusion. 3, 6

It is not established practice to screen for progressing ischemic cerebral dysfunction in patients with increased stroke risk in the manner that patients are screened for hypertension, hyperlipidemia, etc. Yet there are logical arguments to do so. The gradual development of large and small vessel atheroma or hy-
pertensive arteriosclerosis leads inexorably to increase of cerebral vascular resistance and eventually flow constricting arteriopathy. Before CBF falls into the ischemic range, oligemic values or unphysiological asymmetries of CBF may develop which potentially could be more accurately predictive of impending stroke.7

Given the persuasion that functional studies are needed in stroke assessment, what techniques are available and how available and to what degree are they established for clinical use? What are the advantages and problems associated with each technique and in what situations is it appropriate to use a particular methodology? What does the future hold in terms of new techniques being developed?

The measurement of flow in vessels has had an important role in contemporary stroke management. Cerebral arteriography is essentially a static anatomical technique, although dye transit times have been used to qualitatively assess brain perfusion prior to the development of more satisfactory techniques. Furthermore, angiography is not indicated in all stroke patients and comes with a risk of morbidity because of its invasive nature. Largely due to the latter, a number of techniques have been developed to avoid or potentially replace angiography. Mentioned earlier, ultrasonic doppler studies have come some way in achieving this objective and are routinely used in the non-invasive investigation of large vessel disease.

When an external ultrasonic frequency is "bounced" off the moving column of blood and received by a detector there is a difference between the emitted and received frequency equal to the "doppler shift." This doppler shift forms the basis for carotid doppler ultrasound (CDU). Generally this technique is capable of detecting a point of vessel lumen stenosis within 1 cm and its severity within 10% accuracy.8 The greatest accuracy of CDU is when a stenotic lesion is greater than 75% — as the specificity and sensitivity of accurately detecting this grade of lesion is greater than 95%. There are two basic types of CDU. Continuous wave doppler is the most popular method as it allows a wider spectrum of frequency analysis and the probe head is small (little larger than a pencil) so it can be used in tight places — especially below the mandible — a common site of ICA stenosis.

A recent study has correlated over 1500 angiograms with C-W doppler to evaluate its reliability in detecting intracranial disease.9 Supraclinoid occlusions of the ICA were reliably demonstrated as was atherosclerotic carotid siphon stenosis greater than 60% of the lumen diameter. However, the majority of acute middle cerebral artery (MCA) occlusions could not be detected largely because this will not significantly reduce the relative end-diastolic flow velocity because of more effective collateral circulation compared to the intracranial ICA.9 Because of these limitations, indications for angiography should not be based solely on C-W doppler findings. Pulsed-gated doppler allows complementary analysis by scanning the lumen from wall to wall at different depths, in small steps, permitting the display of flow changes associated with an ulcerated plaque.

CDU becomes valuable when both spectral analysis (so that the frequency shift can actually be measured) and orbital directional doppler are used. This latter technique allows detection of reversed blood flow (from face to brain) when the stenosis is greater than 90%. Modern equipment routinely incorporates both methods. Spectral analysis (fast Fourier analysis of the acoustic properties of the signal) of a carotid bruit is considered more accurate than angiography as the residual lumen diameter is computed from the signal and not from the physical appearance of the lumen.10 B-Mode imaging (BMI) is real time ultrasound imaging with magnification of the artery and thus the direct
Oculoplethysmography (OPG) is a simple method of because of its inaccuracy with high grade stenosis. Oculeoplethysmography (OPG) is a simple method of looking for hemodynamically significant extracranial occlusive disease by measuring ophthalmic systolic pressure, ocular pulse amplitudes and a derived ocular blood flow. The recent advances in CDU/BMI have rendered OPGs less essential. Furthermore with bilateral CVD the results become increasingly difficult to interpret. An essentially useless and misleading technique that is commonly available in pulsed models is the direct “pictorial” graphic display of arteries. Here the technician “paints by number.”

Transcranial doppler (TCD) has been developed for the noninvasive assessment of intracranial CVD. Actual velocities of flow can now be determined at the basal intracranial cerebral arteries, akin to the ultrasound methods for studying the extracranial vessels. Increased flow velocity can be seen through a stenosed vessel related to the loss of flow energy and increased flow volume. There is an inverse relationship between vessel diameter as measured by angiography and flow velocity found in doppler recordings. Flow velocity is equal to flow volume divided by the cross-sectional area of the vessel lumen. Proximal MCA flow velocities can be determined as mean and peak flows. Anterior and posterior cerebral artery flow velocity can also be studied in most individuals. Flow velocities in the basal cerebral arteries have a wide normal range in part due to great individual variation that may occur from differences in heart rate, blood pressure, vascular compliance, vessel caliber, and arterial pCO2. These parameters need to be carefully measured and correlated. Further preliminary data suggests the TCD signal sensitivity varies for different subgroups of the population based on race (J. Halsey, personal communication).

TCD can provide hemodynamic data for problems such as velocity distributions, intracranial steal, functional stenosis, acute embolic occlusion and disocclusion (fig. 3), collateral supply, and vasospasm. To date, studies with angiographic and physiologic correlating data are few. Lindegaard et al11 correlated TCD with angiography in 77 patients with carotid artery disease finding that a measure of transmitted pulsatility was reduced in the ipsilateral MCA when the luminal area of the ICA was reduced by 75% or more. Interestingly, bilateral carotid stenosis (75–89%) further decreased the pulsatility index, suggesting impaired potential for collateral flow. Retrograde flow through the proximal anterior cerebral artery was demonstrated in 29 of 31 patients when this flow pattern was seen angiographically. More extensive studies are needed to assess the sensitivity and specificity of this new technique before it should be introduced into routine clinical practice.

NMR imaging of flow in cerebral vessels both qualitative and quantitative is a most exciting recent development although still in its experimental stage.12 Mo...
low uptake of tracer in ischemic tissue, any method that measures washout is unable to detect regions of zero or very low flow. Conversely, luxury perfusion or very fast flows are consistently underestimated because of delay in fitting the washout curve. This can be overcome somewhat by fitting the input function of the total curve and new mathematical procedures to adjust for airway artifact should improve the accuracy of flow measurements, particularly for fast flows. A further major disadvantage is that heterogeneities of the partition coefficient for $^{133}$Xe in an ischemic focus cannot be built into the calculation. For this reason perfusion indices such as the initial slope index (ISI) have been introduced. Finally, the technique provides two-dimensional planar data which does not permit an easy comparison with CT or NMR imaging.

These problems notwithstanding, it is very appropriate to use the method for serial measurements of global cortical ischemia and if probe-pair asymmetries are analyzed than an approximate focus of cortical ischemia can be localized. Where the technique has unrealized potential is in the assessment of extracranial and intracranial large vessel obstruction which causes reproducible alteration in cortical perfusion indices and asymmetrical regional CBF patterns. If low CBF or the development of flow asymmetries become an established stroke risk factor than the technique will be an ideal screening device because of its general availability and the safety with which repeated measures can be made.

The stable Xenon/CT (Xe/CT) method of imaging CBF has the major advantage of being commercially configured within the GE9800 CT scanner making it readily accessible. 30–35% Xenon is inhaled with close clinical monitoring as toxic reactions can occur. No significant complications however have been reported in over 2,000 studies (H. Yonas, personal communication). An additional 15 minutes is required beyond the time necessary to obtain a CT image and flow data is available 14 minutes after data acquisition is completed. Thus as soon as possible after head CT, and possibly subsequent angiography, physiological data is available to complement imaging data of the brain and blood vessels. A major theoretical benefit of this technique over others is the ability of Xe/CT to measure zero or very low flow in relatively small regions of superficial and deep, anterior or posterior brain structures. Thus the extent and location of acutely reduced and/or enhanced CBF can be studied with direct potential application to early accurate diagnosis of stroke (fig. 4). For example patients studied within 6 hours of ischemia showed well defined large or small regions with regional CBF levels of 0.1–5 ml 100 grams/brain/minute (H. Yonas, personal communication). All patients with fixed deficits had low attenuation in comparable regions on later CT study. Other patients had increased CBF within low attenuation regions on early CT that subsequently represented smaller regions of tissue loss with zero flow on CT/CBF follow-up, presumably due to embolic migration and early reperfusion.

There are significant problems with the method. In the inert Xe/CT technique, as in every indicator dilution technique, there are several assumptions made as to experimental conditions. It is assumed that the signal is proportional to the indicator concentration, that a steady physiological state exists in the organ in which blood flow is being measured, that the input function of indicator concentration is well-known, and that, in the case of the inert Xe/CT techniques, only one compartment of flow is represented in each volume element.

To some extent, all these assumptions are violated in the inert Xe/CT technique. Beam hardening, due to the skull and more problematically due to the Xenon in the tissue itself, means that the signal (photon absorption) is not uniformly proportional to indicator concentration across the volume of interest. In addition, partial volume effects, particularly in cortex and ventricles, again lead to the conclusion that the signal in these physiologically important areas is not proportional to the indicator concentrations. Xenon in concentrations of 30–35% has been found to alter cerebral blood flow upward by as much as 30–40%, thus violating the assumption of a steady physiological state. The meth-
ods used for assessing the arterial input function (end-tidal sampling) are not ideal, and, for an uptake experiment, errors due to inaccuracy in input function determination may produce large errors in blood flow determinations. Finally, the volumes under consideration must violate the assumption of a single tissue compartment, with a single partition coefficient and a uniform blood flow. These fundamental violations of the assumptions of indicator dilution theory should make absolute measures of flow by this technique unreliable.

The optimum time of scanning for determination of low flow (1.5–2.5 minutes) is less than the optimum for determining slow flow, generating uncertainties in flow distribution between gray and white matter. Finally the radiation dose of a Xe/CT study is not trivial, limiting the possibility for serial measurements in the same patient and perhaps the evaluation of young patients with CVD. The above problems are somewhat counteracted by the decided advantage of being able to image and derive the heterogeneities of the blood brain partition coefficient in the ischemic tissue.

Despite its disadvantages the Xe/CT technique could establish itself, particularly in the investigation of acute stroke. However, although the measurement of zero or near zero flow is advantageous, the Xenon induced flow activation may cause a "steal" phenomenon which could account for the extremely low flow sensed by the method. Therefore, vigorous validation and cross correlation with other CBF methods is essential as are clinicopathological correlations. Unless such validation is carried out the easily available commercial software package may prove a mixed blessing when used by investigators less alert to the limitations and disadvantages of the method.

Single photon emission computerized tomography (SPECT) employs 64 sodium iodide scintillation crystals arranged to produce 3 tomographic slices, each 2 cm in thickness with the centers 4 cm apart. Currently the two pharmaceutical agents most widely used to measure CBF by SPECT are 133Xe and N-isopropyl (I-123) p-iodoamphetamine (IMP). The latter, lipid soluble compound passes the blood brain barrier and is extracted by the brain in proportion to the rate of CBF. Comparison of inhaled 133Xe versus intravenous IMP SPECT in the determination of rCBF showed good agreement between methods.16 This is an advantage since 133Xe is more practical, affordable, easily repeatable and quantifiable without necessitating arterial sampling and with a lower radiation exposure to patient and personnel than IMP.133Xe inhalation, however, introduces airways artefact which significantly detracts from imaging the anterior-inferior portions of the frontal lobe. CBF determinations by IMP SPECT also have higher resolution than 133Xe.

SPECT derived CBF in general has poor resolution being somewhat under 1.7 cm at the center of the transverse section causing a certain amount of artefact imaging. The technique in general also has poor sensitivity. Small variations in cerebral IMP content of the order of 2% may be interpreted as significant flow decrease. Thus if there is inhomogeneous IMP uptake, even in normal brain, image abnormalities may be overlooked or noise mistaken for decreased flow or reduced perfusion. These uncertainties are increased by partial volume effects which also explain the frequently artefactual measures of flow recorded in ventricular spaces. All of the above factors serve to make the problems of accurate head repositioning and tissue slice comparisons for serial statistical study, common also to CT and PET, even more exaggerated in the case of SPECT. The problem of IMP are compounded by the necessary cyclotron production of 123I and accordingly expense and limited availability. The radiation dosimetry is significant and thus limits frequent serial studies. Accordingly, the search for the ideal rCBF SPECT imaging agent continues. A newly developed agent Hm-PAO seems promising in terms of distribution and dosimetry.

These limitations aside, SPECT has increasingly proven useful in the investigation of stroke. Like Xe/CT the technique has diagnostic utility inasmuch as reduced rCBF can be imaged before structural changes are present on CT or NMR. Anatomical and functional slice comparisons have revealed more extensive regional decreases in CBF than would be predicted by the CT lesion, in some instances as much as twice the volume of the infarct seen on CT.17 Such measurements have permitted more exact functional correlates of clinical neurological deficit.18 The SPECT is very suitable for CBF activation studies in patients with TIA or RIND (see fig. 2). Unlike Xe/CT, SPECT does not readily measure zero flow and accordingly observation of flow thresholds in ischemic brain are unachievable. The limited resolution of the method causes small areas of infarction to be missed more often than Xe/CT.

PET is considered the "gold standard" for non-invasive functional imaging of the brain and is currently the only technique whereby CBF and metabolism can be studied jointly. The effectiveness of this technique in stroke has been the subject of a recent STROKE editorial. The theoretical limit of imaging resolution with PET is in the few millimeter range; currently 3–4 mm is the practical limit. With this technique picomolar concentrations of radioisotope can be measured in brain, fortuitously also the concentration range of pharmaceutical agents and neurotransmitters. Tracer uptake models have been developed based on input functions and tissue response to measure regional CBF, CBV, CMRO2, glucose consumption (CMRG1) and to derive the fraction of oxygen extracted by tissue (OEF). A measure of pH can also be approximated.

Because of certain practical limitations with PET most of the available data has been acquired beyond 72 hours after the onset of the stroke, but a few earlier studies have been possible. Enough data has become available to derive useful flow and metabolic profiles of differing ischemic conditions (table 1). Factors such as CMRG1, pH and neurotransmitter dysfunction remain to be incorporated into a working pathophysiological hypothesis of human stroke. Diaschisis
TABLE 1  Profiles of Stroke Pathophysiology as Viewed by PET

<table>
<thead>
<tr>
<th>State</th>
<th>CMRO₂</th>
<th>CBF/CBV</th>
<th>OEF</th>
<th>CBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemodynamic</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>reserve (vasodilation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased oxygen</td>
<td>↓</td>
<td>↓</td>
<td>↑*</td>
<td>↓</td>
</tr>
<tr>
<td>extraction reserve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>↓</td>
<td>variable</td>
<td>↓</td>
<td>variable</td>
</tr>
<tr>
<td>Early infarction</td>
<td>↓</td>
<td>variable</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Late infarction</td>
<td>↓</td>
<td>variable</td>
<td></td>
<td>↓</td>
</tr>
</tbody>
</table>

= normal; ↑ = increased; ↓ = decreased.

*If CBF/CBV is less than 5.5, an increase in OEF is seen. (adapted from RSJ Frackowiak et al. MRC Cyclotron unit, Hammersmith Hospital, London, England).

has been observed in subcortex ipsilateral to the ischemic focus and in the contralateral hemisphere and cerebellum.19

In terms of technique the radiation dosimetry to the patient is significant and probably prohibitive for frequent serial study. The practical resolution of most prototype machines is 4–8 mm. Valid tracer models are imperative; recent criticism of the glucose model has been strong! There is sparse information available on tracer-tissue partition coefficients in disease states such as ischemia. It may be inadequate to express quantitative PET data “per ml of cerebral tissue”; ideally we need knowledge of the uptake per unit of viable cell or subcellular structure. Formulation of tracer models using complex mathematics makes for more difficult communication and validation of methods between laboratories. Reproducibility of the image slice position makes precise comparative study of repeated images problematic. Finally, availability is limited; less than 50 centers worldwide will have an active PET facility within the next 1–2 years. Despite the above drawbacks PET, when introduced into routine clinical practice, can reasonably be expected to enhance our understanding of stroke pathophysiology beyond its already salutary contribution.

The techniques reviewed so far are suitable for the study of flow in vessels and flow and metabolism in tissue or at a cellular level. The experimental literature argues the need to perform studies at a subcellular level if the effects of acute progressive ischemia are to be ameliorated or protected against. This hitherto daunting prospect for routine non-invasive study now seems feasible in the not too distant future. NMR functional imaging of Na⁺ has been successfully achieved in ischemic tissue.20 When able to identify ionic shifts between extracellular and intracellular compartments this technique will be of inestimable value in the monitoring of cell viability and edema. Although imaging of high energy phosphates may only be realistic at prohibitively high magnetic field strength for human studies, in vivo 31P NMR spectroscopy, though currently of limited resolution, is capable of measuring these compounds and their turnover and seems likely to find a place in monitoring the effects of acute progressive ischemia on brain energetics, at least in moderate volume cortical stroke21 (fig. 5). NMR also affords the opportunity to measure intracellular pH and lactate which are perhaps more critical to irreversible cell damage than energy status.3 The prospect of tracing disturbances of carbon containing metabolic pathways in ischemia looms temptingly on the horizon, limited only perhaps by ingenuity of software development, magnet strength and availability of C-13 for enrichment studies. Although only limited nuclei are NMR sensitive the enlightened use of paramagnetic compounds may in the future render others visible so that
ions such as $Ca^{++}$ and $Mg^{++}$, critical to ischemic pathophysiology, can foreseeably be observed.

In vivo reflectance spectrophotometry has been long in development and although a qualitative method, offers a means of observing shifts in redox status of the cell. There is now the feasibility of measuring cytochrome oxidase activity, a critical enzyme in the electron transfer chain, noninvasively from human cortex. This could prove the most critical measure of all for assessing cell viability and monitoring therapeutic effects.

This review makes clear that no one technique can provide all the needed functional information for the ideal clinical management of acute and chronic ischemia. Societal and humanitarian demand for a noninvasive approach to functional measurements is being met, but requires technology of great complexity and, accordingly, expense. In the case of cerebrovascular disease this would argue in favor of regional stroke centers where such technologies are concentrated and investigative teams are prepared for active intervention and where stroke management can be rigorously, scientifically and informatively assessed. The prevalence of stroke and the social and economic impact of stroke morbidity justifies this strategy.

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