EDITORIAL

Of Cerebral Blood Flow, Stroke and SPECT

Robert H. Ackerman

In an article in this journal Hill et al discuss the applications in stroke disease of a technique for single-photon emission computed tomography (SPECT) that uses N-isopropyl-(I-123)-p-iodoamphetamine (I23IMP) as a cerebral blood flow tracer agent. Although cerebral blood flow (CBF) is a basic biological process, historically the clinical significance of disturbed patterns and measured values of flow has confounded medical investigators. The quest for more clinically meaningful flow information provides an important rationale for the development of SPECT CBF techniques.

Kety and Schmidt made the first quantitative measurements of brain blood flow, in the 1940's, at the University of Pennsylvania, using the nitrous oxide technique to determine mean hemispheric blood flow and mean hemispheric metabolic function. Contrary to expectations, such new physiological approaches had limited clinical impact. The events that opened our current era of interest in and understanding of ischemic stroke disease were related more to developments in therapy, diagnostic techniques and clinicopathological correlations. The use of anticoagulant therapy for treatment of "cerebral thrombosis", in 1946, made imperative the differential diagnosis between ischemic stroke and cerebral hemorrhage. The widespread application of arteriography in the 50's and 60's permitted in vivo demonstrations of the pathoanatomic basis for cerebrovascular insufficiency. Fisher's description of the clinical syndrome of carotid occlusive disease, in 1951, provided a new rationale for better characterizing the causes of cerebral ischemia. It was clear that for CBF measurement also to be of clinical value, techniques were required that could show differences at least between regions of cerebral infarction and normal tissue, rather than methods which gave only mean hemispheric values.

The Kety-Schmidt technique indirectly measured the mean hemispheric tissue concentration of nitrous oxide by determining changes in its arteriovenous concentration during uptake or clearance from the brain. The femoral artery and internal jugular vein were used to obtain the arteriovenous data. The technique lent itself to the measurement of mean hemispheric blood flow and mean hemispheric oxygen metabolism, but could not provide regional blood flow data or information about flow in gray or white matter. The introduction of techniques for monitoring radioactive flow tracers with detectors placed adjacent to the brain, made it possible to measure cerebral tracer concentrations directly and thus determine regional brain blood flow. Moreover, in each region one could discriminate between fast flow, which normally represents gray matter, and the slower flow in "white matter". The advent of regional CBF studies, however, led to fewer clinical investigations of brain metabolism, as no tracer techniques were available for studying regional metabolic function.

For physical and biological reasons, 133-xenon (I33Xe) became the most widely used tracer for regional cerebral blood flow measurements. Initially most centers administered it directly into the carotid artery, as part of a neuroradiological procedure. This invasive approach limited the number of patients one could study and usually restricted a CBF examination to one hemisphere. In the absence of comparative data from the opposite hemisphere, the need to relate flow in areas of suspected abnormality to some "normal" level was met by transposing the regional quantitative data into percents of the mean hemispheric value; the observed percent in each area was compared to that expected. Making sense out of changes in these percent representations was difficult, as a major insult often would disturb the mean itself and hence all relationships to it. Only with the introduction of the I33Xe inhalation technique of Obrist and its intravenous modification could large numbers of subjects be studied and quantitative data be obtained routinely for both hemispheres. As a result, the absolute mean and regional data in each hemisphere could be analyzed more meaningfully. However, because the CBF calculation depended on the use of a I33Xe brain/blood partition coefficient that might change unpredictably in injured tissue, the reliability of the values in areas of acute insult remained uncertain.

Despite a considerable output of time, effort and money, techniques for measuring cerebral blood flow produced relatively little information that proved to be of clinical value in ischemic stroke disease. Workers using the I33Xe inhalation and intravenous techniques suggested that the two-dimensional representation of the data obscured important information. In other words, in the stroke-prone patient and in acute stroke disease the CBF values in the area of the lesion might be partially averaged with more normal superficial, deep or adjacent tissues; where no blood flow is pres-
ent, as in an evolved infarct, the detector would "look through" the area of cavitation at normal tissue surrounding it. Given these considerations, applications to CBF measurements of computed tomographic three-dimensional reconstruction techniques might be expected to provide additional information that would make CBF data of clinical value.

Three-dimensional studies of the brain began with Kuhl's development of methodology for measuring cerebral blood volume. Three sub-types of tomographic imaging of blood flow have emerged. The first employs positron-emitting radionuclides and positron imaging devices to obtain high resolution, three-dimensional representations of CBF. The pairs of photons given off as a result of positron interactions in tissue and the detection of these photon pairs characterizes positron emission tomography (PET). Standard nuclear medicine techniques employ radionuclides and instruments that emit and detect, respectively, single photons. When the data are reconstructed three-dimensionally the method is called "single-photon emission computed tomography (SPECT)." Whereas positron-emitting radionuclides, such as $^{133}$Xe, $^{123}$I and $^{18}$F, can be tagged to a number of metabolically-active compounds and used to measure cellular function, single-photon tracers are most applicable for monitoring blood flow, blood volume and blood-brain barrier integrity. They have not yet been tagged routinely to specific metabolic markers. Moreover, with SPECT, resolution changes with tissue depth, so that activity distributions are not measured at uniform resolution, as they are with positron emission tomography. The third tomographic imaging technique for monitoring blood flow uses fast CT scanners to detect the uptake, clearance or circulation of radiodense materials: for example, iodinated compounds and non-radioactive xenon. The time course of absorption values in each pixel is used to calculate CBF. This technique has advantages in that it permits high resolution imaging of CBF. In the case of xenon it facilitates calculation of actual partition coefficients, and thus determination of more precise quantitative data. However, the technique uses relatively large amounts of costly xenon gas, which must be given in near anesthetized doses to maximize signal to noise ratio with most current instruments. With iodinated compounds the input concentration to the area sampled must be precisely determined, which is not always easy. The method in general requires sequential scans at each brain level, which means repeated exposure of the patient to x-rays, and necessitates exact reproducibility of patient position during the study, which limits application of the technique to cooperative subjects. Nevertheless, using dynamic CT to measure blood flow holds great promise, especially applying the cold xenon method with the newer generation of CT scanners.

In the past year considerable enthusiasm has been generated by single-photon techniques. This enthusiasm has been predicated upon the belief that SPECT provides three-dimensional representations of blood flow non-invasively and can do this in a practical fashion with relatively low radiation doses and inexpensive modifications of conventional nuclear medicine equipment. The two principle CBF SPECT techniques use either $^{133}$Xe or $^{123}$IMP as the tracer, although others are being explored. The initial results of Hill et al show correlations between observed disturbances in $^{123}$IMP distributions and evidence of clinical and tissue abnormalities. As Lassen and Bonte have demonstrated with the $^{133}$Xe technique, SPECT can show blood flow in three dimensions in normals and identify changes in tracer distributions in stroke-prone and acute stroke patients, even when the CT scan is normal. Such findings were not possible with two-dimensional $^{133}$Xe methods, although they were with two-dimensional position imaging. In comparison to $^{133}$Xe, which is a metabolically inert tracer that is taken up by the brain and cleared in proportion to blood flow, $^{123}$IMP is taken up largely in its first passage through the brain and is fixed intracellularly. It resembles the now outdated PET method of measuring blood flow using intravenous injection of $^{15}$N-ammonia. The acute neurological disorders the $^{123}$IMP distributions may not represent blood flow because changes in the tissue environment — related to pH, availability of amine receptor sites or permeability — may impair uptake or fixation. The fact that in acute stroke patients, hyperemias are not visualized with this technique probably indicates that $^{123}$IMP is no longer a CBF tracer agent in acute situations. It may, however, represent something more important, and be an index of impaired cellular function. PET data suggest that in acute neurological diseases, such as ischemic stroke, blood flow is no longer a clinically meaningful parameter by itself, but essentially is an epiphenomenon, only indirectly reflecting disturbed metabolism. If the $^{123}$IMP technique can be shown to provide an index of this dysfunction it may have even more meaningful clinical application.

Although the $^{133}$Xe technique in the past has not been demonstrated to be of use in routine clinical diagnosis or management, the method does provide specific information on blood flow, and when blood flow and metabolism are coupled the data can be used as an index of tissue function per se. The $^{133}$Xe technique is an important research tool, even when used two-dimensionally. Three-dimensional representations of blood flow using $^{133}$Xe and $^{123}$IMP might unveil a number of relative regional changes in CBF that are clinically relevant. However, quantitation with these techniques to date remains limited by unresolved problems related to physical considerations. Moreover, to understand differences in quantitative values between individuals or between sequential studies in the same subject the observed data still might not be sufficient. Increasingly it appears that CBF values must be interpreted in the context of whole blood viscosity effects. Hematocrit, fibrinogen and an interaction between these blood constituents are the main determinants of viscosity and can cause alterations in CBF even when they are in physiological ranges. Similarly, variations in the oxygen carrying capacity may result in differences in CBF even between normal individuals.
In assessing relative differences in regional values the primary clinical imperative in the future may be to measure physiological activity in small tissue volumes, especially in impaired but still viable tissue surrounding an infarct. By treating disturbances in the "penumbra" one might be able to limit stroke morbidity.\textsuperscript{26} Certainly, new PET imaging devices with spatial resolutions of 0.7–1 cm. should be able to define this penumbra. It is not clear if SPECT will have a comparable effective resolution, at least using standard nuclear medicine equipment. The authors of this journal have shown that a conventional nuclear medicine Anger camera cannot resolve small lesions as well as a dedicated SPECT device.\textsuperscript{12} Whichever equipment is used, SPECT images of $^{123}$IMP distributions should, however, have better spatial resolution than those of $^{133}$Xe. The higher energy of the $^{123}$I photons allows data from deep tissues to be better represented than with $^{133}$Xe and generates less scattered radiation. Because $^{123}$IMP is fixed in tissue, data can be collected over long periods in order to obtain counting statistics sufficient for good intrinsic spatial resolution. However, fixation in tissue of a relatively long half-lived tracer such as $^{123}$I, ($t_\text{1/2} = 13$ h), means that sequential studies — for example, before and after therapeutic intervention — cannot be undertaken for almost two days. The short biologic half-life of $^{133}$Xe, despite its long physical half-life ($t_\text{1/2} = 5.35$ d), permits test-retest studies approximately one half hour apart.

Information on the relationship between blood flow and metabolism obtained with PET studies may be transposable to the SPECT field, making more comprehensible the SPECT data obtained during the evolution of a stroke lesion. If, in fact the $^{123}$IMP findings in acute stroke disease are an index of impaired cellular function, PET/SPECT correlations may teach us how to use the $^{123}$IMP data as indices of impaired metabolism. Such comparisons also can help in the assessment of the role of more specific SPECT metabolic tracer agents that may be developed.

In the long run, whether a technique is useful depends not only on the precision of its quantitative values, its spatial resolution and its cost, but whether the data can be correlated with clinical findings to help in diagnosis or choice of therapy. No special procedure has ever been introduced into clinical medicine at a time when the information that it produced was fully understood. Even with the CT scan the cause of the low absorption values in stroke disease still is debated. What is important in making new CBF tools clinically useful is extending the traditional process of clinico-pathological correlation to the physiological arena.\textsuperscript{13} Comprehensive clinico-physiological correlations and comparison of the functional data obtained with different physiological monitoring techniques might help make SPECT of clinical as well as research value.

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