Regional Cerebral Blood Flow: Estimation by Means of Nonmetabolized Diffusible Tracers—An Overview

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Visualization and measurement of functional activity throughout the human brain has been made possible by positron emission tomography (PET) using tracers, the accumulation of which in the various regions of the brain are functions of regional blood flow or energy metabolism. Certain principles and mathematically expressions describing the exchange of diffusible, nonmetabolized substances between capillary and brain, published nearly 40 years ago, have been useful in this development. This is a US government work. There are no restrictions on its use.

The nitrous oxide technique1 useful for the measurement of blood flow, oxygen, and glucose consumption of the human brain as a whole, was incapable of measuring these functions in individual small regions throughout the brain. When the technique was applied to the study of schizophrenia, the values for blood flow and oxygen consumption were within the normal range.2 It was pointed out that this did not rule out significant changes in particular regions of the brain, and the next objective became the measurement and study of regional blood flow and metabolism. The most promising approach appeared to lie in a more exhaustive study of the physical processes on which the nitrous oxide technique was based, i.e., the exchange of nonmetabolized, diffusible molecules between capillary and tissue.3

In the development of the nitrous oxide technique, the familiar Fick principle had been converted to differential form and made applicable to the accumulation of an exogenous nonmetabolized substance in the brain, rather than the absorption of oxygen in the lungs, i.e:

$$\frac{dQ_b}{dt} = F(C_a - C_v)$$  \[1\]

where $Q_b$, $C_a$, and $C_v$ represent the quantity of the substance in the brain and its concentration in arterial and mixed cerebral venous blood, respectively, and $F$ represents total cerebral blood flow.

To solve the resulting expression for cerebral blood flow it was necessary to evaluate concentrations of the tracer in arterial and mixed cerebral venous blood, both of which were obtainable, but also the amount taken up by the brain as a whole. For a nonradioactive gas like N2O, which could not be measured by external detectors, this could nevertheless be done by continuing its inhalation at a constant low concentration until the brain and its effluent blood were in virtual equilibrium, at which time $Q_b$ would be equal to $C_aW\lambda$, where $W$ represents the weight of the brain and $\lambda$, the partition coefficient of the substance between mixed brain tissue and blood. Thus,

$$\frac{F}{W} = \lambda C_a(T)/\int_0^T (C_a - C_v) \, dt$$  \[2\]

where $F/W$ represents mean flow per unit weight of brain, and $T$ represents the time required after the onset of inhalation of a constant partial pressure of nitrous oxide for equilibrium to be achieved. In a process of equilibration extending over several minutes, the limiting factor is not diffusion between capillaries and their surrounding tissue, but the disparities between tissues with different perfusion rates and partition coefficients and the rate at which the tissue with the slowest perfusion approaches the rest of the brain in respect of tracer concentration. It was shown theoretically, and verified experimentally, that for the normal brain, and for most abnormal situations aside from major cerebral infarction, ten minutes of equilibration is sufficient for a measurement of average cerebral blood flow with an error of 5%.

In the development of the principle for measurement of blood flow in small regions throughout the brain, equation 1 led directly to the expression for the concentration of tracer in an individual tissue region ($C_l$):

$$\frac{dC_l}{dt} = \frac{F_l}{\lambda_l W_l} (C_a - C_v).$$  \[3\]
The situation was different here from that for blood flow in the brain as a whole, where the concentration of tracer in the arterial and effluent venous blood was accessible to measurement, and a means had to be devised for estimating the mean concentration of tracer in the whole brain. In the case of an individual small region, on the other hand, there appeared to be no way of measuring the concentration of tracer in the effluent blood, but by using a radioactive tracer it should be possible to measure its regional concentration in the brain by autoradiography in animals and by external detectors in man. Under appropriate conditions it would then be possible to derive the concentration of tracer in the venous blood from a small region through its tissue concentration.

Where diffusion is not significantly limiting, a tracer in the entering capillary blood will achieve practical equilibrium with the surrounding tissue at the time of its exit, i.e., \( C_i = C_i / \lambda_i \). Substituting, rearranging, and integrating yielded an expression for the concentration of tracer in a small tissue region at a time \( T \) in terms of blood flow through the region, partition coefficient of the tracer between the tissue and blood, and the past history of the tracer in the arterial blood from the time of its introduction:

\[
C_i(T) = \frac{k_i \lambda_i \exp(-k_i T)}{\lambda_i} \int_0^T C_i e^{k_i(t)} dt. \tag{4}
\]

where \( k_i = F_i / \lambda_i W_i \).

In the simple special case where the tracer is being cleared from the tissue in the presence of a negligible arterial concentration, equation 4 reduces to:

\[
C_i(T) = C_i(T_0) \exp(-k_i T). \tag{5}
\]

This equation was derived in 1949 for the clearance of \(^{34}\)Na from an intramuscular injection site. There is some diffusion limitation for sodium ion through the capillary wall, however, so the assumption of instantaneous capillary-tissue equilibrium could not be made, and a factor \( m \) was introduced representing the fraction of complete equilibrium achieved by a particular substance in each passage through the tissue, now becoming \( mF / \lambda W \) for each region. The technique was later improved by Lassen et al. who substituted a radioisotope of an inert gas for the sodium ion.

It was desirable to elucidate the physical and biological factors on which the capillary-tissue equilibrium of a diffusible and unmetabolized substance depends, and to ascertain the conditions under which it would not be limiting, i.e., where \( m \) would be sufficiently close to unity that it could be neglected. Thirty years before, Krogh had used a model consisting of parallel capillaries, each with a cylinder of surrounding tissue, to calculate the diffusion gradients of oxygen in muscle. Earlier, Bohr had described the equilibration of pulmonary capillary blood with alveolar oxygen in terms of its diffusion coefficient, capillary geometry, blood flow, and the capacity of hemoglobin for oxygen. In a steady state, oxygen gradients would be constant, but in the case of an unmetabolized substance the gradients would change with time and introduce another level of complexity.

By building on Bohr's derivation, and with the use of Krogh's model, it was possible to derive an expression for the exchange of an inert but diffusible tracer between flowing capillary blood and the surrounding tissue in terms of perfusion rate \( F \), the capillary diffusing surface \( S \), and the diffusion coefficient of the tracer through the capillary membrane \( D' \):

\[
m - 1 - \exp(-D'S/F).
\]

That derivation was a first approximation because it made two simplifying assumptions: that, after diffusing through the capillary wall, the tracer was instantaneously dispersed uniformly throughout the external phase, and that its concentration there did not change appreciably in the time of a single transit of blood through the capillary. Since the capillary volume in the brain is less than 5% of the parenchyma, the latter assumption should introduce a negligible error. In respect of the first assumption, Copperman made further calculations, taking into consideration radial diffusion from the capillary through the tissue. Since the capillaries of the brain are arranged in baskets around the cellular components rather than in parallel along muscle fibers, radial diffusion processes should be the better model. These calculations supported the prediction that inert gases and other substances with a high lipid solubility would achieve practical equilibrium between each tissue in the brain and the perfusing blood during a
single passage. For a wide range of other substances to which the capillary wall was less permeable, the expression for m became a measure of their capillary permeability.9

The first application of the principles described above was in 1955 by Landau et al.10 with the measurement of blood flow in 28 structures in the brain of the cat. The radioactive tracer used was the gas trifluoriodomethane labeled with 131I, administered intravenously in solution. At the end of one minute, during which the arterial concentration of the radioactive gas was monitored, the animal was killed and the head sectioned and frozen in liquid nitrogen. Autoradiograms were made at low temperatures and from these, values for mean concentration in the various structures were obtained with reference to radioactive 131I standards incorporated in each section. The tissue: blood partition coefficient for each structure was obtained from autoradiograms prepared after complete equilibration.

Among the most significant observations made with the use of the original technique were those reported by Sokoloff11 on the effects of thiopental and photic stimulation. Thiopental anesthesia differentially reduced blood flow in cortical regions and subcortical structures subserving sensory functions, while photic stimulation was associated with marked increases in perfusion of the striate cortex, lateral geniculate ganglia, and superior colliculi. Although there had been a few reports suggesting an increase in perfusion accompanying increased functional activity, this was the first clear demonstration of that important homeostatic relationship, and of the perceptive inference by Roy and Sherrington12 nearly 100 years ago that local neuronal activity, metabolic rate, and perfusion were closely coupled. That early demonstration of the coupling of functional activity and local cerebral perfusion was succeeded 16 years later by autoradiograms of the stimulated visual system using 14C-deoxyglucose, and demonstrating with high resolution the optical dominance columns in the visual cortex.13

The original tracer (F131I) was unsatisfactory for a number of reasons. As a gas at room temperature, it required that autoradiograms be made at -40 °C, and the radioisotope emitted a beta ray so penetrating as to impair the resolution of the image. Posternak14 improved the image considerably with the use of 14C ethanol, and Reivich et al.15 used 14C-antipyrine in studies of regional cerebral blood flow in slow wave and rapid eye movement (REM) sleep. Because the latter substance was diffusion limited at higher flows, Sakurada et al.16 substituted iodo-14C-antipyrine, to which the capillary wall was considerably more permeable.

Ingvar and Lassen,17 in 1961, were the first to apply the principles of capillary-tissue exchange of an inert gas to measurement of regional blood flow in man, using 85Kr. It was later found that 133Xe was more satisfactory.18 The tracer dissolved in saline was administered by intracarotid injection in conjunction with cerebral angiography. Cortical blood flow was measured as the initial semi-logarithmic slope of the clearance of the tracer from the region under study. By injecting the radioisotope into the internal carotid, background from the contralateral hemisphere, extracranial structures, and respiratory system was minimized, and the measurement was made in less than one minute. The technique has been widely used in neurologic and psychophysiologic studies, and has demonstrated the localization and extent of changes in perfusion, reflecting neuronal activity in a wide range of psychologic states.

Much effort has been placed on developing less invasive techniques for regional blood flow measurement in the human brain. In 1965, Veal and Mallett19 administered 133Xe by inhalation, monitored the levels in the brain by external counting, and analyzed the resultant curve as means of a two-compartment model. Obstet al.20 simplified this approach by monitoring arterial concentration of the gas through end-tidal air sampling, and estimated cortical blood flow from an early tangent of the semi-logarithmic clearance curve. The procedure is noninvasive and relatively inexpensive; it has been used extensively in neuropsychiatric disorders and in studies of psychologic function. It is subject to certain potential errors, however, which with sufficient care can be minimized. Background radioactivity from the other hemisphere may account for as much as 25% of the counts recorded; that from the respiratory tract may not be completely eliminated by ignoring the first 30 seconds of the clearance curve. That expedient,
on the other hand, may diminish the influence of the most rapid perfusion rates while the background from extracerebral tissues of the head, magnified by proximity to the counters, may unduly reduce the values obtained from the portion of the clearance curve used in the calculations. Each of these sources of error would tend to reduce values for cortical blood flow obtained by means of this technique. Positron emission tomography offers the most advanced and theoretically soundest approach to the noninvasive measurement of regional cerebral blood flow in man which is presently available. Background problems are minimal, and the resolution is higher than that which has been obtained with earlier methods of external counting. Water labeled with the positron emitting isotope of oxygen ($^{15}$O) has been the tracer most used. Tomita and Gotoh have addressed some of the theoretical sources of error in the application of equation 4 to clinical studies, finding them small enough to be negligible, except for conditions of severe ischemia and infarction. Herscovitch, Raichle, and their co-workers have examined the several assumptions inherent in the derivation and evaluated their validity both theoretically and experimentally. They found that heterogeneity of tissue in the minimum volume examined by the technique introduces an error of less than 4% if the duration of measurement is maintained at one minute or less as used in the original autoradiographic application. With appropriate correction for the fact that water, in contrast to krypton or xenon, does not diffuse freely through the entire capillary wall and has a value for $m$ which is appreciably less than 1, regional blood flow measurement with $H_2^{15}$O is accurate over a range of 10 to 155 mL/100 g/min. In a fruitful collaboration with the department of psychiatry, Raichle and Herscovitch used this technique and demonstrated a significant abnormal right:left asymmetry discretely localized to the parahippocampal gyrus in patients with lactate-sensitive panic disorder.

Two other approaches currently in use for measuring regional cerebral circulation depend upon the rapid and almost total uptake by the tissues of certain radioactively-labeled substances, or the equilibrium concentration of an extremely short-lived tracer in the tissue. Their application in clinical studies is described in some of the following reviews.

REFERENCES

6. Krogh A: The number and distribution of capillaries in muscles with calculation of the oxygen pressure head necessary for supplying the tissue. J Physiol (Lond) 52:391–408, 1919