Newer Techniques of Cerebral Blood Flow Measurement

BY JEROME B. POSNER, M.D.

Abstract:
Newer Techniques of Cerebral Blood Flow Measurement

A variety of methods for measuring cerebral blood flow have been developed in the past 25 years since Kety and Schmidt developed their method based on the Fick principle. None of the currently used methods approaches the clinical ideal, since none of the techniques are accurate, reproducible and noninvasive. Most accurate techniques involve catheterization of internal carotid artery and/or jugular vein with those attendant risks. There has been considerable enhancement of our understanding of the pathophysiology of cerebral circulation, particularly in the areas of brain injury and disordered systemic metabolism, but the clinical usefulness of the test at the present time is limited.

Additional Key Words
- blood flowmeters
- cerebral blood flow
- cerebral vascular disease
- 133Xenon clearance
- 15O clearance

Introduction

It is just a little over 25 years since Kety and Schmidt, in a brilliant series of experiments, demonstrated that one could utilize the Fick principle to measure blood flow to the brain. The technique which they developed allowed them to measure cerebral blood flow (CBF) by intermittently measuring the concentration of an inert, nonmetabolized gas (nitrous oxide) in an artery and the jugular bulb (brain venous blood) while the subject breathed the inert gas. The results in cc blood flow/100 gm brain/min, when multiplied by the arterial-venous substrate differences, yielded metabolic rates for oxygen and substrate utilization or CO2 production. These experiments opened a whole new field for neurologists, neurophysiologists and neurochemists, and the literature in that field continues to expand.

The purpose of this brief review, modified from a presentation at the Eighth Princeton Conference on Cerebral Vascular Disease, is to consider some of the methodology of cerebral blood flow measurement currently in use, commenting on the advantages and disadvantages of the individual methods and some of their clinical and physiological applications. The subject is so large that one must restrict one's self, and I plan to discuss only some
selected techniques useful in humans. The subject has been reviewed thoroughly several times in the past few years, the most comprehensive report being a monograph by Carr and Fisher2 called A Study of New Methods of Measuring Cerebral Circulation. Several proceedings of international cerebral blood flow meetings have also been published recently, parts of which address themselves to methodology.3–5

**SOME CHARACTERISTICS OF AN IDEAL CBF TECHNIQUE**

1. Non-invasive
2. Instantaneous and repeatable
3. Regional and total flow
4. Flow and metabolism

![FIGURE 1](image)

An ideal technique for measuring CBF in the human is not currently available. If it were, it would be (fig. 1): noninvasive, i.e., neither arterial nor venipuncture technique would be necessary; instantaneous, so that minute-to-minute differences in the patient’s physiological state would not affect the measurement; and repeatable, so that one might do several measurements on a given patient during changes in physiological states. The ideal method should measure total flow both to the brain and to the brain’s various regions. It should identify nonperfused areas. It should have the capacity to measure not only flow but substrate metabolism as well. Carr and Fisher2 suggest as additional properties that the technique should measure extracranial flow, intracranial flow and venous drainage, that it should not require hospitalization, and that no radioactivity be used. Whether one accepts the criteria listed in figure 1 as ideal or requires the more stringent criteria suggested by Carr and Fisher, it is obvious that no ideal technique is either currently available or likely to be developed soon. Each of the currently used methods has advantages as well as serious disadvantages which limit its properties as an ideal method of measuring flow.

Table 1 lists several of the ways in which one can presently measure cerebral blood flow. One can apply the Fick principle measuring, as Kety and Schmidt did, the arteriovenous difference of an inert gas either using the venous blood at saturation to represent the brain value or directly measuring the brain concentration by extracranial counting of an isotope. One can apply isotope clearance methods using several isotopes, the most widely used of which is 18O and the newest of which is 18O. One can apply the Stewart-Hamilton principle, using either diffusible or nondiffusible indicators and measuring their dilution in brain venous blood after an arterial injection, the most recent technique being that of J. S. Meyer using hydrogen and a hydrogen electrode. One can measure brain transit time by extracranial counting after an intravenous injection. Mechanical methods, using thermistors, magnetic fields or sound waves, are also available.

Kety and Schmidt originally measured the arterial-venous difference of the inert gas nitrous oxide. The subject breathed 15% nitrous oxide for ten minutes, during which

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<td><strong>II. Stewart-Hamilton principle (indicator dilution)^15</strong></td>
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several arterial and jugular venous blood samples were drawn. The concentration of the gas was laboriously measured utilizing Van Slyke's manometric technique. The gas was subsequently changed to radioactive krypton, which could be counted, and it was discovered that desaturation curves were more accurate than saturation. The most recent development has been the use of the mass spectrometer (fig. 2). The setup is like that of the original Kety-Schmidt method and requires catheterization of an artery (not necessarily the carotid) and of the jugular bulb. Blood gases are drawn by vacuum from the blood through a gas-permeable membrane mounted on the tip of a flexible plastic tube and into the mass spectrometer. After the initial calibration, using standard gas analysis, no blood need be drawn and oxygen, CO₂, nitrous oxide or 10% argon can be measured every 20 to 40 seconds throughout the saturation and desaturation periods. The curves are quite smooth and, using the appropriate solubility factor, results are similar to those achieved with other techniques. The advantages of this technique (table 2) are the advantages of all the A-V difference techniques, namely that it measures flow and metabolism together and that no carotid artery puncture is required. Additional advantages of the mass spectrometer are that once the machinery is set up, the measurement is easy to make, it is quite accurate and one gets so many points on the curve that there is virtually a continuous measurement of gases. The disadvantages of this technique are also the same as the disadvantages of the A-V difference technique. One must assume the blood flow is constant over a fairly long time course, especially when the flow is low; unperfused brain tissue receives no gas and thus is

![Diagram](http://stroke.ahajournals.org/)

**FIGURE 2**

The set-up for determining cerebral blood flow by the A-V difference method using a mass spectrometer. The procedure is bloodless since gas is removed from the blood by the vacuum and carried through catheters to the mass spectrometer, where its concentration is determined. The illustration is from the laboratory of Dr. William Hass.
TABLE 2

Advantages and Disadvantages of Some Methods of Measuring Cerebral Blood Flow in Humans

I. Fick principle methods
   A. Inert gas arteriovenous difference by mass spectrometer
      1. Advantages: no carotid arterial puncture required, both flow and metabolism are measured, measurement is easy and accurate, and blood and inert gas are continuously monitored.
      2. Disadvantages: each test is long — 18 to 20 minutes, regional values are not measured, unperfused tissue is not identified, and equipment is expensive.
   B. Radioactive isotope clearance 133Xe
      1. Advantages: regional flow can be measured, gray and white matter flows are calculated, and the test can be repeated several times.
      2. Disadvantages: carotid puncture is required (intravenous or inhalation techniques not yet fully reliable), metabolism is not measured, and self-absorption and scatter of isotope lead to overlap of regions.
   C. Radioactive isotope clearance 18O2
      1. Advantages: measures both regional flow and metabolism, can be repeated several times, has partition constant of water (unity), and isotope has little self-absorption.
      2. Disadvantages: requires carotid puncture, isotope has short half-life (two minutes), each test requires two injections, and collimation problems limit number of regions examined.

II. Indicator dilution methods
   A. Diffusible indicator — hydrogen
      1. Advantages: measures hemispheric flow and metabolism.
      2. Disadvantages: requires bilateral carotid and bilateral jugular (lateral sinus) catheterization, and each test takes 20 to 30 minutes.

III. Measurements of brain transit time
   A. Intravenous nondiffusible isotope
      1. Advantages: atraumatic, simple and inexpensive, and repeatable.
      2. Disadvantages: measures transit time, not CBF, and no metabolic measurements.

IV. Mechanical flowmeters
   A. Electromagnetic flowmeter
      1. Advantages: continuous, instantaneous measurement.
      2. Disadvantages: requires surgical exposure of vessel, difficult to calibrate, and measures flow in only a single vessel unless multiple probes are used.
   B. Ultrasonic Doppler probes
      1. Advantages: noninvasive, atraumatic, and instantaneous and continuous measurements.
      2. Disadvantages: measures blood velocity in single large vessels only, affected by movements and orientation of probe, and semiquantitative only.

not identified at all. One assumes that jugular venous samples represent mixed venous blood from the brain and that there is no extracerebral contamination. The results give only total cerebral blood flow and do not give regional values. In addition, the mass spectrometer scans the atomic weight of the inert gas only once every 20 to 40 seconds. Since the first portion of the arterial curve is critical, one must take great care to begin the test just before the machinery reaches the atomic weight of the inert gas. The unit is expensive.

One can also utilize 79Kr or 131I antipyrene and measure A-V differences while one counts brain concentration from an extracranial counter. This method has the advantage of continuously measuring cerebral blood flow and recognizing minute-to-minute changes but is cumbersome and technically difficult and, to my knowledge, is not being

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used clinically in any laboratory at the present time.

Isotope clearance methods also utilize the Fick principle and extracranial counting and have become exceedingly popular in the years since they were introduced by Lassen and Ingvar. The test (fig. 3) requires the injection into the internal carotid artery of an isotope which can be counted extracranially. The appearance and clearance of the isotope through one or several extracranial counters are recorded. The technique, which began with a single counter placed in a burr hole directly over the cortex, has evolved to techniques in which as many as 250 counters are used to detect smaller and smaller regions of the brain. Blood flow can be calculated in two ways (figs. 4 and 5): Mean blood flow through a region seen by the counter can be calculated by dividing the height of the curve multiplied by the partition coefficient by the area under the curve (fig. 4). The formula, based on the Fick principle, is similar to the Kety-Schmidt equations. The curve can also be expressed as two exponential functions (fig. 5) and a compartmental analysis can also be done as described by Lassen and his co-workers in which the half-times for decay of a fast and slow curve can be divided by gray and white matter partition coefficients to yield flow in fast and slow compartments, which are believed to represent gray and white matter.

The technique has several advantages (table 2). It measures many regions of the brain simultaneously.
A curve similar to that in figure 4 but plotted on semilogarithmic paper. The dotted line represents the actual clearance curve; the straight line is a two-compartmental analysis; the line with the steeper slope represents flow through gray matter, and the other compartment is white matter. $T_{1/2}^F$: half-time for fast and slow compartments of gray and white matter. [From Harper,16 reprinted by permission of the publishers, Little, Brown & Co.]

\[133\text{Xe clearance curve from the brain. } H \text{ is the maximum height of the radioactivity; } A \text{ is the area under the clearance curve for total integrated radioactivity. [From Harper,15 reprinted by permission of the publishers, Little, Brown & Co.]}\]
and size of those two compartments. It can be repeated after a short time because the isotope is readily cleared from the brain. There are also several disadvantages, the major one of which is that it requires an internal carotid artery puncture and thus is usually done at the time of arteriography. The second disadvantage is that, although it measures flow, it does not measure metabolism. Potchen\textsuperscript{21} has raised some questions about the use of $^{133}\text{Xe}$, an isotope which, because of its low energy, undergoes considerable self-absorption in the head before it reaches the counters and undergoes much Compton scatter. Thus, the regional probes show considerable overlap. At its best energy levels, somewhere between 13\% and 20\% of the counts are the result of Compton scatter. It also counts relatively more counts from the surface than it does from the depths, and it is likely that during the course of the flow study there is diffusion first from gray to white matter, as the gray matter saturates first, and then from white to gray matter, as the gray matter desaturates first.

The disadvantages of carotid puncture can be obviated by the use of intravenous injection or inhalation of $^{133}\text{Xe}$. These techniques both suffer from serious difficulty with the handling of the calculations because there is extracerebral contamination by the isotope and there are problems of recirculation when the isotope is inhaled. The methodology has been critically reviewed by Obrist.\textsuperscript{22} A three-compartment analysis (gray matter, white matter and extracerebral counts) can be carried out if the flow is followed for 40 minutes, which is, unfortunately, a prohibitively long time for clinical studies. More recently, Obrist\textsuperscript{23} has devised a shorter procedure in which only the fast (gray matter) blood flows are extracted from the inhalation curve. With short periods of inhalation, he was able to achieve values for fast flow which were comparable to those following internal carotid injection. At present the technique does not appear to be as good as that following carotid injection, but it does raise the hope for the future of an atraumatic isotope counting technique. Fieschi and his colleagues,\textsuperscript{24} in their most recent report on the intravenous xenon technique, have still found it unsatisfactory for true quantitative measurements.

A new and exciting development was described by Ter-Pogossian\textsuperscript{11} at the last Princeton meeting and involves the use of $^{18}\text{O}$ injected as either oxyhemoglobin or water into the carotid artery with clearance curves counted over the head. Two cubic centimeters of the patient’s blood tagged with $^{18}\text{O}$ are injected into the internal carotid artery; $^{18}\text{O}$ has a half-life of two minutes. Several collimators over the head count positron emissions. This injection is followed after six minutes by a second injection using blood labeled with $^{18}\text{O}$-water. The brain extracts oxygen from the hemoglobin, metabolizes that oxygen and converts it into water which is then counted as it is washed out of the brain. The ratio of the amount of labeled water formed to the amount of oxygen perfusing the tissue, both values derived from the clearance curve, is a measure of fractional oxygen utilization. The injection of the labeled water provides a measurement of blood flow using the usual clearance curve since the brain cannot extract and metabolize the $^{18}\text{O}$ from water. Multiplying the fractional oxygen utilization from the $^{18}\text{O}$-hemoglobin curves by the blood flow and the arterial oxygen content provides a measure of oxygen utilization rate by the brain. This method has the enormous advantage of measuring both regional flow and metabolism essentially simultaneously. It also emits positrons at a high energy so that problems of self-absorption, as with Xenon, are less. Because water is used to measure cerebral blood flow, water being almost equally soluble in gray and white matter, the partition coefficients of both those compartments are the same. In fact, Ter-Pogossian\textsuperscript{11} has found that although mean cerebral blood flow is similar to that achieved with the xenon regional methods, compartmental analysis gives considerably different values than those achieved by the xenon method. The method, like isotope clearance with xenon, is repeatable after a short period of time. The disadvantages of the method are, like the other regional techniques, that it requires internal carotid puncture. In addition, the high energy of the positron makes shielding of the columns difficult and yields collimation problems, and the isotope has such a short half-life that a cyclotron must be available on the premises. It is obvious that not very many places will be measuring regional blood flow and metabolism by this method, but where the equipment is available it would appear that the advantages
POSNER

of this technique for research in human cerebral metabolism are tremendous.

Indicator dilution methods using non-diffusible isotopes have been used for a long time, but because they were technically so difficult they have fallen out of vogue. Meyer14 has recently introduced an indicator dilution method using a bolus injection of hydrogen gas into each internal carotid artery and measuring the clearance of this material from both internal jugular veins simultaneously. Using the Meier-Zierler modification12 of the Stewart-Hamilton principle (which states that the mean circulation time \( t \) of indicator through an organ equals the integral of concentration of the indicator times the time divided by the integral of the indicator concentration) and measuring at the outflow orifice, the flow is expressed as the integral of the tension of hydrogen over time. Since the partition coefficient is unity, flow equals the reciprocal of transit time. The A-V differences for various substrates between the artery and the two jugular bulbs (or, as Dr. Meyer uses, the transverse sinuses) are measured by calculating the percentage of blood represented in each transverse sinus by each hemisphere. One can estimate hemispheric blood flow and metabolism. This is the only extant method which makes such a division and thus has the advantage of being able to compare one hemisphere with the other (table 2). It has the disadvantage of requiring not only bilateral jugular or transverse sinus catheterization but also the hazards of bilateral internal carotid artery catheterization, and the cooperation of the patient over a period of time in which both carotid arteries are injected and the hydrogen gas cleared. If the physiology of the patient changes over that period, which takes at least 20 minutes, comparative hemispheric flows are not accurate.

There are also a variety of other methods which can be used to represent flow measurements. Dr. Oldendorf15 has done considerable work measuring brain transit time after an intravenous injection of radioisotope and counting extracranially. His technique measures the arrival of isotope at the brain, which gives a measure of arm-to-brain circulation time, as well as its disappearance, which gives a measure of the transit time across the brain. Its advantages (table 2) are that it is atraumatic, is easy to perform and repeatable, and requires minimal equipment. The disadvantages are that it does not really measure cerebral blood flow but only transit time across the brain. Transit time by this technique is inversely but not linearly proportional to blood flow.

Several mechanical methods of measuring the velocity of blood in individual vessels have recently become popular, particularly in animal work. Each of the mechanical methods listed in table 1 is based on a different principle. Thermal velocity and thermal dilution measurements are based on the principle that a heated probe will be cooled more rapidly by faster-moving than by slower-moving blood. Thermal methods have found little use in human measurement. Electromagnetic flowmeters measure a voltage generated by the arterial blood which behaves as a conductor as it moves through a magnetic field set up by the mechanical device. These devices (table 2), once they are calibrated, are quite accurate and measure flow continuously and instantaneously. However, they can only measure flow in individual vessels around which the probe must be surgically placed, making the technique not useful for most clinical studies. The Doppler ultrasonic flowmeter is a new development based on the Doppler principle that shifts in sound frequency are proportional to the velocity of the substance through which the sound waves are being transmitted. This technique has the great advantage (table 2) of being noninvasive since it can be placed transcutaneously over the vessel to be measured. It is also instantaneous and gives continuous measurements of velocity. However, it can be used over only one vessel at a time. It is quite sensitive to extraneous movement and to changes in its orientation relative to the vessel. It does not appear very useful for small vessels and generally can give only semiquantitative measurements, yielding only relative changes in blood velocity with changes in patients' physiological state. It offers much promise for the future, especially as a screening technique, if it can be made easier to use and some technical difficulties can be solved.

Thus, there is no ideal technique for measuring cerebral blood flow and metabolism, although there are several techniques which give satisfactory results in particular situations. The vast literature on this subject indicates the continuing interest in this measurement, and
after 25 years of clinical and experimental use, one may inquire how useful is the technique.

Usefulness of Cerebral Blood Flow Measurements in Man

The clinical usefulness of cerebral blood flow has been discussed most recently by Harper and figure 6, modified from his paper, lists all of the areas in which he believes cerebral blood flow measurements have diagnostic or therapeutic importance. The list is his—the marks after the listings are mine. It appears to me from my review of the recent literature that the one clinical area in which cerebral blood flow measurement is uniquely useful is that of evaluating a patient with an intracerebral aneurysm for carotid artery ligation. Drs. Jennett, Harper and Gillespie have demonstrated that if regional cerebral blood flow decreases 25% or more when the carotid artery is clamped, the patient will develop either immediate or, more importantly, delayed hemiparesis. If the flow reduction is less than 25%, there are no neurological complications. If, in larger studies, the predictive value of this technique proves reliable, there will be no question of its clinical usefulness. The other areas of clinical usefulness which Dr. Harper lists are more questionable. Regional cerebral blood flow techniques, and indeed arterial-venous techniques, can frequently demonstrate areas of cerebral ischemia and decrease in hemispheral or overall brain metabolism. Measurements of regional blood flow have led to the concepts of “luxury perfusion” and “intracerebral steal,” and such measurements were directly responsible for the suggestion that hyperventilation be used in the treatment of acute strokes. Dr. Paulson reports a controlled study indicating that hyperventilation in the acute treatment of strokes is of no value. Others are using cerebral blood flow methods to test the therapeutic efficacy of other cerebral vasoconstrictors and of cerebral vasodilators in stroke patients. As yet, no dramatic advances can be reported. Whether continued measurement of regional or overall cerebral blood flows will be of diagnostic or therapeutic value remains to be seen.

It is doubtful that measurement of blood flow will have much value in predicting the outcome of carotid endarterectomy (fig. 6). Since it is likely that most of the ischemic attacks are produced by embolization rather than from decreased flow, measurement of changes in flow before or after endarterectomy are not likely to be of much help. Measurements of cerebral blood flow and metabolism have been used to predict the outcome of coma and brain injury but, although statistically reliable (i.e., in a large series, patients with lowest flows and metabolism have poorest outcome), it is not of any individual use except when there is near-zero flow, in which case the patient is brain dead. However, brain death can be diagnosed as easily by clinical examination and electroencephalography, and predicting the outcome of coma is no better by measurement of cerebral blood flow than it is by clinical examination. Measurements of cerebral blood flow may someday be helpful in developing treatment for stroke and brain injury but so far the concepts which they have engendered have not in careful studies been shown to be of any major clinical benefit. The fact that hyperventilation decreased intracranial pressure and might benefit patients with acute brain injury was known long before cerebral blood flow measurements were made. Finally, Dr. Harper indicates that in migraine one might differentiate between the effects on intracranial and extracranial cerebral circulation of chemical substances which may be implicated in the etiology of that disease. If this leads to useful therapy for migraine, it will indeed be a major clinical advance, but at the moment its value is sheer speculation. Thus, with the sole exception of patients about to undergo carotid artery ligation, it seems that the clinical usefulness of cerebral blood flow is unproved. That little of direct clinical value has
come from 25 years of intensive work in the area is disappointing. It suggests, but does not prove, that further work along the same lines is not likely to produce too much of direct clinical importance.

However, it is not vital that a physiological technique have direct and immediate relevance to diagnosis and treatment of patients. Any technique which enhances our understanding of the physiology of the brain and pathophysiological states is useful and we should thus ask whether studies of cerebral blood flow and metabolism in man have taught us about that organ’s function. Here the picture is brighter, but by no means overwhelming. It was measurements of cerebral blood flow and metabolism which first clearly established the obligate use of glucose by the brain, and it was measurements of cerebral blood flow and metabolism which more recently have proved that under certain select circumstances the brain is able to utilize fatty acids for its metabolism. These studies have important clinical implications. It was measurements of cerebral blood flow which called attention to and finally established the important regulatory effect of pH of the extracellular space of brain on flow, but although this concept has been advanced and refined by these measurements, the evidence that extracellular pH regulated vessel diameter was present long before current methods for measuring cerebral blood flow were developed. The concept of luxury perfusion was a direct result of measurements of regional cerebral blood flow by Lassen and his colleagues, and this has greatly enhanced our understanding of abnormalities on arteriograms around brain tumors and strokes, as well as led to some presumptive therapeutic concepts in the treatment of stroke. However, it was Penfield who first observed red brains at operation during the course of a focal seizure, so evidence for the concept predated our current methods of measurement. Finally, the concept of autoregulation has great current interest for those measuring cerebral blood flow. This concept too predates current blood flow measurement. Thus, it seems that, while much of pathophysiological interest has come out of cerebral blood flow measurements, none of its concepts are entirely new; all were anticipated by precerebral blood flow measurements.

Conclusions
There are a variety of methods for measuring cerebral blood flow, all of which have disadvantages and advantages, and none of which approach the ideal. The relevance of these measurements to diagnosis and treatment of a patient with cerebrovascular disease is limited and one wonders if standard cerebral blood flow measurements in humans are worth the discomfort to the patient and the risk, even though it be minimal. There has been considerable enhancement of our understanding of the pathophysiology of cerebral circulation, particularly in areas of brain injury and disordered systemic metabolism.

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