METHODS FOR CEREBRAL BLOODFLOW MEASUREMENTS IN MAN

BY

DAVID H. INGVAR* AND NIELS A. LASSEN

Laboratory of Clinical Neurophysiology, University Hospital, Lund, Sweden, and Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, Denmark

Only a few methods of study of the cerebral circulation in man yield quantitative information on the cerebral bloodflow. This is mainly due to the inaccessibility of the brain within the skull and to the complexity of the cerebral arterial and venous systems.

Before reviewing the various methods used in man, it is appropriate to mention that much valuable information has been obtained from techniques only applicable to animals. Measurements of the diameter of cerebral vessels in the pia mater antedates even the classical study of Roy and Sherrington (1890) of the regulation of the cerebral bloodflow. This technique reached its full development in the pial window procedure described by Forbes (1928). The interested reader is referred to the review by Wolff (1936) and to the fundamental study of the pial arteries by Fog (1934). Autoradiography of brain slices was the first quantitative animal method used to measure local bloodflow in ml/g/min in all the different parts of the brain employing CF1I131, or, more recently, I131-antipyrine, as indicator substance (Kety, 1960).

FLOW MEASUREMENTS ON THE CEREBRAL ARTERIES AND VEINS

The flow in an artery or vein can be measured by applying an electromagnetic flowmeter directly on to the vessel. Several studies have been carried out with such instruments in patients with obliterative disorders of the great vessels of the neck, especially the carotid arteries, in order to record the flow before and after reconstructive surgery (Kristiansen and Krog, 1962; Meyer et al., 1964).

A direct flow measurement on a single cerebral artery does not, however, permit conclusions about the cerebral bloodflow, since the four large arteries anastomose in the circle of Willis and in the leptomeningeal network. In fact, all four cerebral arteries may be occluded, and yet the cerebral bloodflow remain normal because it is kept up by collaterals (Hoedt-Rasmussen, personal communication, 1964).

On the venous side, cerebral bloodflow measurements in man have been carried out from within the jugular bulb by means of a thermo-velocity method (Meyer, 1964). With this technique, one combined needle, or two separate ones, are introduced into the vessel and kept with the tip(s) in the centre of the stream. “Boluses” of “heat” are administered at regular brief intervals and a semi-continuous record of the internal jugular flow is thus obtained.

Direct cerebral venous flow measurements are limited by the fact that the internal jugular veins do not always drain one half of the brain each. Furthermore, one of them, usually the left, receives slightly more cortical venous blood than the other. This may cause side-to-side differences (Munck and Lassen, 1957; cf. also Nylin et al., 1960). Hence, it is necessary to measure bilaterally if internal jugular flow measurements are to yield the total cerebral bloodflow.

IMPEDANCE PLETHYSMOGRAPHY

It has been claimed that variations in the cerebral bloodflow give rise to changes in the electrical impedance of cranial tissues to high frequency alternating current, applied to scalp electrodes. There have been published studies indicating that this method, “rheoencephalography”, might be clinically useful (Jenkner, 1962), but in the hands of others the method was found to be of no value (Meyer and Perez-Borja, 1963). The impedance measured depends upon a number of factors which cannot be easily controlled, such as, for example, the bloodflow in non-cerebral parts of the head, the size of the electrode contact surfaces, the heart rate, and the age of the patient (Geddes et al., 1965).

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Recently, Shalit (1963) used tissue impedance measurements in a new and interesting fashion in animals for cerebral bloodflow studies on the exposed cortical surface. He produced transitory changes of the trans-cerebral impedance by injections of small amounts of concentrated saline solutions into the cerebral arteries. By repeated injections a semi-continuous relative record of the cerebral bloodflow was obtained.

INERT INDICATOR METHODS

This is the most important group to be considered. In principle, the inert indicator is supplied to the brain and then removed by the bloodstream. The bloodflow is measured by the rate of indicator clearance, or by its dilution, either directly in the tissue, or by sampling of arterial and cerebral venous blood. There are two groups of these methods which differ in a most important respect, depending upon whether the inert indicator is (a) non-diffusible and remains within the cerebral vascular bed, or whether it is (b) freely diffusible.

Non-diffusible Indicator Methods.

In this group cerebral arteriography should be mentioned first. The clinical importance of this method needs no emphasis. Serial angiograms of the intracranial distribution of the radio-opaque contrast material give an outline in three dimensions of the cerebral vessels (down to about 0.1-0.2 mm in diameter). The transit time of the contrast bolus can be measured according to Greitz (1956). Recently, attempts have been made to measure the bolus passage time regionally in the brain, or in single cerebral vessels, by means of quantitative photometric-arteriographic techniques (Hilal, 1964).

The turnover time of an inert non-diffusible indicator through the cerebral vascular bed may also be studied by intra-arterial, or intravenous, injections of a gamma-emitting radio-active bolus (usually RISA* or I 131-hippurate) which is then monitored by external detection, either over the whole brain (Di Pietrantonj and Fieschi, 1960; van der Berg and van den Drift, 1962; Oldendorf and Kitano, 1965) or locally (Eichorn, 1958).

Neither of the above-mentioned non-diffusible inert indicator techniques can yield direct quantitative information on the cerebral blood flow, since the cerebral blood volume cannot be measured. The volume of the cerebral vascular bed may, in fact, be substantially reduced—with a resulting parallel reduction of bloodflow—and still both the arteriographic pattern and the transit time of the non-diffusible indicator may remain essentially normal (Ingvar et al., 1964; Cronqvist, Ingvar and Lassen, 1964).

Non-diffusible indicators can also be used for brain bloodflow measurements in accordance with the Stewart-Hamilton dye-dilution principle (Gibbs, Maxwell and Gibbs, 1947). Since the amount of dye injected is known, dilution curves for calculation of the total cerebral bloodflow (in ml/min) can be obtained from internal jugular samples which, preferably, should be taken bilaterally (see above; Shenkin, Harmel and Kety, 1948). The same principle is used in the Nylin-Hedlund procedure (Nylin et al., 1960) in which, instead of a dye, radioactively labelled red blood cells are injected into the cerebral bloodstream.

Freely diffusible Indicator Methods.

Heat clearance.

In this context heat may be considered an inert freely diffusible indicator which can be applied locally to the cerebral tissue and then cleared by the bloodstream. Several workers have applied thermo-electric (heat clearance) devices (Gibbs, 1933) to the brain for measurements of regional bloodflow through the intact cortical surface of animals (Kanzow, 1961; Betz and Hensel, 1962) and in man (Betz and Willenweber, 1962).

Heat clearance instruments have the disadvantage that larger vessels close to the measuring surfaces may cause a non-linear relationship between heat clearance and the tissue bloodflow. However, these instruments may be very useful for relative measurements of regional cerebral bloodflow in parts of the brain which have a uniform vascularity. They are also stable enough for chronic implantation. Recently, it has been shown that heat clearance probes for brain bloodflow measurements can be calibrated in quantitative terms by the intra-arterial Krypton 85 injection method to be mentioned below (fig. 1; Betz et al., 1965).

* Radio-active iodinated serum albumin.
Calibration curves of heat clearance probes with the intra-arterial Krypton 85 injection technique for quantitative measurement of regional cerebral bloodflow. The measurements were made at steady state on two symmetrical areas on the exposed cerebral cortex in cats and dogs under pentobarbitone anaesthesia. A linear relationship was obtained when the heat clearance probe was placed on areas of uniform vascularity. When larger vessels were close to the measuring surfaces of the probe, a non-linear relationship was obtained (from Betz, Ingvar, Lassen and Schmahl (1965), J. Physiol. (Lond.).
The nitrous oxide technique of Kety.

This well-known method is based upon the Fick principle. Nitrous oxide is used as the freely diffusible inert indicator (Kety and Schmidt, 1948). The arterial and cerebral venous (jugular bulb) blood concentrations of this gas are sampled at intervals during a 10-minute period of its inhalation. The total average cerebral blood-flow (CBF) is calculated according to the formula:

\[ \text{CBF} = 100 \times \lambda \times \frac{A_{10}}{H_{10}} \text{ml/100 g/min}, \]

where \( \lambda \) is the brain: blood partition coefficient for nitrous oxide (close to unity), \( H_{10} \) is the nitrous oxide content of the internal jugular blood at the end of the 10-minute inhalation period, and \( A_{10} \) the area outlined by the arterial and venous nitrous oxide concentration curves during the 10-minute saturation period.

At low flow rates the duration of the study must be extended beyond 10 minutes. This problem is of special importance in relation to anaesthesia (Lassen and Munck, 1955; Alexander et al., 1964a; Lassen and Klee, 1965).

This method has been extensively used for clinical research in combination with studies of cerebral metabolism by means of the simultaneous determinations of the arterio-venous difference of various metabolites (oxygen, carbon dioxide, glucose, etc.). Several comprehensive reviews of the principal findings have appeared (Schmidt, 1950; Kety, 1955; Lassen, 1958).

There are several studies with the Kety technique of the effects of anaesthetic agents upon the human cerebral circulation and metabolism (see reviews by Lassen, 1958; Pierce et al., 1962; Alexander et al., 1964b; Wollman et al., 1964; see also contribution by McDowall in this issue). Interestingly enough, it appears that the relatively small side-to-side differences of the two internal jugular inert gas saturation curves are reduced during anaesthesia. Hence, unilateral studies will probably be adequately representative of the whole brain.

The original Kety technique has been modified by, amongst others, Lassen and Munck (1955) who used Krypton 85 as the inert indicator instead of nitrous oxide, and by McHenry (1964) who calculated bloodflow from the desaturation curve, a procedure which increases the experimental accuracy. In regard to McHenry’s technique, it should be noted that at low flow rates a prolonged period of inert gas saturation (30 min) must be employed in order to saturate the brain evenly before one follows the desaturation curve.

Regional Cerebral Isotope Clearance following Intracarotid Injection.

Recently, Lassen and Ingvar (1961) developed an intra-arterial isotope injection method for quantitative measurement of regional tissue bloodflow in animals and man (Ingvar and Lassen, 1961, 1962). Originally, beta-counting from Krypton 85 was used for measurements of regional bloodflow on the exposed cerebral cortex. In a later modification, with Xenon 133 or Krypton 85 and external gamma detection through the intact skull, the method was adapted for clinical use (Lassen et al., 1963; Hoedt-Rasmussen, Sveinsdottir and Lassen, 1965; Ingvar, Cronqvist and Ekberg, 1965; cf. also Lassen and Ingvar, 1963; Ingvar et al., 1965).

According to this method, one hemisphere is labelled with the isotope by means of an instantaneous injection of a small amount of isotopesaline solution into the internal carotid artery. The uptake and clearance of the isotope is recorded by means of collimated detectors placed over the skull (fig. 2).

The regional bloodflow is calculated in terms of ml/100 g/min from the clearance curve recorded. The formula used is the same as in the Kety method (Hoedt-Rasmussen, Sveinsdottir and Lassen, 1965):

\[ r\text{CBF} = 100 \times \lambda \times \frac{H_{10}}{A_{10}} \text{ml/100 g/min}, \]

where \( r\text{CBF} \) is the regional bloodflow in the part of the brain recorded from. This part varies with the collimation of the detectors used. \( H_{10} \) is the difference in counts per minute between the maximal height of the clearance curve (immediately following the instantaneous injection of the isotope) and the height of the curve after 10 minutes of clearance. Lambda (\( \lambda \)) is the solubility coefficient for the gas in brain tissue. \( A_{10} \) is the area of the clearance curve during the first 10 minutes of clearance. It can easily be determined by recording the total number of counts during these 10 minutes. A graphical analysis of
Diagrammatic representation of the intracarotid radioactive inert gas (Xenon 133 or Krypton 85) injection technique for multiple simultaneous measurements of regional cerebral bloodflow in man.

To the left the principal arrangement is shown. Note that only the homolateral hemisphere receives the indicator. The recirculation is small due to effective clearance of the gas in the lungs. Non-overlapping parts of the hemisphere can be measured from by suitable collimation of the scintillation detectors. The isotope dose used corresponds to a gonadal radiation of 0.1 millirad.

To the right a clearance curve from one of the detectors in a normal young man is shown (after an initial steep rise following the instantaneous injection*). In the lower right part the same curve is analyzed graphically. There are two main components of the original curve which presumably correspond to the flow in the grey and white matter. A mean flow is calculated as a weighted average of the contributions of the two components (Lassen and Ingvar, 1963). Another method of calculating the mean regional cerebral bloodflow is the "10-minute area" method, described in the text.

(*) Too faint to be visible in the reproduction.)
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the clearance curve can also be used to calculate the regional cerebral bloodflow (fig. 2). Mean rCBF values obtained in seven normal young men of 50.2 ± 7.2 ml/100 g/min at an arterial Pco₂ of 40 mm Hg have shown a good agreement with normal values obtained by the Kety method (Ingvar et al., 1965).

For routine clinical purposes, multiple detectors may be used for simultaneous measurements of regional bloodflow in several areas of a hemisphere. In this way local circulatory disturbances can be quantitatively measured. Abnormalities of the brain bloodflow in regions not primarily involved in the lesion can also be studied (Ingvar et al., 1964; Hoedt-Rasmussen and Skinhøj, 1964). The method may also be used to detect shunts in arterio-venous malformations and tumors (Häggendal et al., 1965; Cronqvist et al., 1964). There is also evidence that the clearance curve from the brain consists of two components, which represent a fast and slow type of flow, probably corresponding to the flow in the grey and the white matter of the region under study (Hoedt-Rasmussen et al., 1965).

The Xenon 133 inhalation technique.

Veall and Mallet (1963) have attempted cerebral bloodflow determinations by external detection following inhalation of Xenon 133. As shown by Jensen et al. (1965), this procedure is open to criticism, since the isotope clearance in a number of non-cerebral compartments influences the composite wash-out curve recorded. The result of the Xenon 133 inhalation procedure is especially difficult to evaluate in situations in which both the ventilation and the peripheral circulation (bloodflow in the scalp over the brain) change. Such situations may be encountered in anesthesia or in patients with serious cardiopulmonary pathology (Harper et al., 1964; Isbister, Schofield and Torrance, 1965).

The gamma camera.

Recently, various instruments for simultaneous two-dimensional gamma detection have been constructed. Using intracarotid injections of freely diffusible gamma-emitting isotopes (Krypton 85 or Xenon 133) a gamma camera gives a momentary picture of the intracranial distribution of the isotope. Figure 3 shows such a picture from a normal young man. If serial pictures are taken, the isotope clearance can be displayed in a stepwise fashion and calculated quantitatively for a given area. Shunts should show up as areas of high isotope concentration which disappear rapidly, and infarcts as more or less pronounced “holes” in the pictures. Recent technical development has increased the resolution of these cameras and it will soon be possible to evaluate them more fully for cerebral bloodflow studies in man.

DISCUSSION

Present evidence shows that the cerebral bloodflow is normally regulated mainly by “intrinsic” mechanisms which pertain to the oxidative metabolism of the nerve cells (Schmidt, 1950; Lassen, 1958; Kety, 1955; see also contribution by Harper in this issue). It is commonly held that carbon dioxide which is generated by the tissue metabolism and which has a marked vasodilating influence upon the cerebral vessels, is one of the...
most important factors which secure an adequate adaptation of the cerebral bloodflow to metabolic demands. Due to the intimate coupling between bloodflow and metabolism in the brain at normal PaO₂, it may be justified—within limits—to draw certain conclusions as to the oxygen uptake of the cerebral tissue from measurements of total or regional cerebral bloodflow.

Such conclusions cannot, however, be substitutes for direct measurements of the cerebral metabolism. At present the best method for measurements of the bloodflow, as well as the overall metabolism of the human brain, is the Kety method. This is also, in fact, the only one of all the methods mentioned above which so far has been used clinically to a larger extent. Most of our present knowledge of the bloodflow and metabolism of the human brain under normal and abnormal conditions—as well as in anaesthesia—stems from investigations with the Kety technique.

The quantitative intra-arterial isotope injection technique for measurement of regional cerebral bloodflow (Lassen et al., 1963) seems at present to hold its greatest promise in clinical use as an adjunct to cerebral arteriography in the study of regional cerebral disorders, mainly of the circulatory type. On the exposed brain, however, and in combination with other measuring procedures, it may offer certain possibilities for continuous quantitative measurements of the cerebral oxidative metabolism in circumscribed parts of, for example, the cerebral cortex (fig. 4).

**SUMMARY**

This brief review outlines methods which have been used to study the cerebral circulation in man. There are three main groups: measurements on cerebral arteries and veins, impedance methods, and inert indicator methods. The last group is the most important and contains two subgroups, methods with non-diffusible and with freely diffusible indicators. Measurements with freely diffusible indicators permit quantitative determinations of (a) total average, or (b) regional cerebral bloodflow in terms of ml/100 g/min.

**REFERENCES**


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**BOOK REVIEWS**


In these days of rapidly advancing knowledge everyone has trouble in keeping track of current literature. Anaesthetists, in spite of the excellent indexes and abstracts which are available from so many sources, have a more difficult task than most of their colleagues, for articles of interest to them are published in so many journals. To those who wish annually to survey the literature, this year book is a godsend. It contains within its 400-odd pages abstracts of important articles from most of the English language journals of anaesthesia. Far more important, however, is its presentation of material from the many surgical and specialist journals which an anaesthetist might otherwise miss in the course of his reading. In addition there are abstracts of articles from journals devoted to the basic sciences. There is a fully adequate presentation of material from British journals, both of anaesthesia and physiology and pharmacology, though very little has been culled from journals in languages other than English. There is an excellent index, both of authors and subjects and in so many places one finds a fitting comment by the editor which so aptly puts what has preceded it in its proper perspective.

We commend this volume, like its slightly smaller predecessor, to all anaesthetists. A. R. Hunter


The dust jacket of this book suggests that Dr. Moore has addressed his text to obstetricians and obstetrical residents, to physician anaesthetists and residents in anaesthesia, and to nurse anaesthetists. This is a pretty wide audience by any standard, but as a statement of intent coupled with the avowedly practical nature of the contents it tends to make the reviewer's task difficult. Didactic teaching, particularly in terms of technique, is often necessary when training people with a limited knowledge and understanding of the science of anaesthesia, but Dr. Moore has been far from didactic. Indeed, he has obviously taken considerable pains to present a fair and broad picture which is subdivided into fundamental considerations, general anaesthesia, regional analgesia, and resuscitation of the infant. The extent of this approach, the soundness of the facts and the very comprehensiveness of the references make for a rational and scientific understanding of the various problems likely to be encountered in this branch of anaesthesia. As a result this is a very good book but, in the reviewer's opinion, one for physician anaesthetists—in training or trained—who will value such a catholic method and build on its excellent foundations. W. D. Wylie