The Measure In Vivo of Regional Cerebral Oxygen Utilization by Means of Oxyhemoglobin Labeled with Radioactive Oxygen-15

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A B S T R A C T   Regional cerebral oxygen utilization rate is measured in vivo by the following method:

A small volume of blood with radioactive oxygen-15–tagged hemoglobin is rapidly injected into the internal carotid artery of the patient under study. The first injection is followed by the injection carried out under identical circumstances but with blood labeled with water-^{15}O. After each injection, the distribution of the radioactive label in the brain is measured and recorded, as a function of time, by six collimated scintillation probes placed over the subject's head. The recording, subsequent to the first injection, reflects (a) the arrival of the labeled oxygen into the tissues, (b) its partial conversion into water of metabolism, and (c) the washout of labeled water from the brain. The ratio of the amount of labeled water formed to the amount of oxygen perfusing the tissues, which can be derived from the recording, is a measure of fractional oxygen utilization. The second injection provides a measure of blood flow by the interpretation of the washout of labeled water from brain tissues. The product, fractional oxygen utilization × blood flow × arterial oxygen content, gives a measure of oxygen utilization rate. Some aspects of the validity of this method are tested by the injection of a nondiffusible indicator, carboxyhemoglobin-^{15}O.

Regional cerebral oxygen utilization rates for a series of patients with cerebral pathology are reported.

INTRODUCTION

The acute dependence of the integrity of brain function on the adequate supply of oxygen suggests the usefulness, as well for clinical purposes as for physiological studies, of methods for the in vivo measure of regional cerebral oxygen supply and utilization. Oxygen is supplied to cerebral tissues by the flow of blood perfusing them, and a number of fruitful methods, many of them derived from the now classical Kety-Schmidt method (10), have been developed for the determination of regional cerebral blood flow (CBF) (1). While adequate blood flow perfusing tissues is a necessary condition for supplying the required oxygen, it is not axiomatic that sufficient supply of oxygen to cerebral tissues can be equated to normal utilization. To this date, however, no method for the in vivo determination of regional cerebral oxygen utilization in man has been described, although a number of studies of cerebral hemisphere oxygen consumption have been reported (1).

METHODS

We have developed the following method for the determination of regional cerebral oxygen utilization rate: The internal carotid artery of a subject is injected first with a small volume of his own blood with the oxyhemoglobin labeled with radioactive oxygen-15. Then a second injection is performed under identical conditions but with blood labeled with water-^{15}O. After each injection, the distribution of the radioactive label in the brain is measured, as a function of time, by means of a series of narrowly collimated scintillation probes placed over the subject's head. The recording obtained after the first injection reflects (a) the arrival of the oxygen label into the tissues, (b) its partial conversion into water of metabolism, and (c) the washout of that water from the brain. The ratio of the amount of labeled water formed to the amount of oxygen presented to the tissues provides a measure of fractional oxygen utiliza-

TABLE I

Radiation Doses, in Millirads, Resulting from the Intracarotid Injection of 3 mCi of ^{15}O-Labeled Blood
("Standard" Man)

Label	Whole body		Critical structure		
$H_2^{15}O$	2.9	$\begin{cases} 2.0\ \beta^+ \\ 0.9\ \text{annih. rad.} \end{cases}$	Injected cerebral hemisphere	160	$\begin{cases} 135\ \beta^+ \\ 25\ \text{annih. rad.} \end{cases}$
Oxyhemoglobin-^{15}O	3.0	$\begin{cases} 2.1\ \beta^+ \\ 0.9\ \text{annih. rad.} \end{cases}$	Injected cerebral hemisphere	72	$\begin{cases} 61\ \beta^+ \\ 11\ \text{annih. rad.} \end{cases}$
Carboxyhemoglobin-$C^{15}O$	5.0	$\begin{cases} 3.4\ \beta^+ \\ 1.6\ \text{annih. rad.} \end{cases}$	Blood	49	$\begin{cases} 47\ \beta^+ \\ 1.6\ \text{annih. rad.} \end{cases}$

Abbreviations: annih. rad., annihilation radiation.

tion. The measure of the rate of washout of the water sub-sequent to the second injection permits the determination of cerebral blood flow. The product, fractional oxygen utilization × blood flow × arterial oxygen content, gives a measure of regional oxygen utilization rate.

Apparatus and technology. The radioactive label for oxygen is oxygen-15 which decays with a half-life of 124 sec by the emission of positrons. It may appear that the short half-life of this isotope would preclude its use for the described purpose. Most of these studies were, however, completed in less than 12 min, and the rapid decay of ^{15}O was restrictive only in requiring a correction of the measured activity for this variable. In fact, the short half-life of this label is considered desirable because, in many instances, it can be administered in large quantities affording good counting statistics with a relatively low exposure of the patient to radiation.

Oxygen-15 is prepared by means of the Washington University Medical School Cyclotron by the irradiation of nitrogen with 7 Mev deuterons (2). The target which is nitrogen gas containing about 2% of oxygen carrier is continuously circulated through the deuteron beam. The labeling of oxyhemoglobin with ^{15}O is achieved by bubbling the irradiated gas for about 6 min through blood. This labeling, which is carried out under sterile and pyrogen-free conditions, yields typically 1 mCi of oxygen-15/ml of blood. The

preparation of $H_2^{15}O$ and of $C^{15}O$, which are also utilized in this study, is described in detail elsewhere (2–4).

The annihilation radiation resulting from the absorption of oxygen-15 positrons in cerebral tissues subsequent to the injection of the labeled blood is detected by means of six identical scintillation probes placed over different areas of the brain as shown in Fig. 1. Each probe utilizes a sodium iodide crystal, 3 inches in diameter and 2 inches thick. Collimation of radiation is achieved by means of converging 19-hole collimators with isosensitivity response as shown in Fig. 2. The probes are embedded in lead and positioned to preclude overlap of their fields inside the 10% isosensitivity surfaces.

The signal from the scintillation probes, after suitable electronic processing including narrow pulse height analysis, is recorded on magnetic tape. After completion of the measurement, the tape is replayed through a graphic recorder which displays counting rate vs. time. The loss of information between the scintillation probe and the graphic recorder due to electronic dead time was measured to be less than 5% up to 10,000 cps and negligibly low below 8000 cps. When needed, the recorded data are corrected for these losses.

Experimental procedure. Patients whose carotid artery is punctured for cerebral angiography are subjected to the following procedure[1]: A volume of 2.0 cc of the patient's blood, after labeling with oxyhemoglobin-^{15}O, is injected in less than 0.5 sec, selectively, into the internal carotid artery and recordings of the radioactivity in the brain, as a function of time, are obtained by means of the scintillation probes. After approximately 14 min, a second injection is made under similar conditions, but with the patient's blood containing ^{15}O-labeled water. The second injection is followed, after another period of 14 min, by an injection of the patient's blood labeled with carboxyhemoglobin-^{15}O. The purpose for the injection of carboxyhemoglobin-^{15}O is explained further in this text. In all instances, the activity injected varies between approximately 1 and 2 mCi. The doses of radiation delivered to the patient as a result of these studies are shown in Table I. The observed typical counting rates ranged from a maximum of 10,000 cps immediately after injection to a low value of 10 cps subsequent to the egress of the label and to radioactive decay. The initial high counting rate component of the study is recorded with integration times of 0.2 sec, and this time is progressively increased to a maximum value of 10 sec at the end
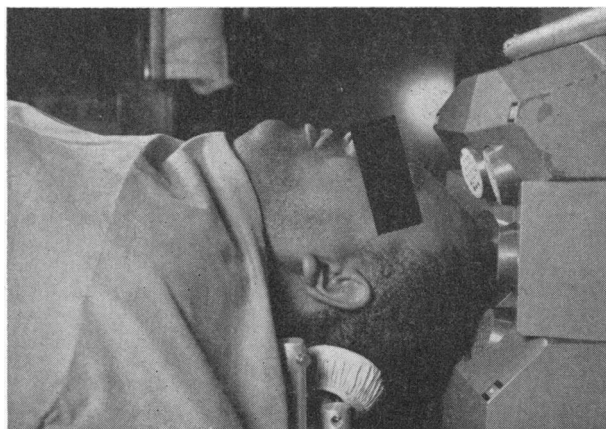

FIGURE 1 Placement of six scintillation probes with respect to subject's head. Two sets of three probes are symmetrically positioned with respect to the midline.

[1] These studies were carried out with the informed consent of the patients under investigation.

of the recording. The results obtained are corrected for radioactive decay and for electronic losses and normalized to the amount of activity injected. Fig. 3 shows typical recordings thus obtained.

RESULTS

Measure of oxygen utilization. Oxygen utilization is derived from the data obtained after the oxyhemoglobin-^{15}O injection.

The physiological handling of the oxygen-15 label mirrored by the recorded curve (Fig. 3) is interpreted as follows:

The ^{15}O label in the oxyhemoglobin-^{15}O injected blood bolus occupies two compartments: oxyhemoglobin-bound-^{15}O (area 1, Fig. 4) in equilibrium with approximately 2% of ^{15}O dissolved in the blood (area 2, Fig. 4). As the labeled blood passes through the capillary bed, the dissolved oxygen diffuses into the tissues (area 3, Fig. 4) where it combines with hydrogen ions supplied by the cytochrome system to form water of metabolism

(area 4, Fig. 4). During this process, the depleted dissolved oxygen compartment is replenished by desaturation of the hemoglobin. The unused balance of the hemoglobin-bound oxygen is carried away into the venous return.

The behavior of the ^{15}O label as it goes through this process deserves scrutiny. Since there is no radioactive oxygen in the tissues when the labeled blood bolus reaches the capillary bed, there is an egress of the label from the dissolved oxygen compartment in the blood into the dissolved oxygen compartment in the tissues and then into the water compartment. When the unused ^{15}O in the labeled blood reaches the lung field, there is a gain of inactive oxygen by the hemoglobin by exchange of oxygen with the air of respiration. This exchange results in loss of ^{15}O from the hemoglobin because of the initial absence of labeled oxygen in the air of respiration. The remainder of the labeled blood is distributed throughout the subject, and only a small fraction of the originally injected ^{15}O, estimated
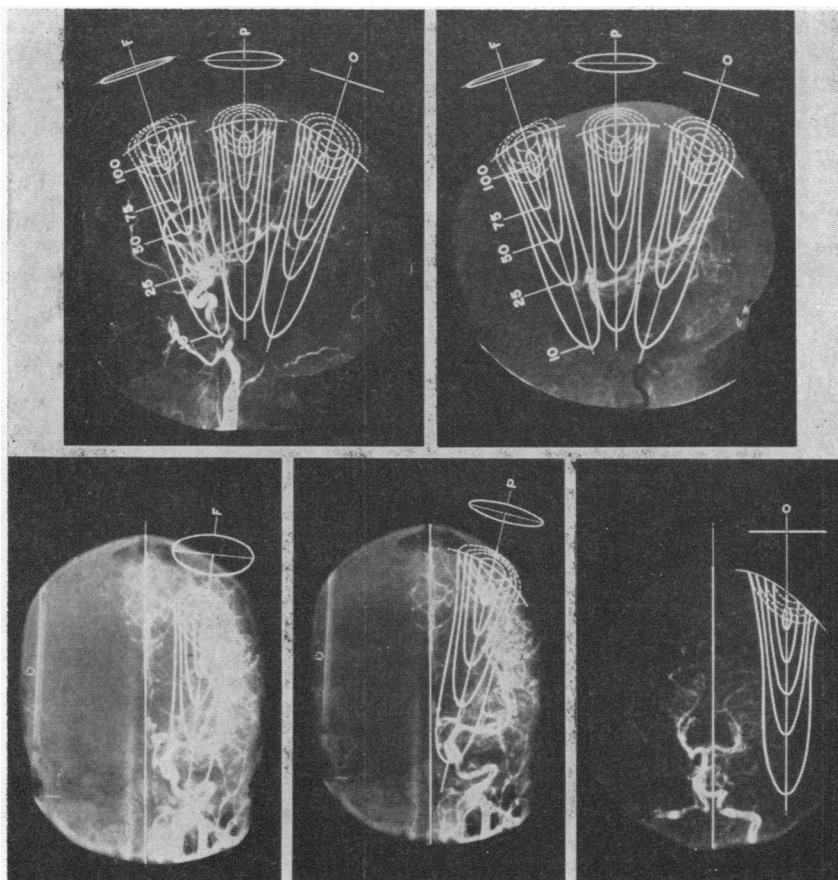

FIGURE 2 Isosensitivity curves for three probes ("frontal," "parietal," and "occipital") superimposed over cerebral angiograms. The isosensitivity curves were obtained from a "point source" of strontium-85. Angiograms of different subjects are shown in this display.
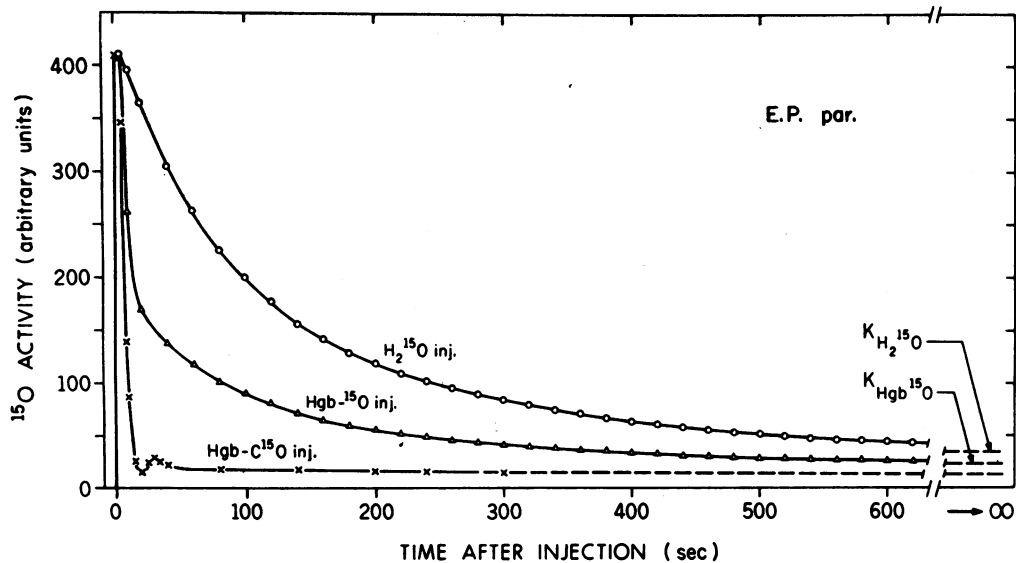
FIGURE 3 (patient E. P.): Plots of the recordings obtained with the parietal probe subsequent to the injection of blood labeled with (a) water-^{15}O, (b) oxyhemoglobin-^{15}O, and (c) carboxy-hemoglobin-^{15}O. The curves are corrected for radioactive decay and for electronic losses, and they are normalized to reflect the same activity injected. $K_{H_2^{15}O}$ and $K_{Hgb^{15}O}$ are the values reflecting the equilibration of the labeled water subsequent to the injection of $H_2^{15}O$ and Hgb-^{15}O, with rapidly exchangeable components of the subject's water pool.

to be about 2%, returns to the injected cerebral hemisphere.

The ^{15}O which egresses into the cerebral tissues is rapidly converted into water of metabolism. The water thus labeled diffuses from the tissues into the blood, is washed out by blood circulation, and equilibrates with the total body water pool (area, Fig. 4).

The recording as a function of time of the presence of the radioactive label in a volume of brain is interpreted as follows: The maximum value "a" (Fig. 5)
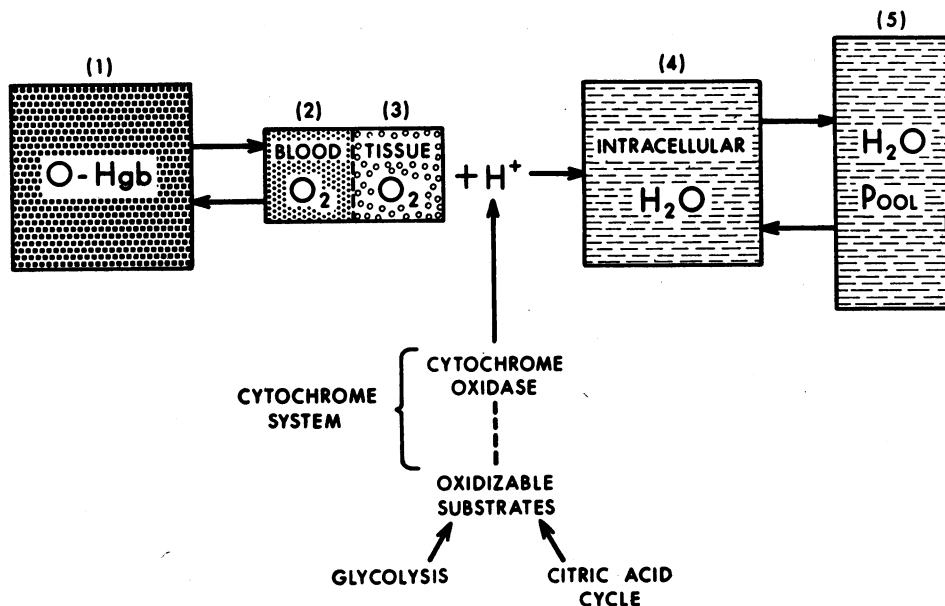

FIGURE 4 Block diagram of the fate of the ^{15}O label subsequent to the intra-arterial injection of oxyhemoglobin-^{15}O.

384 M. M. Ter-Pogossian, J. O. Eichling, D. O. Davis, and M. J. Welch

reached by the curve is proportional to the amount of oxygen perfusing the tissues. This peak is followed by a rapid drop in activity followed by a much slower egress of the ^{15}O label. The rapid loss of activity represents the egress of the fraction of hemoglobin-bound ^{15}O not utilized by the tissues and which is carried out of the volume under examination by the bolus of labeled blood. The balance of the ^{15}O label is rapidly utilized in the tissues and converted into water. The slower phase of the egress shown in Fig. 5 represents the washout of this water. Fig. 6 is a semilogarithmic plot of the data shown in Fig. 5. Conventional curve subtraction shows that the rapid portion of the egress of the oxygen label is well represented by a single phase exponential with a half-period of approximately 2 sec. The egress of the labeled water is, as it will be discussed later, a more complex function representing the washout of at least two compartments with different blood flows.

The back extrapolation "v" of the water egress curve to the abscissa of the maximum a (Fig. 6) is proportional to the amount of oxygen converted into water. The ratio v : a represents the fraction of oxygen utilized by the tissues and provides, therefore, a measure of fractional cerebral oxygen utilization. The value of v can be calculated from the rate of egress of the labeled water after the passage of hemoglobin-labeled bolus of blood: If the duration of the recording is sufficiently long (10–12 min), the egress of labeled water from cerebral tissues can be represented to a high degree
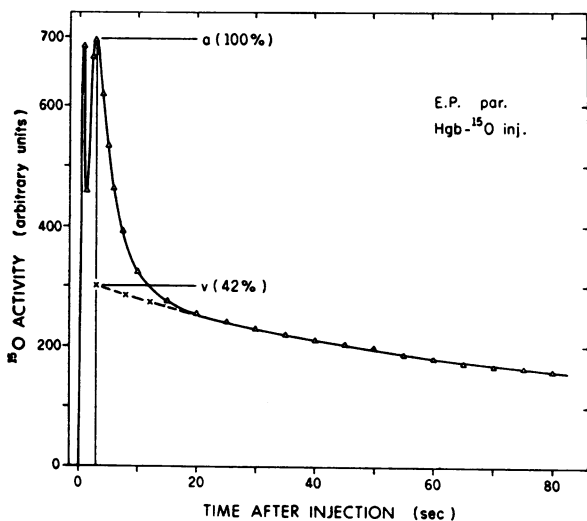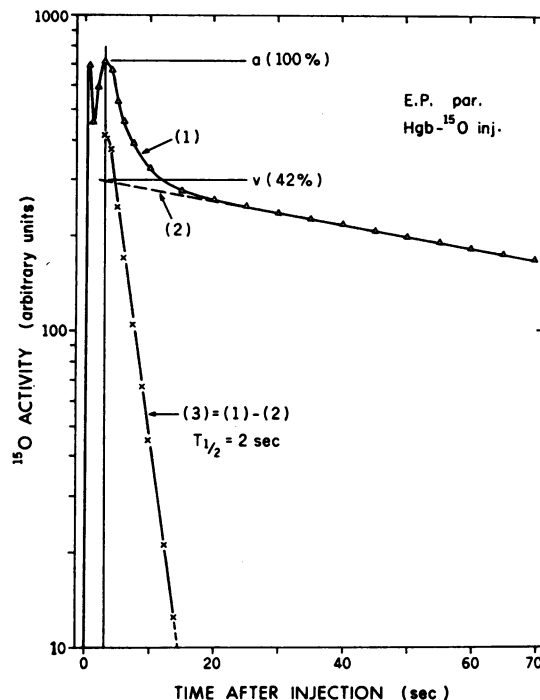

FIGURE 6 Curve 1 is the semilogarithmic plot of the data plotted on linear scale in Fig. 5. Curve 2 is a portion of curve 1 representing the egress of ^{15}O-labeled water of metabolism. This curve is well represented between 25 and 60 sec by a straight line. Curve 3 is obtained by subtracting curve 2 from curve 1.

of fidelity, as it will be shown in the following section, by the sum of two exponential functions and an equilibrium value. The analysis of this function into its components (as in Fig. 8 b) allows the extrapolation of the value of this function to the time of the peak reached by the nutritional flow of blood a.

However, v can also be evaluated to an adequate degree of precision by a procedure less fatiguing for the patient which requires only a period of recording of approximately 1 min after the injection of the oxygen label. This method consists in extrapolating graphically the 25–60 sec nearly linear interval of the semilogarithmic plot of the egress of the labeled water (Fig. 6). The degree to which the biexponential func-

FIGURE 5 (patient E. P.) : Recording for the parietal probe subsequent to the injection of hemoglobin-^{15}O, showing the method used to determine the fraction of oxygen utilized. This curve represents the data shown for the Hbg-^{15}O curve in Fig. 3 but plotted with an expanded time scale with the purpose of resolving the "fine structure" of the early phase of the recorded data.

TABLE II

Error of Short-Interval Extrapolation Method

Model	A_0	$t_{1/2(a)}$	B_0	$t_{1/2(b)}$	K	Δ
	arbitrary units	sec	arbitrary units	sec	arbitrary units	%
I	58	44	37	138	5	2
II	51	33	41	145	8	3
III	60	47	33	156	7	1.5

tion: A_0 exp. $- (0.693t/t_{1/2(a)}) + B_0$ exp. $- (0.693t/t_{1/2(b)}) + K$ behaves as a single exponential function over this time interval was determined for mathematical models based on physiological parameters encountered in our study (Table II). Error denotes the deviation of the value of v obtained by the short-interval extrapolation method with respect to the value obtained from the biexponential function. It was found that the short interval extrapolation underestimated systematically v by 1.5–3% with a mean value of about 2%. It was deemed that the application of the short-interval extrapolation method to the evaluation of v provides a sufficient mathematical accuracy (about 1%) to the analysis o fthe data, provided the value of v thus obtained is increased by 2%.

The following assumptions implied in the above interpretation of the physiological phenomena represented by the data require analysis:

(*a*) The oxygen-15 label remaining in the tissues, after passage of the blood bolus, is in the form of ^{15}O-labeled water. (*b*) Only a small amount of the ^{15}O label returns to the injected hemisphere by recirculation. (*c*) The presence of large blood vessels in the field of the scintillation probes does not invalidate the determination of regional oxygen utilization by adding a spurious component to the value representing tissue blood perfusion.

The validity of these assumptions was tested as follows:

(*a*) Three anesthetized miniature Pitman-Moore pigs were prepared by lifting a bone flap to expose a region of parietal brain tissue. During the procedure, the animals were maintained on artificial respiration. The internal carotid artery feeding the site exposed was catheterized. A small volume of the pig's blood, labeled as previously described, was rapidly injected and a sample of brain tissue (approximately 2 g) was rapidly withdrawn, approximately 40 sec after the injection, by the insertion of a trocar. It is estimated that the removal of the "plug" of tissue took less than 5 sec. No effort was made to favor in this withdrawal either gray or white matter. The sample of brain was rapidly transferred to a glass container which was immediately closed to prevent escape of activity. It was deemed that only a negligible fraction of the ^{15}O label was lost from the sample during its removal and transfer. The brain sample thus obtained was assayed for radioactivity by means of a well counter, homogenized with alcoholic hydroxide, and placed in a flask fitted to a distilling apparatus. The sample was heated and the liquid fraction boiling between 95° and 103°C was collected for about 10 min. The collected distillate and the sample residue were than counted. It was found that all the activity originally in the brain sample was recovered either in the distillate

or the residue and that 94 ±5% of this activity was present in the distillate. The identity of the activity in the distillate was confirmed to be in the form of $H_2{}^{15}$O gas-solid radiochromatography using a Poropak "Q" column and a flow proportional counter. It appears, therefore, that approximately 40 sec after the injection at least 90% of the oxygen in the brain sample is in the form of labeled water. The activity remaining in the sample after distillation was unidentified, but it is highly unlikely that under the conditions of the distillation this activity could be in the form of either dissolved oxygen, oxyhemoglobin, or carbon dioxide. Due to the short time available for the distillation, the unidentified fraction could be unextracted water.

(*b*) All the patients subjected to the injection of oxyhemoglogin-^{15}O–labeled blood were subsequently injected with a sample of their blood labeled with carboxyhemoglobin-^{15}O. The C^{15}O was prepared by passing O^{15}O over charcoal at 900°C, and carboxyhemoglobin was prepared by bubbling the labeled gas through blood. A typical recording obtained subsequent to the injection of carboxyhemoglobin is shown in Fig. 3. The passage of carboxyhemoglobin-labeled blood through the brain tissues mimics the passage of a bolus of oxyhemoglobin-^{15}O but without oxygen utilization. This study shows that the amount of ^{15}CO label recirculating in the injected hemisphere is small, typically about 2%.

(*c*) The measure of the amount of ^{15}O utilized by the tissues relative to the amount of ^{15}O presented to the tissues is based on the assumption that the amount of blood perfusing the tissues can be identified in the recorded data. The presence in the field of view of a probe of arteries which do not perfuse the tissues included in the field of the probe may invalidate this assumption. This difficulty can be circumvented by the analysis of the "fine" structure of the curves representing passage of the blood bolus through the field of the scintillation counter (Fig. 7). This analysis is made possible by the high counting rates and of the large number of points sampled. It is apparent that these curves result from two components, a sharp "spike," apparently contributed by the passage of the blood through the large blood vessels (nonnutritional flow), and a broader component representing perfusion of tissues. This interpretation is supported by the observation that when the field of the probe contains only a small fraction of large blood vessels (parietal and occipital probes, Figs. 2 and 7), the contribution of the spike is less marked than for the frontal region. These spikes appear also in the recordings subsequent to the injection of $H_2{}^{15}$O and hemoglobin-C^{15}O. On the basis of these observations, it is concluded that the study of the fine structure of the labeled blood passage curve does allow the identification of the tissue perfusion component.

Measure of blood flow. Blood flow is measured in this study by the intracarotid injection of blood labeled with water-^{15}O.

The usefulness of water labeled with oxygen-15 as a diffusible indicator for regional cerebral blood flow determination is described elsewhere (4), and it is discussed here only briefly. Water is freely diffusible from tissues to blood. The tissue-blood partition coefficient for water is known for most tissues and is equal to the ratio of the water content of that tissue to that of blood. The electromagnetic radiation resulting from the annihilation of the positrons emitted by ^{15}O is well suited for external measurements. A disadvantage of water for this purpose results from the fact that this indicator is not cleared in its passage through the lung field as it is the case for inert gases. This disadvantage, however, was found to be minimal because the water in the labeled cerebral hemisphere represents only a small fraction of the total body pool, and the equilibration

between these pools lends itself to mathematical analysis (4). The presence as a function of time (F[t]) of the ^{15}O-labeled water in the injected cerebral hemisphere can be expressed as a first approximation by:

$$F(t) = A_0 \exp. -\left(\frac{0.693}{t_{1/2(a)}}\right) t$$

$$+ B_0 \exp. -\left(\frac{0.693}{t_{1/2(b)}}\right) t$$

$$+ C_0 \exp. -\left(\frac{0.693}{t_{1/2(c)}}\right) t \ldots + K. \qquad (1)$$

A_0, B_0, and C_0 are the amounts of water present in different compartments of the brain, at time $t = 0$, with corresponding washout half-periods, $t_{1/2(a)}$, $t_{1/2(b)}$, and $t_{1/2(c)}$, etc. . . . . K is the value reached by F(t) when equilibrium is achieved for $t = \infty$. The various constants in the equation are extracted from the experi-
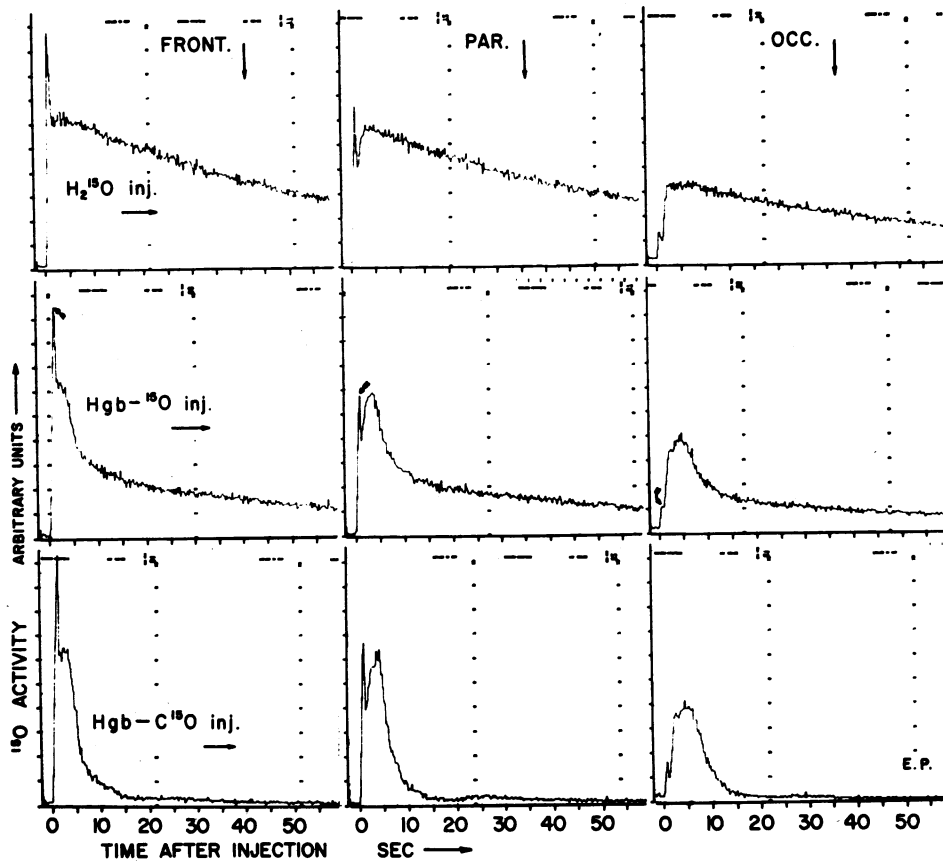

FIGURE 7 (patient E. P.): Photographs of recordings showing the "nonnutritional" spike (arrows Hbg-^{15}O injection) preceding the tissue perfusion component of the curves. These curves are not corrected either for radioactive decay or for electronic losses. Note the high value reached by the nonnutritional spike in the frontal recordings resulting from the inclusion of a large portion of carotid flow is the field of this probe.

mental results (a) by subtracting the equilibrium value, K, from the data points, (b) by plotting the results obtained on semilogarithmic scale, and (c) by standard curve subtraction. Such analysis of the washout of the water in Fig. 3 is shown in Fig. 8 a. This curve can be resolved into two phases with different rates of egress. The intercept of the egress curves for the two compartments with the ordinate allows a relative evaluation of the two compartments (A_0 and B_0), equilibrating with periods $t_{1/2(a)}$ and $t_{1/2(b)}$. The above analysis applied to the washout period (Fig. 3) following oxyhemoglobin-^{15}O injection is shown in Fig. 8 b. It is apparent that the rates of washout are identical, within experimental errors, with those obtained after the injection of water-^{15}O, which confirms the fact that the ^{15}O label is washed out in the form of water-^{15}O. It should be noted, however, that the relative size of the compartments A_0 and B_0 is, in general, different for oxyhemoglobin-^{15}O and for water-^{15}O injections.

Derivation of blood flow and oxygen utilization from the experimental data. The cerebral oxygen utilization rate can be expressed as the product fractional cerebral oxygen utilization × carotid blood oxygen content × regional blood flow. The measure of fractional cerebral oxygen utilization is described above, and internal carotid blood oxygen content is easily measured by the

analysis of blood withdrawn from the subject under study.

It is generally agreed that cerebral blood flow consists of at least two components with different flow rates, and which are often attributed to grey and white matter flows. This multicomponent nature of cerebral blood flow has been demonstrated by a number of different methods including the type of analysis of diffusible indicator washout curves as shown in Fig. 8. The measure of cerebral blood flow can be derived from the washout curve of a diffusible indicator either by the analysis of this curve into its different components (5), or by extracting the mean transit time ($\bar{t}$) of the indicator in the different cerebral tissues (6) by the equation:

$$\bar{t} = \frac{A}{H_0},\qquad(2)$$

where H_0 is the maximum value reached by the washout curve and A the area under this curve (Fig. 9).

The analysis of the washout curve by either of these methods yields a measure of cerebral blood flow per unit mass of tissue provided the tissue-blood partition coefficient for the observed structures is known. If information about blood flow in the individual cerebral compartments is required, the multicompartmental analy-
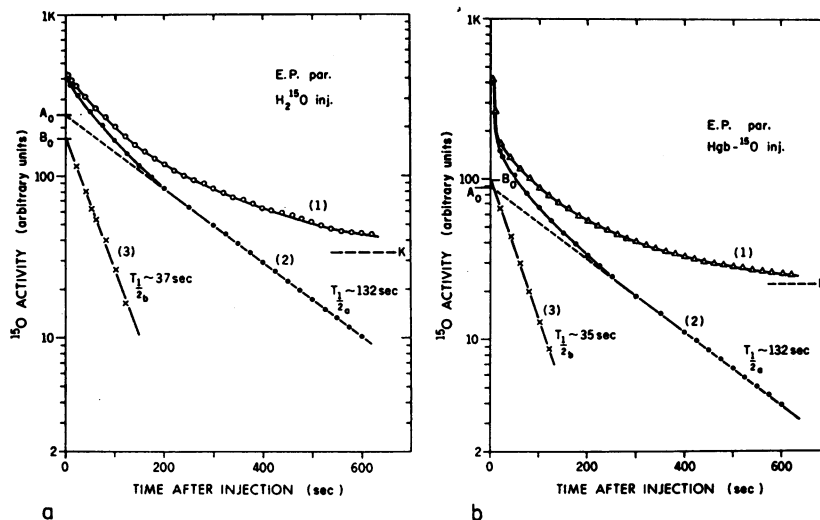

FIGURE 8 a and b (patient E. P.) : Analysis of the recordings shown in Fig. 3 subsequent to the injection of H_2^{15}O (a) and Hbg-^{15}O (b). Curve 1 is the semilogarithmic plot of the data plotted on a linear scale in Fig. 3. Curve 2 is obtained by subtracting the suitable equilibrium value "K" from curve 1. Curve 2 is analyzed into two single-phase exponential components: straight portion of curve 2, and curve 3. A_0 and B_0 are the intercepts of the components of curve 2, they represent the maximum magnitude of the compartments occupied by the ^{15}O label after injection. Notes: (a) The washout rates for Hbg-^{15}O and for H_2^{15}O are interpreted to be identical within experimental errors. (b) The ratio $A_0:B_0$ for Hgb-^{15}O is different from that for H_2^{15}O.
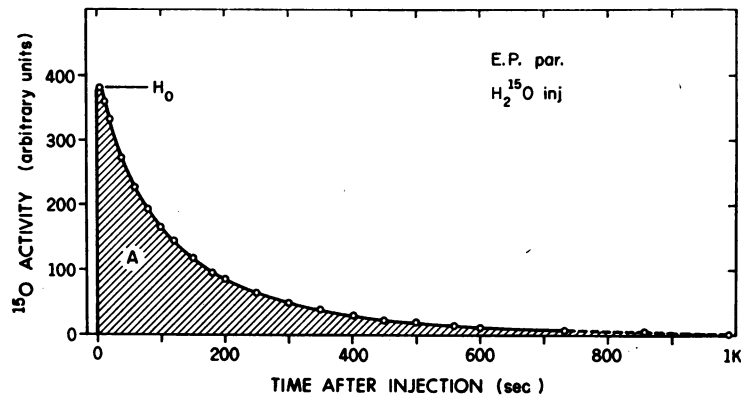
FIGURE 9 (patient E. P.) Parietal probe recording subsequent to the injection of water-^{15}O, minus the equilibrium value $K_{H_2}{}^{15}O$. The ratio $\bar{t} = (A)/(H)$ is the mean transit time for the ^{15}O label.

sis must be applied, while Zierler's approach (6) yields only a mean flow value for the tissues observed.

Since the relative oxygen utilization in the present study is not identified with specific brain tissues, the Zierler approach (6) is used for the derivation of blood flow from the water washout curves by the equation:

$$F = \frac{\bar{\lambda}}{\bar{t}} = \frac{H_0}{A} \bar{\lambda}, \quad (3)$$

where $\bar{F}$ is the mean blood flow and $\bar{\lambda}$ the mean tissue-blood partition coefficient for the tissues observed. If it is assumed that brain is mostly composed of grey and white matters, the effective partition coefficient is given by:

$$\bar{\lambda} = a\lambda_g + b\lambda_w, \quad (4)$$

where a and b are the relative fractions of grey and white matter in the volume seen by the probe, and λ_g and λ_w are the partition coefficients for these tissues.

The relative amount of grey and white matter in cerebral tissues is approximately in the ratio of 60:40% (7), and the water partition coefficients for these tissues can be calculated from the relative water content of white and grey matter and blood:

$$\lambda_g = \frac{\text{water content of grey matter}}{\text{water content of blood}}$$

$$= \frac{84 \text{ g}/100 \text{ g}^{(\ )}}{81 \text{ g}/100 \text{ g}^{(9)}} = 1.04 \quad (5)$$

$$\lambda_w = \frac{\text{water content of white matter}}{\text{water content of blood}}$$

$$= \frac{71 \text{ g}/100 \text{ g}^{(8)}}{81 \text{ g}/100 \text{ g}} = 0.88. \quad (6)$$

Thus, the mean value for λ for brain tissue is:

$$\bar{\lambda} = (0.6) \times (1.04) + (0.4) \times (0.88) = 0.98. \quad (7)$$

One of the advantages exhibited by water over most diffusible indicators for the described purpose is that the partition coefficients for water do not vary much for different cerebral tissues, and an error in the evaluation of the relative amounts of different tissues comprised in the field of the probe does not affect strongly the mean value of the partition coefficient.

DISCUSSION

Although the purpose of this paper is to present a new method for the study of regional cerebral flow and regional cerebral oxygen metabolism, some results obtained during patient studies are also presented (Table III). The method for selecting the patients in Table III was as follows: Patients undergoing carotid arteriography, indicated by clinical assessment, were consulted about the possibility of their having blood flow studies in conjunction with the arteriogram. If the patient agreed, after an explanation of the study, and the internal carotid artery as seen on the early films was found suitable for selective catheterization, the study was carried out. Thus, a considerable amount of selection occurred, and no "normal" patients were examined. However, some patients whose clinical work-up was unremarkable may be considered for our purposes as normal patients, even though no surgical or necropsy evaluations are available and the follow-up is relatively short so that we cannot be absolutely certain that neurological disease does not exist. The most likely diagnosis, however, in some of these normal cases is hysteria.

The number of patients studied is quite small and does not warrant a thorough analysis of the results or a comparison of these results with the values obtained by other methods, such as xenon-133 or nitrous oxide techniques. The blood flows measured by this technique are, however, by gross inspection, similar to those measured by xenon-133, lending additional support to the validity

of our method. The oxygen uptake measurements, however, are somewhat higher (about 6%) than the previously reported values for the whole brain in normal subjects (1, 10, 11). The reasons are not clear, but perhaps our placement of external probes emphasizes the counts from the superficial cortical gray matter, thus raising the values toward the higher gray matter metabolic rate. The established methods for calculation of oxygen utilization, using the arteriovenous oxygen difference, would reflect a general or average value for the entire hemisphere and would be more accurate for total metabolism. Whether our method is an advantage in clinical studies remains to be seen.

A few comments about the clinical cases may be in order. In cases with obvious lesions such as tumor or postoperative changes, the flow in the zone of the lesion seems to be decreased (cases 1, 2, and 4). In case 4 however, the occiptal flow, at some distance from the frontal glioblastoma is quite high. The angiogram revealed however that there was extensive venous drainage into the occipital region from this lesion and perhaps this accounts for the somewhat higher CBF posteriorly. More generalized lesions, or those at the base of the brain, seem to cause lower over-all flow, which is in agreement with results reported by earlier investigators. Finally, the very few pathologic cases available seem to show a higher cerebral oxygen utilization rate than the other, more normal, cases. This is uncertain, however, and deserves further study, and will be reported on in the future.

TABLE III
Patient Data

	Patient	Diagnosis	Arterial Pco₂	Frontal		Parietal		Occipital	
				rCBF	rCMO₂	rCBF	rCMO₂	rCBF	rCMO₂
			mm Hg	ml/min per 100 g		ml/min per 100 g		ml/min per 100 g	
1.	T. C.	Parietal glioblastoma	34	53	4.8	45	3.9	52	4.5
2.	A. D.	AVM, clipped	33	39	3.9	35	3.2	40	3.4
3.	G. G.	? Hysteria	35	62	4.4	60	4.5	64	4.4
4.	E. J.	Glioblastoma, deep frontal	30	32	2.3	29	3.6	29	3.9
5.	N. M.	Cluster headache	37	59	3.2	54	3.3	65	3.0
6.	E. P.	Basilar aneurysm	38	46	3.8	42	3.1	45	3.3
7.	D. C.	Spinal tuberculosis	39	38	3.4	36	3.2	41	4.1
8.	G. F.	Middle cerebral artery occlusion	28	44	2.9	42	3.3	47	3.5
9.	S. D.	Right brain atropy	33	49	3.6	38	3.0	39	3.0
10.	C. K.	? Hysteria	31	59	3.9	54	3.6	65	4.1
11.	D. H.	Grand mal seizure	33	65	4.2	56	4.3	56	4.4
12.	J. P.	Right hemisphere abnormality	35	52	4.0	49	3.2	59	5.0
13.	L. H.	Suprasellar mass	33	47	3.1	49	3.3	51	3.6
14.	W. T.	Moderate spasm; after surgery	30	45	4.1	43	4.3	52	4.1
15.	G. G.	Repeat of patient 3	34	57	2.9	59	3.5	73	4.9
		Mean		50	3.7	46	3.6	52	3.9

Abbreviations: CBF, cerebral blood flow; CMO₂, cerebral oxygen metabolism; r, regional.

APPENDIX (Table III)

Brief summary of the case histories of the patients studied:

1. T. C., 41 yr old man with occipital headaches and right-sided weakness. Left cerebral angiography showed a large vascular mass in the deep parietal area extending across the posterior corpus callosum. This was a glioblastoma multiforme at surgery.

2. A. D., 56 yr old man suffered a subarachnoid hemorrhage 3 days before admission. The patient was left with a mild left arm drift. Course: Left cerebral angiography showed a small AVM in the left parietal region (at sensory motor area). This was partially excised. Postoperative angiography (followed by ¹⁵O studies) showed some residual feeders to site of AVM was not significantly changed in size.

3. G. G., 30 yr old woman with history of left headache, memory impairment, and some right extremity motor function impairment. Decreased touch and pin prick perception on the right side was found. Cerebrospinal fluid (CSF) protein was 65 mg/100 ml. A left carotid arteriogram (at which time the first flow study was done) was normal. She was discharged and readmitted 2 months later because of increasing right leg weakness. There was limping without abnormal reflexes. Some decreased sensory perception on the

right side was again present. The CSF protein was 44 mg/100 ml. A brain scan, pneumoencephalogram, and left carotid arteriogram (at which time the second flow study was done) were normal. Hysteria is suspected.

4. E. J., 60 yr old man with 2 wk history of confusion, staggering, and bizarre behavior. Papilledema was present but neurological examination was normal. Left cerebral angiography showed a large vascular glioblastoma multiforme in the frontal region extending deeply and across the corpus callosum.

5. N. M., 42 yr old man with history of episodic left eye pain spreading to forehead. A negative carotid angiogram completed an unrevealing work-up. Patient was felt to have cluster headaches.

6. E. P., 58 yr old woman who began to lose vision in her right eye 1½ yr before admission. An angiogram revealed a large basilar artery aneurysm presenting as a suprasellar mass.

7. D. C., 45 yd old man with known pulmonary and spinal tuberculosis with flacid paraplegia and incontinence. A right carotid arteriogram was normal. There was no clinical evidence of direct involvemnt of the brain by the infection.

8. G. F., a 37 yr old female who had sudden onset of left hemiparesis and hemihypesthesia. At angiography, the right middle cerebral artery was occluded, with evidence of collateral circulation from the anterior cerebral artery to the territory of the middle cerebral artery.

9. S. D., 33 yr old woman with sarcoidosis who had a sudden onset of hemiparesis, lasting a few days, 10 months before the flow study. After a seizure on the day of admission for this study, a left hemiplegia and homonymous visual field defect were present. Electroencephalogram (EEG) showed diffuse right hemisphere delta-wave abnormality. There was uptake on the brain scan in the right parietal-occipital region. The right carotid arteriogram showed suggestion of right-sided hemispheric atrophy.

10. C. K., 24 yr old woman with a 3 month history of right-sided weakness. No abnormalities on radiographic or laboratory investigation were found. No diagnosis was established. Hysteria suspected.

11. D. H., 36 yr old woman who had a grand mal seizure. EEG showed a right temporal sharp focal trend but clinical, laboratory, and radiologic investigations including pneumoencephalogram, brain scan, and carotid arteriogram showed no abnormalities.

12. J. P., 28 yr old man with progressive left extremity paresis and increase in the left reflexes without a sensory deficit. The left plantor response was extensor. A right carotid arteriogram was normal but the CSF protein was 112 mg/100 ml. No definite diagnosis yet established.

13. L. H., a 58 yr old woman with decreased visual acuity without other neurological abnormalities. There was suprasellar extension of a chromophobe adenoma.

14. W. T., 34 yr old man who had a subarchnoid hemorrhage from a small aneurysm at the bifurcation of the internal carotid artery, with moderate spasm. After the aneurysm was clipped, severe decompensation followed. Angiography demonstrated severe spasm which was partially cleared at further angiography. ^{15}O study was performed at time of last angiogram. Patient has not recovered.

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