In Vivo Determination of Cerebral Blood Volume with Radioactive Oxygen-15 in the Monkey

By John O. Eichling, Marcus E. Raichle, Robert L. Grubb, Jr., Kenneth B. Larson, and Michel M. Ter-Pogossian

ABSTRACT

A method for the in vivo determination of cerebral blood volume was tested in 15 adult rhesus monkeys. The technique utilized external residue detection and required the serial measurement of two mean transit times, namely, that of an intravascular tracer, C₁⁵O-hemoglobin, and that of a diffusible tracer, H₂¹⁵O. In computing the mean transit time for the intravascular tracer, the conventional Hamilton extrapolation of the downslope of the recording obtained for the washout of the tracer from the brain subsequent to an intracarotid bolus injection was found to be inadequate, yielding a mean transit time that systematically underestimated that parameter. Alternatively, the use of a power law extrapolation, as proposed by Huang, allowed a more accurate prediction of the vascular mean transit time. The preliminary studies testing the method predicted that the relationship between cerebral blood volume (CBV) and cerebral blood flow (CBF) was adequately represented by the equation $\text{CBV} = 0.80 \times CBF^{0.84}$, with a correlation coefficient of $r = 0.90$ for the cerebral blood flow range of 16 to 134 ml/100 g min⁻¹ with a normocapnic cerebral blood volume of 3.5 ml/100 g perfused brain tissue (arterial Pco₂ = 37 torr, CBF = 50 ml/100 g min⁻¹).

Cerebral blood volume is considered an important factor in cerebral hemodynamics, but its assessment is a difficult undertaking. Various methods have been proposed for the in vivo measurement of cerebral blood volume, and some disparity exists in the reported results (Table 1). In the present study, the cerebral blood volume of rhesus monkeys was determined by an in vivo tracer method using radioactive oxygen-15 (¹⁵O) and residue detection. The procedure required the serial determination of two mean transit times, namely, that of a vascular tracer, ¹⁵O-labeled carboxyhemoglobin, and that of a diffusible tracer, ¹⁵O-labeled water.

Methods

Cerebral blood volume was determined subsequent to serial intracarotid injections of 0.2 ml of whole blood labeled with (1) C¹⁵O-hemoglobin and (2) H₂¹⁵O, respectively, in 15 adult rhesus monkeys. To facilitate the injection of the labeled materials into the internal carotid artery, all branches of the right external carotid artery were ligated 2 weeks prior to the experiments. The tracers were then injected into the common carotid artery through a small (0.21 cm in diameter) catheter inserted in the femoral artery and positioned in the common carotid artery under fluoroscopic observation. The monkeys were anesthetized with phencyclidine, paralyzed with gallamine, and passively ventilated with 100% oxygen. End-tidal carbon dioxide tension (Pco₂), arterial blood pressure, and rectal temperature were continuously monitored. Temperature was maintained between 37 and 39°C with a heating pad. Arterial pH, Pco₂, and oxygen tension (Po₂) were measured before and after each injection.

The time course of each tracer through the injected hemisphere was monitored with a 3 x 2-inch NaI(Tl) scintillation detector appropriately collimated and positioned to ensure essentially uniform detection efficiency for the injected hemisphere. The detector signal was routed through a pulse-height analyzer with an energy window of acceptance adjusted symmetrically around the 511-kev photopeak (481-541 kev) to eliminate scattered radiation. The accepted events (counts) per time frame were stored in the memory of a small laboratory (LINC) computer. Data processing, including corrections of the raw counts for electronic dead-time losses, physical decay, and background and conversions to count rates (counts/sec) as a function of time, was performed by the computer. Routine data retrieval was in the form of processed count rates as a function of time plotted with an x-y plotter. Optimum temporal resolution was achieved in the initial portion of each recording by employing integration times of 0.1 second. Statistical fluctuations of the recorded signal were minimized by injecting sufficient label to achieve peak counting rates of 10,000–20,000 counts/sec for H₂¹⁵O (~200 μc/0.2 ml).

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Reported Values (In Vivo) of Cerebral Blood Volume (CBV)

<table>
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<tr>
<th>Reference</th>
<th>Animal</th>
<th>Average CBV (%)</th>
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</thead>
<tbody>
<tr>
<td>Grubb et al. (1)</td>
<td>Man</td>
<td>3.2*</td>
</tr>
<tr>
<td>Lowell and Bloor (2)</td>
<td>Monkey</td>
<td>14.0</td>
</tr>
<tr>
<td>Nylin et al. (3)</td>
<td>Man</td>
<td>9.0</td>
</tr>
<tr>
<td>Phelps et al. (4)</td>
<td>Monkey</td>
<td>5.8*</td>
</tr>
<tr>
<td>Smith et al. (5)</td>
<td>Goat</td>
<td>4.8*</td>
</tr>
</tbody>
</table>

* Arterial Pco₂ = 37 torr.

and 2,000-5,000 counts/sec for C¹⁸O-hemoglobin (~40 μc/0.2 ml).

Preparation of the H₂¹⁸O and the C¹⁸O-hemoglobin utilized in this study has been described in detail elsewhere (6-8).

Several investigators have proved the validity of the fundamental relationship that the product of mean transit time and flow equals the volume for both vascular and diffusible tracers (9-15). This relationship, the "central volume principle," can be stated as

\[ \bar{t} = V_o/F, \]  

(1)

where \( F \) is the volumetric flow rate of vascular fluid, \( V_o \) is the apparent or equivalent volume of distribution of the tracer at equilibrium, and \( \bar{t} \) is the mean transit time of tracer particles in the observed system.

Application of the cerebral volume principle to the transport of labeled red blood cells gives the expression

\[ \bar{t}_{RBC} = V_{RBC}/F_{RBC} = \frac{Htc_c V_c}{Hct_{LV} F_c} = \frac{fV_c}{F}, \]  

(2)

where the red blood cell distribution volume in the brain, \( V_{RBC} \), is the product of mean cerebral hematocrit, \( Htc_c \), and the brain blood volume, \( V_c \). The flow rate of red cells to the brain, \( F_{RBC} \), is the product of the large vessel hematocrit, \( Hct_{LV} \), and the brain blood flow, \( F_c \). The factor \( f \) is then the ratio of mean cerebral hematocrit and large vessel hematocrit, i.e., \( f = Htc_c/Hct_{LV} \).

Although it is well established that the mean hematocrit of vascular beds is less than that of large vessels (14, 16), only a few studies have attempted to determine the ratio of mean cerebral hematocrit to large vessel hematocrit. Reported values (Table 2) include only two in vivo determinations. Both measurements were made in man and yielded values of 0.92 (17) and 0.84 (18) for the ratio \( f \). An \( f \) value of 0.85 was used in the present study.

For the diffusible tracer, H₂¹⁸O, the central volume principle leads to the relationship

\[ \bar{t}_{H_2O} = V_{H_2O}/F_{H_2O} = \frac{\bar{a}_T V_T/\bar{a}_D F}{\bar{a}_H_2O V_T/F}, \]  

(3)

where the apparent equilibrium volume of distribution is the product of the mean water content of monkey brain, \( \bar{a}_T \), and the brain tissue volume, \( V_T \). The flow rate of water, \( F_{H_2O} \), is the product of the mean water content of blood, \( \bar{a}_D \), and the brain blood flow, \( F \). The ratio of \( \bar{a}_T \) to \( \bar{a}_D \) defines the mean equilibrium tissue-blood partition coefficient of water, \( \bar{a}_H_2O \).

To express the cerebral blood volume (CBV) in units of volumetric flow per unit mass of brain, Eq. 3 must be modified:

\[ \bar{t}_{H_2O} = \bar{a}_H_2O V_T/r_D F, \]  

(4)

where \( V_T \) is the mass of the tissue volume \( V_T \) and \( r_D \) is the tissue physical density. From the average water content of rhesus monkey brain (ml/g) (23) and that of blood (ml/ml) (23), the ratio of the mean brain-blood partition coefficient to the tissue density, \( \bar{a}_H_2O/r_D \), can be computed to be 0.95 ml/g.

For the condition of constant cerebral blood flow (stationarity), division of Eq. 2 by Eq. 4 and rearrangement yields

\[ CBV = \frac{V_c}{F} = \frac{0.95}{\bar{a}_H_2O} \frac{V_T}{r_D} f_{RBC}. \]  

(5)

Thus, Eq. 5 permits the determination of the vascular volume per unit tissue volume (CBV, ml/g).

The C¹⁸O-hemoglobin mean transit time was determined by utilizing residue detection (24) of the time course of the labeled red blood cells through the injected hemisphere. The clearance curve was used to calculate the red blood cell mean transit time (\( \bar{t}_{RBC} \)) from the relationship

\[ \bar{t}_{RBC} = \int_0^\infty \frac{q(t)}{q_s} dt = \frac{A}{H_0}, \]  

(6)

where \( q(t) \) is the level of detected radioactivity in the region under study as a function of time, \( t \), \( q_s \) is the radioactivity level detected for the injected bolus, \( A \) is the area under the residue recording curve of the injected bolus can be represented beyond the truncation point by the function, \( C_{Ex} = A t^{-m} \), where \( A \) and \( m \) are adjustable parameters. Thus, by plotting the downslope on log-log paper, the clearance curve can be continued linearly past the point where recirculation interferes.

The H₂¹⁸O mean transit time (\( \bar{t}_{H_2O} \)) was determined by a previously described method (8) that utilizes residue detection to monitor the passage of the labeled water bolus through the injected hemisphere. The calculated value of \( \bar{t}_{H_2O} \) was used to compute the cerebral blood flow from Eq. 4, i.e.,

\[ CBF = \frac{(0.95/\bar{a}_H_2O)(100)}{(ml/100 g \ min^{-1})} \]  

(7)

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FIGURE 1
Typical detector response to an intracarotid injection of labeled 15O-carboxyhemoglobin. The region of the recording obscured by tracer recirculation was reconstructed by utilizing a log-log extrapolation of the downslope of the tracer washout. See text for further discussion.

Results

Table 3 lists the individually obtained values for cerebral blood volume, cerebral blood flow, and arterial Pco2. The interdependence of cerebral blood volume and cerebral blood flow is shown in Figure 2. The relationship is adequately represented by the equation

\[ CBV = 0.80CBF^{0.38}, \]

which has a correlation coefficient of \( r = 0.90 \) for the flow range of 16 to 134 ml/100 g min\(^{-1}\). For this cerebral blood flow interval, a doubling of the flow is accompanied by approximately a 30% increase in cerebral blood volume. The regression line predicts a normocapnic cerebral blood volume of 3.5 ml/100 g (arterial Pco2 = 37 torr, CBF = 50 ml/100 g min\(^{-1}\)).

Discussion

MEAN TRANSIT TIME AND CEREBRAL BLOOD FLOW

Valid use of the equation developed for the calculation of cerebral blood volume requires, among other conditions, that (1) the maximum height of the residue recording, \( H_o \), be proportional to the quantity of injected tracer reaching the monitored tissue, (2) the area described by the residue recording of the clearance of the injected bolus be adequately assessed, e.g., appropriately corrected for tracer recirculation, (3) the detection coefficient be spatially uniform within the monitored tissue, (4) the observed system be in a steady-state condition, i.e., both the blood flow and the blood volume must not change during the course of the study, and (5) the observed systems be linear with respect to tracer stimuli. However, there are practical difficulties in satisfying these...
TABLE 3

<table>
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<tr>
<th>Expt.</th>
<th>Arterial Pco₂ (torr)</th>
<th>CBF (ml/100 g min⁻¹)</th>
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FIGURE 2

Relationship between cerebral blood volume (CBV) and cerebral blood flow (CBF) for 15 adult rhesus monkeys for the flow range of 16 to 134 ml/100 g min⁻¹.

\[
\bar{t} = \int_{t_0}^\infty q(t) \, dt / q_0 \approx A/H_0,
\]

is valid as long as the original bolus of tracer is injected outside the monitored region regardless of whether the bolus becomes dispersed prior to reaching the monitored volume (12). However, the entire injected activity must be in the monitored volume at some time to correctly assess \( q_0 \) without independent knowledge of the detection efficiency. Use of the maximum height, \( H_0 \), of the detector response curve to estimate the response that would be observed for the total amount of injected tracer, however, can underestimate \( q_0 \) and thus overestimate the tracer mean transit time if the pulse (bolus) is so dispersed that some tracer leaves the monitored volume before arrival is complete. Errors from this source were largely eliminated by the rapid intra-arterial injection of a small volume (0.5 seconds, 0.2 ml) and by the employment of sampling times sufficiently short (0.1 second) to provide adequate temporal resolution for the correct assessment of \( H_0 \). Adequacy of these steps was confirmed by comparing the respective upslopes of the recordings obtained for the labeled red blood cells and a freely diffusible flow-limited tracer, \(^{133}\text{Xe} \), which revealed that the early portion of the vascular recording was indeed an accumulation curve. This favorable circumstance can be ascribed to the great reduction of linear velocity of blood through the brain on reaching the small vessels of the brain’s venous vascular bed. The result is to delay the departure of tracer and to confine it to the monitored volume prior to outflow.

Another practical problem is imposed by tracer recirculation. The computed area,

\[
A \approx \int_{t_0}^\infty q(t) \, dt,
\]

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should include no contribution due to recirculation of tracer to the monitored volume. This problem of recirculating tracer generally has been dealt with by use of the "Hamilton extrapolation" (25). If the major portion of the primary circulation curve can be recognized, then the ingenious method of Hamilton et al. (25) can be applied, in which it is assumed, as a first-order approximation, that the terminal portion of the primary washout curve can be represented beyond the truncation point by a single exponential,

\[ C_{ex} = Ae^{-kt}, \]

where \( A \) and \( k \) are adjustable parameters. Thus, by plotting the downslope on semilog paper, the clearance curve can be continued linearly past the point where recirculation occurs. Although there is no physiological basis for assuming that the washout is monoexponential, it is generally thought that if the tail portion represents a small portion of the total area any error in the assumed extrapolation is of minor importance. Such a conjecture might be valid for a vascular tracer.

However, Huang (13), in his modeling of transit time curves through vascular beds, has shown that the tail behavior of a transit time curve for a vascular tracer follows a power law (\( \propto t^{-m^{-1}} \)). In other words, if the downslope portion is plotted with logarithmic scales for both the vertical and the horizontal coordinate, the tail should be a straight line. Huang (13) supported his contention with experimental transit time curves obtained from isolated hind limbs of rats; further evidence of the validity of his contention can be obtained by extrapolating washout data from perfused organ studies in which there is no recirculation (26, 27). In such cases, the log-log plot faithfully describes the terminal portion of the washout data, whereas the conventional Hamilton semilogarithmic plot of the data underestimates that portion of the data. As Lassen et al. (27) have pointed out, one cannot simply use the initial part of the downslope for semilogarithmic extrapolation as is customarily done. In fact, Hamilton et al. in their original thesis (25) warned that the extrapolation was generally valid only for circulation systems with a mixing chamber, e.g., heart, interposed between the injection site and the point of monitored washout.

By applying conservation of tracer mass, it is easy to show that if the tail of a vascular tracer outflow curve behaves according to the power law \( t^{-m^{-1}} \), then the tail of the residue curve \( q(t) \) for the same tracer behaves like the power law \( t^{-m} \). The integral implied by Eq. 6 of the tail of the last function will exist provided \( m > 1 \). All values of \( m \) obtained from slopes of log-log plots of our data met this condition; consequently, it was possible in all cases to compute the area under the tails of our residue curves analytically and therefore to derive a value of \( \bar{t} \) according to Eq. 6.

The adequacy of the Hamilton and the Huang extrapolations in correcting for tracer recirculation of labeled red blood cells was tested by comparing the mean transit time determined by each extrapolation technique with that obtained using a more general model developed by Larson and Snyder (28) that accounts specifically for tracer recirculation. The method based on this model employs two injections, one in the artery supplying the monitored organ and the other at the venous outflow of the organ. The mean transit time is then computed from the equation,

\[ \bar{t} = \int_0^\infty [q_a(t) - \bar{q}_w(t)] dt/(1 - \bar{q}_w), \]

where \( \bar{q}_a(t) \) is the normalized response following arterial injection, \( \bar{q}_w(t) \) is the normalized response following venous injection, and \( \bar{q}_w \) is their common normalized equilibrium value. Thus, the mean transit time is numerically equal to the area between the normalized arterial and venous response curves divided by the quantity \( (1 - \bar{q}_w) \). One normalization procedure simply involves scaling the curves to the same equilibrium value. Experimental validation of the method has been reported for perfused heart studies in dogs (29).

Results of the comparison of the two extrapolation techniques are shown in Figure 3. The power law extrapolation of Huang yielded vascular mean transit times generally in good agreement with those obtained by the Larson-Snyder method, whereas the Hamilton monoexponential extrapolation led to mean transit times that appear to be systematically underestimated, the discrepancy being progressively worse for longer mean transit times. Thus, it is our opinion that the Hamilton extrapolation is inadequate for describing the portion of the red blood cell response curve obscured by tracer recirculation.

The validity of the mean transit time determination for the diffusible tracer, labeled water, was tested by comparing the computed cerebral blood flow obtained with \( H_2\textsuperscript{15}O \) with that obtained simultaneously with the standard \( ^{133}\text{Xe} \) 10-minute height-over-area method (30). This comparison was accomplished by sequentially injecting \( H_2\textsuperscript{15}O \) and then \( ^{133}\text{Xe} \). The time course of each tracer was monitored and processed with a separate energy window of acceptance adjusted asymmetrically.
Comparison of the Hamilton (semi-log) and the Huang (log-log) extrapolations to correct for tracer recirculation. The mean transit time (t) determined by each extrapolation technique is plotted vs. the mean transit time obtained using the method of Larson and Snyder (28), which takes specific account of tracer recirculation. A line of identity is shown to aid the comparison.

around the 81-kev photopeak of $^{133}$Xe (75-100 kev). Suitable correction was applied to subtract the contribution of the $^{15}$O activity in the $^{133}$Xe window signal. A value of 1.15 ml/ml or 1.10 ml/g (31) was used for the equilibrium brain-blood partition coefficient of xenon. Cerebral blood flow was manipulated by changing the arterial Pco$_2$ (see Methods), and measurements of arterial blood gases bridged each trial to ensure a steady state. Thirteen paired observations were made over the cerebral blood flow range of 20 to 160 ml/100 g min$^{-1}$. The $^{133}$Xe cerebral blood flow was computed assuming that the 10-minute height-over-area method systematically overestimates the true flow by 11% (30, 32). The resultant line of regression was

$$CBF_{H_2^{15}O} = 0.97 CBF_{^{133}Xe} + 0.7,$$

which has a correlation coefficient $r = 0.96$ ($P < 0.001$). The excellent correlation between the two methods of flow determination substantiates the method of computing the water mean transit time and cerebral blood flow with H$_2^{15}$O.

**Cerebral Blood Volume and Cerebral Blood Flow**

At a normocapnic arterial Pco$_2$ in the rhesus monkey (~37 torr), we found an average cerebral blood volume of 3.5 ml/100 g perfused brain tissue. Two other studies provide adequate in vivo data to allow comparison with our results (4, 5). Smith and his associates (5) measured cerebral blood flow, mean transit time, and cerebral blood volume in goats. They used an inert gas ($^{85}$Kr) saturation technique to measure cerebral blood flow and a dye-dilution technique to measure the vascular mean transit time. Cerebral blood volume was then computed using the central volume principle (Eq. 1). They found an average cerebral blood volume of 4.8 ml/100 g, a value appreciably greater than ours. Two factors may account for this discrepancy. First, they reported a normocapnic cerebral blood flow in the goat of 65 ml/100 g min$^{-1}$. Our data predict a cerebral blood volume in the rhesus monkey of 3.9 ml/100 g at this flow. Second, Smith and his associates (5) did not apply a correction for cerebral hematocrit. Since indocyanine green is a plasma tracer, such a correction (assuming $f = 0.85$) would predict a cerebral blood volume of 4.1 ml/100 g at a cerebral blood flow of 65 ml/100 g min$^{-1}$ in the goat. Hence, the great difference between our value for normocapnic cerebral blood volume in the rhesus monkey and that reported for the goat (5) may be due to the different normocapnic cerebral blood flow values used in the two studies and to the omission of the cerebral hematocrit correction in the latter experiment.

In our laboratory, Phelps et al. (4) have utilized stimulated X-ray fluorescence to measure absolute regional cerebral blood volume in the rhesus monkey. They found a normocapnic cerebral blood volume of 4.7 ml/100 g, a value appreciably greater than that reported in the present paper. This lack of agreement may well be due to the extreme difference in regionality in the two methods. In contrast to the mean hemispheric cerebral blood volume obtained in the present report, the stimulated X-ray fluorescence technique assesses volume for a nominal 1 cm$^3$, i.e., for a volume representing less than 2% of a rhesus monkey brain hemisphere. Furthermore, whether the tissue monitored by the fluorescence technique is representative of a larger volume of tissue in terms of a gray-white distribution and contained vascular bed is uncertain.

Despite the apparent lack of agreement between our value for the normocapnic cerebral blood volume and those of these previous studies, there is surprisingly good agreement among all three experiments for the response of cerebral blood volume to acute changes in arterial Pco$_2$. We found that a 100% increase in cerebral blood flow was accompanied by a 30% increase in cerebral blood volume (Fig. 2). The data of Smith et al. (5) indicate that a
100% change in flow is accompanied by a 27% increase in volume. Finally, Phelps et al. (4), utilizing the cerebral blood flow–arterial Pco₂ relationship of Reivich (33), predicted a 28% change in cerebral blood volume for a 100% change in cerebral flow.

We have developed an in vivo technique of determining cerebral blood volume that utilizes external detection and requires the serial measurement of two mean transit times, namely, that of an intravascular tracer, C₁₅O-hemoglobin, and that of a diffusible tracer, H₂¹₆O. In computing the mean transit time for the intravascular tracer, a critical step in our method, we found that the conventional Hamilton extrapolation of the downslope of the recording obtained for the washout of a vascular tracer from the brain subsequent to an intracarotid bolus injection was inadequate. The semilogarithmic extrapolation thus obtained yielded a mean transit time that systematically underestimated that parameter. Alternatively, we found that the use of a power extrapolation, as proposed by Huang (13), allowed a more accurate prediction of the vascular mean transit time. This conclusion results from a comparison of both the Hamilton and the power extrapolation technique with a dual-injection technique based on the model of Larson and Snyder (28), which takes specific account of tracer recirculation in residue detection measurements of mean transit time.

Preliminary studies testing the method in 15 rhesus monkeys predicted a normocapnic cerebral blood volume for that species of 3.5 ml/100 g perfused brain tissue (arterial Pco₂ = 37 torr, CBF = 50 ml/100 g min⁻¹). Furthermore, the interdependence of cerebral blood volume and cerebral blood flow can be represented by the equation 

\[ \text{CBV} = 0.80 \text{CBF}^{0.38} \]  

\[ (r = 0.90, \text{CBV in ml/100 g, and CBF in ml/100 g min}^{-1}) \]

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