Journal of Cerebral Blood Flow and Metabolism
3:141–153 © 1983 Raven Press, New York

Quantitative Measurement of Local Cerebral Blood Flow in Humans by Positron Computed Tomography and ^{15}O-Water

S.-C. Huang, R. E. Carson, E. J. Hoffman, J. Carson, N. MacDonald, J. R. Barrio, and M. E. Phelps

Division of Biophysics, Department of Radiological Sciences, UCLA School of Medicine, and Laboratory of Nuclear Medicine, Laboratory of Biomedical and Environmental Sciences, University of California, Los Angeles, California

Summary: A noninvasive method that employs ^{15}O-water and positron-computed tomography (PCT) was used to measure quantitative local cerebral blood flow (lCBF) in man. ^{15}O-Water (about 30–50 mCi) was introduced through a single-breath inhalation of ^{15}O-carbon dioxide or through an intravenous bolus injection of ^{15}O-water. A sequence of five 2-min PCT scans was initiated at the time of tracer administration. A series of 15–20 blood samples (1 ml each) was withdrawn from the radial artery of the subject over a period of 10 min. Oxygen-15 radioactivities in the blood samples were immediately counted in a well counter to give an input function, which together with the projection data collected by PCT were processed to provide images of lCBF and local water distribution volume. The method was found to be convenient to use and gave good-quality images of lCBF. Quantitative values of lCBF in images were 59 ± 11 and 20 ± 4 ml/min/100 g for gray and white matter, respectively, with a gray-to-white matter ratio of 2.93 and a global flow value of 42 ± 8 ml/min/100 g. Distribution volume of water was 0.85 ± 0.03, 0.76 ± 0.03, and 0.81 ± 0.02 ml/g respectively, for gray matter, white matter, and whole brain. **Key Words**: Cerebral blood flow—Distribution volume of water—^{15}O-water—Positron computed tomography.

Cerebral blood flow (CBF) is an important physiological parameter for assessment of brain function. Cerebral tissues depend on CBF for delivery of nutrients and for removal of metabolic products. Many methods for measuring CBF in man have become available since Kety and Schmidt (1945, 1948*a*) developed the nitrous oxide method (Phelps et al., 1982). Most of these methods require the introduction of a diffusible tracer (NO_2, Xe, Kr, water, iodoantipyrine, etc.) through inhalation, intravenous injection, or carotid injection—the dynamic clearance information of the tracer in cerebral tissue being measured either by sampling the arteriovenous difference of tracer concentration or, in cases of gamma-emitting radioisotope tracers, by residue detection with scintillation detectors (Freygang and Sokoloff, 1958; Harper, 1967). These methods have provided significant physiologic information about brain functions (Kety and Schmidt, 1948*b;* Mangold et al., 1955; Sokoloff et al., 1955; Ingvar et al., 1965; Harper, 1967; Takeshita et al., 1972; Sokoloff, 1976) and have been used for investigation of cerebral disorders (Kety et al., 1948*c;* Novack et al., 1953; Cohen et al., 1967; Ingvar and Risberg, 1967; Ingvar et al., 1970). However, because of the limitations of the measuring instruments, CBF values obtained by these methods are average values over either the whole brain, hemispheres, or a large volume of cerebral tissues.

With the recent development of positron computed tomography (PCT) (Phelps et al., 1975), radioactivity in small local regions of tissue can be measured quantitatively (Phelps, 1977; Phelps et al., 1982). The measurement by PCT is noninvasive and is well suited for human studies. For example, by adapting the deoxyglucose autoradiographic

Address correspondence and reprint requests to Dr. Huang at Division of Biophysics, Department of Radiological Sciences, UCLA School of Medicine, 405 Hilgard Avenue, Los Angeles, California 90024.

Abbreviations used: BBB, Blood–brain barrier; lCMRGlc, local cerebral metabolic rate for glucose; lCWV, local cerebral water volume; OM, orbitomeatal line; PCT, positron computed tomography.

technique (Sokoloff et al., 1977), PCT has been used successfully for measuring local cerebral metabolic rate of glucose (lCMRGlc), with ^{18}F-fluorodeoxyglucose as a tracer (Phelps et al., 1979*a;* Reivich et al., 1979; Huang et al., 1980*b*). Extending the PCT technique for measurement of local CBF (lCBF), however, is not as straightforward. The primary difficulty is that PCT usually requires the radioactivity distribution to be stationary (not changing as a function of time), whereas most CBF methods for human studies use the dynamic information of the delivery/clearance of tracer in tissue.

Generally, there are two ways of resolving this problem. One is to make multiple short scans, so that within the time of each scan, the radioactive distribution does not change much and can be considered as stationary. The other way is to use appropriate tracers or to manipulate the tracer administration schedule so that the radioactivity distribution is not changing with time. The first way is more straightforward and has been used by Yamamoto et al. (1977). In their studies, the subject was given ^{77}Kr gas through inhalation. A series of short scans (30 s each) was taken to image the radioactivity distribution for 6–10 min as a function of time. The initial clearance rate of ^{77}Kr gas in cerebral tissue was used to calculate lCBF. Because of the short scan time of each scan, the total photons collected for each image was low, resulting in images of high noise levels and poor spatial resolution. The data processing time was long because of the large number of images needed to be reconstructed before lCBF was calculated. Furthermore, even with scans as short as 30 s, the assumption of a stationary radioactivity distribution is questionable. Although other methods (Kanno and Lassen, 1979; Holden et al., 1981) have been proposed to improve the short scan time problem, the procedures are generally not straightforward, and the practical advantages of these methods still need to be demonstrated.

In the other way of using PCT for lCBF measurements, two methods have been devised to obtain a stationary distribution that satisfies the requirement of PCT. One method uses ^{13}N-ammonia as a flow tracer (Phelps et al., 1977). Ammonia in plasma is readily extracted by cerebral tissue in a single capillary passage and is retained in tissue for a long time (i.e., has a slow clearance rate) (Phelps et al., 1977, 1981). Thus, ammonia is functionally similar to microspheres. That is, its distribution in tissue reflects lCBF and is stationary for PCT measurements. A drawback of the method is that the extraction fraction of ammonia is less than 100% (and therefore not strictly flow-limited) and is dependent upon the permeability of the blood–brain barrier (BBB), making it difficult to obtain quantitative values of lCBF from the PCT-measured ^{13}N-ammonia distribution in tissue. Despite these problems, ^{13}N-ammonia has been used with PCT to provide very useful information of lCBF in humans (Kuhl et al., 1980).

A second method uses a constant infusion of a short-lived isotope (^{15}O-water). After about 10 min, the net delivery of tracer by blood flow to brain tissue and the physical decay of the short-lived isotope in tissue reach an equilibrium. The equilibrium concentration in tissue is related to lCBF and can be measured with PCT (Jones et al., 1976; Subramanyam et al., 1978; Huang et al., 1979*a*). This method has been used successfully to measure lCBF in humans (Alpert et al., 1977; Frackowiak et al., 1980, 1981; Baron et al., 1981; Rhodes et al., 1981). However, the method requires the delivery of ^{15}O-water or ^{15}O-carbon dioxide (converted to ^{15}O-water by carbonic anhydrase in lung) to be at a constant rate, directly from the cyclotron.

Recently, we have formulated lCBF measurement methods that use ^{15}O-water, but without the requirement of constant infusion (Huang et al., 1981, 1982), and so have others (Ginsberg et al., 1981*b*, 1982; Raichle et al., 1981) for use with PCT. These methods are all based on the original model of Kety and Schmidt (1948*a*). The methods used by Raichle et al. (1981) and Ginsberg et al. (1981*b*, 1982) are quite analogous to the classical autoradiographic technique of measuring lCBF in experimental animals (Landau et al., 1955; Freygang et al., 1958). The method developed by us can measure lCBF and water distribution volume (i.e., partition coefficient) simultaneously, and it combines the kinetics of tracer uptake and clearance into the PCT reconstruction directly. Basically, the method has allowed us to formulate the flow calculation in terms of the time integrals of the tissue radioactivities, which can be reconstructed from the time integrals of the PCT projection measurements. Thus, PCT can be used to measure lCBF from the fast dynamic information, even though the radioactivity in tissue is not stationary during each scan time. Also, because the method deals with the time function of the projection measurements, the method can be used with nonstationary PCT scanners (Huang et al., 1982).

This method has been tested on computer-simulated data and found to give accurate results (Huang et al., 1982). In this paper, we report our initial results of using this method for lCBF measurements in normal humans. The method was found to be convenient to use and provide good

quality images of lCBF distribution. Average values of lCBF in gray and white matter and whole brain, as obtained by the present method, are consistent with those reported in the literature.

METHODS

Mathematical model and theory

The theoretical basis of the technique employed in the present study for the calculation of lCBF and local cerebral water volume (lCWV) has been described previously (Huang et al., 1982). The mathematical model is summarized briefly in the following.

For each volume element that is resolved by the imaging resolution of PCT, the transport of tracer in the element is approximated as a single compartment. That is, tracer concentration is assumed to be uniform inside the resolution element at all times, and the transport of tracer out of the element is proportional to the tracer concentration in the element. If we let V denote the distribution volume of tracer (ml/g) in the element, F (ml/min/g) be the blood flow, $C_i(t)$ be the tracer concentration (μCi/ml) in arterial blood, $C(t)$ be the tracer concentration (μCi/ml) in the element at time t, and $\lambda(\text{min}^{-1})$ be the physical decay constant of radioactive tracer, the rate of change of total radioactivity [$Q(t) = C(t)V$] in the element can be expressed as

$$\dot{Q}(t) = FC_i(t) - FC(t) - \lambda\dot{Q}(t) \quad (1)$$

The first term is the rate of new supply of tracer to element; the second and the third terms are the disappearance rates of tracer due to washout and to physical decay, respectively. In terms of the decay-corrected quantities (denoted by an asterisk), the rate of radioactivity change will be

$$\dot{Q}^*(t) = F\,C_i^*(t) - FC^*(t) \quad (2)$$

By first integrating Eqs. 1 and 2, the quantities F and V can be solved in terms of the tracer concentrations in blood (C_i and C_i^*) and in the tissue element (Q and Q^*) as (Huang et al., 1982)

$$F = \frac{\int Q^*\,dt\,[\lambda\int Q\,dt + Q(T)] - Q^*(T)\int Q\,dt}{\int C_i\,dt\int Q^*\,dt - \int Q\,dt\int C_i^*\,dt} \quad (3)$$

$$V = \frac{\int Q^*\,dt\,[\lambda\int Q\,dt + Q(T)] - Q^*(T)\int Q\,dt}{\int C_i^*\,dt\,[\lambda\int Q\,dt + Q(T)] - Q^*(T)\int C_i\,dt} \quad (4)$$

where the time integrations are over the entire measurement period (from 0 to T). Thus, according to the above equations, both blood flow and distribution volume of tracer in a tissue element can be determined from two measurements: PCT measurement of tissue radioactivity as a function of time and blood-sample measurement of radioactivity concentration as a function of time.

Furthermore, since all the terms involving PCT measurements [i.e., $Q(t)$ and $Q^*(t)$], except $Q(T)$ and $Q^*(T)$, are the time integrals of the quantities, one does not need to reconstruct images of $Q(t)$ and $Q^*(t)$ at all times. Instead, as previously demonstrated (Tsui and Budinger, 1978; Huang et al., 1982), one can integrate the time functions of the PCT-collected projection data and reconstruct images of $\int Q\,dt$ and $\int Q^*\,dt$ from the integrated projection data.

Preparation of ^{15}O-carbon dioxide and ^{15}O-water

Two-minute half-life ^{15}O was produced at the Medical Cyclotron Laboratory by the ^{14}N(d,n)^{15}O reaction. Nitrogen gas, containing 1% oxygen carrier, at 100 pounds/inch^2 gauge pressure was bombarded for 8 min with deuterons entering at 9.3 million eV energy. If ^{15}O-labeled carbon dioxide was desired, the target gas was released from the target chamber, passed over copper oxide granules at 450°C to produce CO_2, then pumped directly to a plastic bag in the Nuclear Medicine Clinic through 450 feet of nickel tubing. A measured volume was then transferred by syringe pump to a breathing bag, from which the patient inhaled the radioactive gas. If ^{15}O-labeled water was required, the target gas was released at the end of bombardment, mixed with a flow of hydrogen gas, and the mixture passed over a heated palladium catalyst. The gas, now containing the ^{15}O in the form of water vapor, was then bubbled through 4 ml of isotonic sodium chloride solution. This solution was drawn through a sterilizing filter membrane into a sealed sterile vial, assayed for radioactivity, and sent to the clinic via a pneumatic tube. Intravenous injections of this labeled water could be made within 4 min of the end of bombardment.

Studies in humans

Studies were done in seven normal volunteer subjects (average age, 27.3 ± 7.3 years SD). Each subject was placed supine on the bed of a NeuroECAT scanner (EG&G Ortec, Oak Ridge, TN) (Hoffman et al., 1981*b*). A headholder was used to reduce the head movement of the subject, and the subject was positioned in the PCT scanner for examination of the preselected brain cross sections. A small needle (23-gauge minicath set) was placed in the radial artery for arterial blood sampling. Before the introduction of the tracer, a blood sample (4 ml) was taken for analysis of P_{CO_2} and pH. A separate sample (1 ml) was taken to determine chemically the water content of the blood.

In four studies, ^{15}O-water was introduced through inhalation of ^{15}O-carbon dioxide. The subject was asked to inhale about 30–50 mCi of ^{15}O-carbon dioxide (300 ml in volume) in a single breath and to hold his breath for 10–15 s. During the breath-holding period, more than 95% of the ^{15}O label of CO_2 in lung was transferred to water in plasma (West et al., 1962). The subject was then returned to normal breathing of room air. In three studies, ^{15}O-water (30–50 mCi) was injected intravenously.

Immediately after introduction of ^{15}O-water into the subject, PCT measurements were started and continued over a period of 10 min, as described below.

Blood samples were taken from the subject for 10 min concurrent with the PCT measurements, at a rate of 1/6–7 s in the first 1–1.5 min and about 1/min afterward, giving a total of about 20 samples in 10 min. Radioactivity concentrations in blood samples were measured immediately in a precalibrated well counter.

In four subjects, a second study was performed about ½ h later to image the cross-sectional levels between the ones selected in the first study. The tracer administration and data collection procedures were all identical to those in the first study. All studies were done under approval of the UCLA human subject protection committee. Total

body radiation dosage to the volunteer subject was estimated to be under 90 mrad/50 mCi of ^{15}O-water introduced. Radiation to the lung, the critical organ, is under 460 mrad/50 mCi of ^{15}O-water.

PCT measurements and data processing

PCT measurements were collected with a NeuroECAT scanner (Hoffman et al., 1981*b*). The "medium resolution sampling," "septa in," and "shadow shield out" options were used. The standard NeuroECAT software system was slightly modified in advance to save all the raw counts between each pair of coincidence detectors and the exact time of data collection, but otherwise run normally. Before administration of the tracer, transmission measurements of the attenuation in the preselected cross sections of the brain were measured with a ^{68}Ga ring source for attenuation correction. At the time of tracer administration, five 2-min scans were initiated. Only the data from the three straight planes (3 cm apart) of the NeuroECAT were collected (i.e., the two crossed planes were ignored). After the scans were completed, regular PCT images for the straight planes were reconstructed. A low-resolution reconstruction filter of NeuroECAT was normally used, giving an image resolution of 1.2 cm full width at half maximum (FWHM) (Hoffman et al., 1981*b*). Data of the raw counts had been saved on disk by the software modification. They were normalized for detection efficiency and were sorted according to the projection position of the coincidence detector pairs to give the time functions of the projection measurements. Because of the redundant samplings employed in NeuroECAT (Hoffman et al., 1981*b*), the time functions have a temporal sampling resolution of 11 s for projections near the center and about 24 s for projections at 7 cm from center. These time functions (both decay-corrected and non-decay-corrected) of the projection measurements were integrated in time (using linear interpolation between the sampled data points) and then reconstructed in the spatial domain by the NeuroECAT PCT reconstruction program (with a low-resolution reconstruction filter) to give the images of $\int Q dt$ and $\int Q^* dt$. The averaged value over the entire brain region of the last two 2-min PCT images was used for $Q^*(T)$. $Q(T)$ was obtained as $Q^*(T)e^{-\lambda T}$. Images of lCBF and lCWV were then calculated according to Eqs. 3 and 4. The software program system BLD (Carson et al., 1981) was used extensively to facilitate the data processing.

The calibration between the NeuroECAT scanner and the well counter (for measurement of blood radioactivity concentrations) was performed according to the established routine previously described in detail (Phelps et al., 1979*a,b;* Huang et al., 1980*b*). Specific gravities (densities) of 1.036 and 1.027 g/ml for gray and white matter (Cho et al., 1975), respectively, were assumed to calibrate the PCT measurements on a per-gram basis. For whole brain values, the specific gravity was assumed to be 1.032 g/ml.

Quantitative values of lCBF and lCWV were obtained by using the NeuroECAT region of interest software program. Circular regions of interest of 1-cm diameter were normally used to obtain lCBF and lCWV values in various gray and white matter regions on the flow and volume images. The locations of the regions of interest were selected on the flow images and applied to both the flow and volume images. The local values in the anterior, the posterior, and the left and right lateral cortical regions of all scanned cross sections were then averaged to give the gray matter value of each study. Values for white matter were the averages of the region of interest values in relatively large (>1.5 cm in diameter) and clearly identifiable white matter regions. Whole brain values were average values over the whole cross-sectional slices.

Determination of water content of human blood and tissue

A carefully weighed aliquot of human blood (typically around 0.5 g) was placed in a 20-ml round-bottom flask and evaporated *in vacuo* in a rotary evaporator (bath temperature = 40–50°C). Repeated evaporations were carried out with anhydrous ethanol to remove the last traces of water until a constant weight of the residue was obtained. Samples were run in duplicate.

RESULTS

Figure 1 shows a sequence of PCT images of two brain cross sections (4 cm above the orbitomeatal line (OM + 4) and OM + 7 cm) from the five 2-min scans taken after the administration of ^{15}O-water through CO_2 inhalation. ^{15}O-Water is initially transported to brain tissue proportionately to blood flow. Subsequently, the larger amounts of tracer transported to the higher flow tissues are cleared faster by the high blood flows. This accounts for the quick loss of contrast between gray and white matter in the later images. Eventually, the water tracer approaches a distribution similar to the distribution volume of water in tissue. Because of the fast physical decay of ^{15}O, the later images are seen to have higher noise levels. The total number of collected coincidence counts per plane in the five sequential scans after administration of 40 mCi of ^{15}O-water in a typical study are about 1.74, 1.07, 0.45, 0.20, and 0.08×10^6 counts. In the studies with i.v. injection of ^{15}O-water, the time sequences of both the image pattern and detected counts were not found to be any different from those resulting from inhalation of ^{15}O-carbon dioxide.

Figure 2 shows a set of ^{15}O-water images of human brain (at cross sections from OM + 8 to OM + 0 cm at 1-cm intervals) in the first 2 min after tracer administration. These images also clearly reveal various gray matter structures, similar to the PCT images of fluorodeoxyglucose (FDG) in brain. The gray-to-white matter ratio in these images is about 2.06.

The time function of a projection measurement as collected by the NeuroECAT scanner in a typical study is shown in Fig. 3. The decay-corrected curve can be obtained from this non-decay-corrected curve by applying appropriate decay correction factors for the measurements at various collection times. As shown by this curve, the time resolution

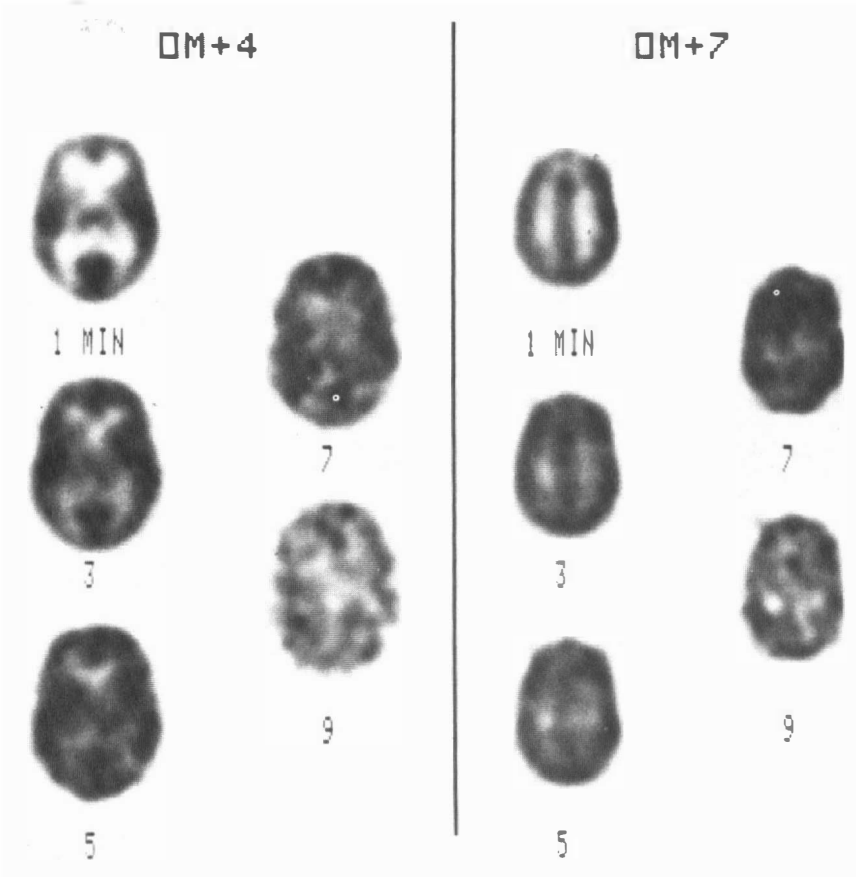

FIG. 1. PCT images of two cross sections (levels as indicated at top) of a human brain at various times after the introduction of ^{15}O-water through a single-breath inhalation of ^{15}O-carbon dioxide or by an i.v. bolus injection. Darkness in image corresponds to tissue ^{15}O-water concentration, with black being the highest concentration. The scan time for each image was 2 min, and the number below each image is the mid-time of the scan. The two sequences of images were taken simultaneously with a NeuroECAT scanner that has a multiplane capability. The contrast in the early images shows ^{15}O-water was initially transported more to gray matter, due to its higher blood flow. However, the flow pattern is gradually diminished due to higher tracer clearance in high blood flow regions. Also, because of the short half-life of ^{15}O (2 min), the radioactivity in brain decreased rapidly and accounts for the high noise level in later images.

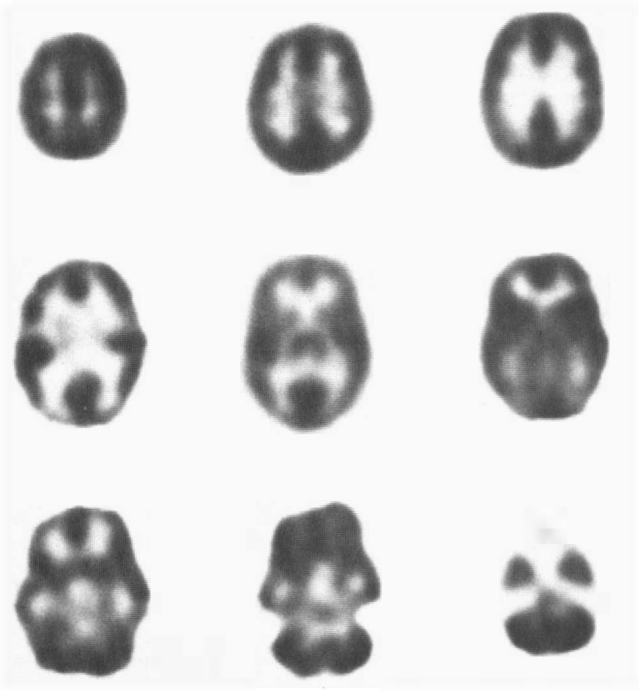

FIG. 2. A composite set (from five individuals) of ^{15}O-water images taken during the first 2 min after tracer introduction. The images correspond to brain cross sections from OM + 8 cm to OM + 0 cm at about 1-cm intervals. Gray matter regions are seen to have higher tracer delivery, and the images show qualitative distribution of blood flow in brain.

in the measurement of the projections was quite adequate.

Figure 4 shows a typical time activity curve in arterial blood after a single breath inhalation of ^{15}O-carbon dioxide. The ^{15}O label is seen to have been transferred quickly from lung to blood. The short duration (<1 min) of the peak in the curve indicates that the ^{15}O-water was quickly distributed throughout the body and rapidly approached a near-equilibrium distribution. The curve after the first 2 min decreases very slowly (at a rate of about 3–6%/min, between 5 and 10 min). In the studies with i.v. injection of ^{15}O-water, the time activity curves in arterial blood were not found to be significantly different from the one shown in Fig. 4.

Figure 5 shows the derived images of lCBF and lCWV at a cross section (OM + 4 cm) of brain, in a study using ^{15}O-carbon dioxide inhalation. By dividing the lCWV image by the lCBF image (on a pixel-by-pixel basis), an image of mean transit time can be obtained (Fig. 5). The lCBF images were qualitatively similar to the first images taken immediately after tracer introduction. A set of lCBF images corresponding to the initial 2-min images in Fig. 2 is shown in Fig. 6 for comparison. The gray-to-white matter contrast in the initial images is seen

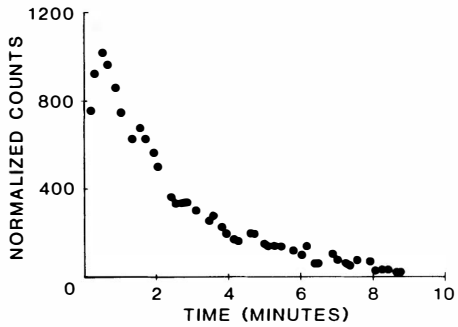

FIG. 3. A plot of the measured projection data (not decay corrected) as a function of time. Data were collected with a NeuroECAT scanner. The measured ^{15}O radioactivity decreases at a rate of about 52% and 39% per min, respectively, at 2 and 5 min after tracer introduction. These rates of decrease are larger than the physical decay rate of ^{15}O (34.7%/min), indicating a net biological clearance of tracer from tissue at those times. The areas under the curves from all projection positions were used to reconstruct an image of $\int Qdt$. Decay-corrected curves can be obtained by applying appropriate decay correction factors, and the areas under the decay-corrected curves provided an image of $\int Q^*dt$.

to be lower than in the lCBF images. This lower contrast is due to the early clearance of ^{15}O-water from the high blood flow tissue (gray matter) that has already begun during the 2-min scan time for the initial images.

Quantitative values of lCBF and lCWV obtained in the seven studies are shown in Table 1. The blood pH and P_{CO_2} values were, respectively, 7.42 ± 0.02 (SD) and 40.0 ± 2.6 (SD) mm Hg, well within the normal range. Average values of lCBF and lCWV

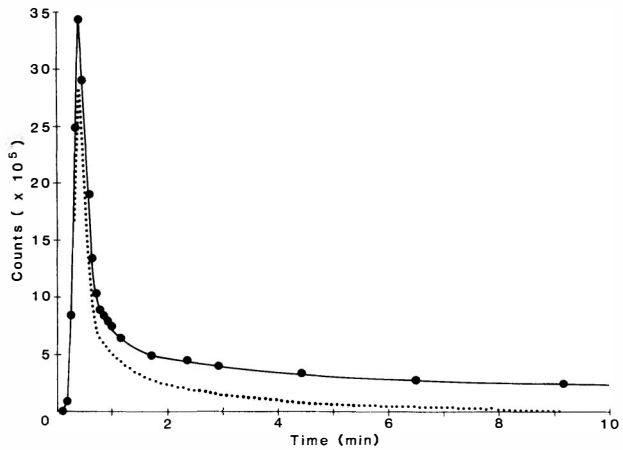

FIG. 4. A typical time-activity curve in arterial blood after introduction of ^{15}O-water. Blood samples were taken from radial artery, counted in a well counter, and decay corrected to tracer introduction time (t = 0). The dotted curve is the corresponding non-decay-corrected curve (i.e., decay corrected to the sampling time of each sample). The narrow peak in the early part of the curve indicates the fast dilution of ^{15}O-water in the body water pool. Between 5 and 10 min after tracer introduction, the decay-corrected ^{15}O radioactivity in blood decreases at a rate of about 3–6%/min, with a smaller rate of change at later times.

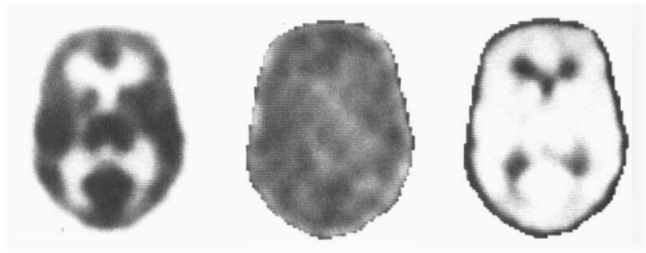

FIG. 5. Typical images of lCBF (left) and lCWV (center) as calculated by Eqs. 3 and 4. Low noise level is seen in the lCBF image, which has a high image contrast between gray and white matter. The lCWV image is much more uniform, with values in gray matter only slightly higher than in the white matter. Image on right corresponds to mean transit time of water. The image was obtained as the ratio of lCWV image to lCBF image (on a pixel-by-pixel basis). Long mean transit time in white matter corresponds to white matter's lower blood flow.

were found to be 58.5 ± 11.4 and 0.85 ± 0.03 for gray matter, and 20.0 ± 3.7 and 0.76 ± 0.03 for white matter, with a gray-to-white matter ratio of 2.93 and 1.13, respectively, for lCBF and lCWV. Average whole brain value was 42 ± 8 and 0.81 ± 0.02 for CBF and CWV.

Percent water contents in whole blood were found to be 78.9 ± 0.7% (SD) in the present studies, consistent with values previously obtained by the

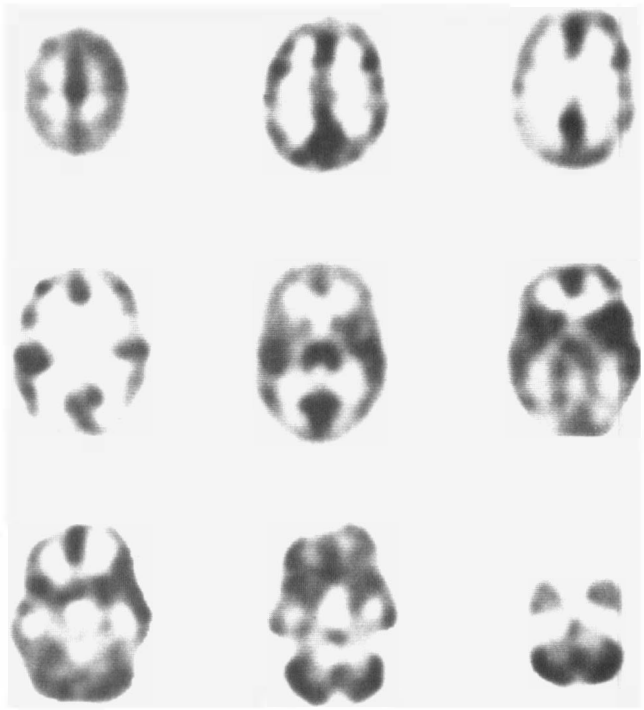

FIG. 6. A composite set of lCBF images corresponding to those in Fig. 2. As compared to Fig. 2, images of lCBF (Fig. 6) are seen to show similar characteristics, but have a higher gray-to-white ratio than images in Fig. 2 (Tables 1 and 2). The lower contrast of Fig. 2 images is due to the partial clearance of ^{15}O-water in gray matter that has already occurred in significant amounts during the first 2 min after tracer administration.

TABLE 1. *lCBF and lCWV in normal humans*

Subject[a] (age)	lCBF (ml/min/100 g)			Gray-to-white ratio of lCBF	lCWV (ml/g)			Gray-to-white ratio of lCWV
	Whole brain	Gray matter	White matter		Whole brain	Gray matter	White matter	
JA (37)	48.5	72.4	23.7	3.05	0.83	0.85	0.81	1.06
TD (27)	29.8	44.3	16.6	2.67	0.78	0.81	0.75	1.08
JH (35)	32.6	45.2	14.1	3.20	0.80	0.85	0.76	1.11
RW (30)	40.9	52.2	20.6	2.53	0.81	0.84	0.75	1.13
RB (25)	43.5	60.0	19.3	3.12	0.81	0.88	0.74	1.19
VD (18)	46.7	68.0	21.2	3.21	0.79	0.86	0.72	1.20
L (19)	50.2	67.4	24.6	2.74	0.83	0.89	0.76	1.16
Average (±SD)	41.7 (7.9)	58.5 (11.4)	20.0 (3.7)	2.93 (0.28)	0.81 (0.02)	0.85 (0.03)	0.76 (0.03)	1.13 (0.05)

[a] Subjects are listed according to the chronological order of study. The first four were studied with single breath inhalation of ^{15}O-carbon dioxide and the latter three with i.v. injection of ^{15}O-water. The first three had one scan each (i.e., two to three cross sections), and the latter four subjects had two scans about 1.5 cm apart.

oven method or the Karl Fisher reagent (David et al., 1953). These results, together with the lCWV values, would imply that the portion of rapidly exchangeable water in brain tissue is 0.67 ml/g in gray matter and 0.60 ml/g in white matter.

DISCUSSION

Images of ^{15}O-water

The present study demonstrates a convenient method of using ^{15}O-water and PCT to measure lCBF and lCWV. The tracer can be introduced through i.v. injection of ^{15}O-water or through a single inhalation of ^{15}O-carbon dioxide [converted quickly to ^{15}O-water by carbonic anhydrase in lung and in plasma (West et al., 1962)]. As far as the tracer delivery of ^{15}O-water to brain tissue is concerned, no significant difference was found between the two administration methods. With either method, tracer is mixed well with blood in the heart chambers before delivery to the tissues. Thus, except for a small difference in transit time through the supplying arteries, all brain tissues are exposed to the same tracer concentration in blood. Since ^{15}O-water is rather freely diffused across the BBB of primates (Raichle et al., 1976), the delivered tracer (the amount of which is proportional to lCBF multiplied by tracer concentration) can diffuse quickly into the extravascular space. In other words, the initial amount of ^{15}O radioactivity deposited in tissue will be directly proportional to lCBF. Because ^{15}O-water is not chemically trapped in tissue, it will be cleared gradually from tissue by blood flow. The larger the blood flow is, the faster the clearance occurs, and the pattern of blood flow distribution is gradually lost. As shown in Fig. 4, the peak concentration of tracer in blood appears at about 20–30 s after tracer administration, and the concentration drops quickly to a relatively low level during the first minute. Thus, after the first minute, the clearance of tracer from tissue is expected to be more than the delivery. This is also supported by the time function of projection measurement (shown in Fig. 3), which, after the initial peak, decreases faster than the physical decay rate of ^{15}O, indicating a net clearance of tracer from brain tissue.

To evaluate the amount of water cleared from tissue during the first 2 min, the initial image was used to calculate approximate flow values, assuming zero clearance, and the approximate flow values were compared with the values obtained in the present studies. Without tracer clearance, flow can be calculated in a manner similar to that of the quantitative microsphere technique (Heymann et al., 1977), which uses the tissue uptake of tracer and a reference blood sample. We consider the initial image as the tissue uptake of radioactivity averaged over the first 2 min, and the average value over the first 2 min of the integrated blood curve (of the corresponding study) as the reference blood sample of unit flow. The approximate flow values were then calculated according to the formula used in the quantitative microsphere technique. The results, as shown in Table 2, are seen to underestimate flows by 20–30% for whole brain, 30–40% for gray matter, and about 5% for white matter, as compared to the values in Table 1. The larger underestimation of flow in gray matter than in white matter is expected, because the rate of clearance is proportional to flow, and accounts for the lower gray-to-white contrast of the initial images than in the lCBF images.

In the present study, the 2-min scan time for the first PCT images was chosen to get more photon counts (less random noise) at the expense of some loss of flow information. By shortening the scan time, the amount of clearance loss is lessened, and

TABLE 2. *Approximate values of lCBF and lCWV obtained from images at 1 and 10 min*

Subject	Approximate lCBF (ml/min/100 g)			Gray-to-white ratio of lCBF	Approximate lCWV in whole brain (ml/g)
	Whole brain	Gray matter	White matter		
JA	34.2	42.5	22.3	1.91	0.95
TD	24.6	30.6	16.2	1.89	0.98
JH	23.8	31.0	15.4	2.01	0.91
RW	29.5	35.0	17.4	2.01	0.96
RB	31.6	39.4	16.8	2.34	1.04
VD	37.1	48.6	21.6	2.25	0.96
L	37.2	46.5	22.7	2.05	0.99
Average (±SD)	31.1 (5.5)	39.1 (7.2)	18.9 (3.2)	2.06 (0.17)	0.97 (0.04)

the initial images may better reflect the lCBF distribution in tissue but will have higher noise levels. However, an optimal scan time length will be dependent on lCBF, which varies throughout the brain and might vary unpredictably in pathology. Also, since the primary emphasis of the present study is to obtain quantitative values of lCBF and lCWV, we have not devoted much effort to finding a scan time length that would optimize the signal-to-noise ratio of the first images to reflect relative flows. By judging from the similarity in distribution between the first 2-min images and the lCBF images in all the studies conducted in this work, the initial 2-min images are considered quite adequate for showing qualitative distribution of lCBF.

The ^{15}O-water concentration in blood falls to a rather low level after the first minute (Fig. 4) and the turnover time of ^{15}O-water in brain tissue is on the order of 1–2 min. Therefore, 9 min (more than three turnover times) after tracer administration, one might expect the distribution of ^{15}O-water in brain tissue to reflect the distribution volume of water. By taking the ratio of the whole brain average value in the last image to the ^{15}O-water concentration in blood at that time, we obtained such an estimate of the distribution volume of water over the whole brain; this is shown in Table 2 as the approximate water distribution volume. As compared to the properly calculated lCWV values in Table 1, the approximate values in Table 2 are generally higher, by 15–20%. The discrepancy is believed to be an indication that the water distribution has not reached an equilibrium, and there is still a net clearance of water from tissue to blood at that time. This is supported by the continual decrease of ^{15}O radioactivity in the arterial blood, even at 10 min after tracer administration (Fig. 4). By assuming a flow rate of 45 ml/min/g and a distribution volume of 0.85 ml/g, and using the measured blood curve obtained in the present study, we found the ratio of tracer concentrations between tissue and blood by computer simulation to be 0.98 ml/g at 9 min, which was 15% higher than the true value of 0.85 ml/g, consistent with the difference between the distribution volume values of Tables 1 and 2. However, because of the short half-life of the ^{15}O isotope (2 min), radioactivity in tissues became very low after 6 min, and the PCT images taken had high noise levels. Thus, without going through the data processing procedure of Eqs. 3 and 4, which use all the collected data, the late images by themselves have limited value for showing the relative distribution volume of water in brain tissues.

Quantitative values of lCBF

In this work, quantitative values of lCBF were calculated. The average whole brain value of 42 ± 8 ml/min/100 g is in general agreement with the value of 40–50 ml/min/100 g reported in the literature (Kety and Schmidt, 1948*a*; Sokoloff et al., 1955; Cohen et al., 1967; Ingvar and Risberg, 1967; Obrist et al., 1967; Takeshita et al., 1972; Yamamoto et al., 1977; Lauritzen et al., 1981). The lCBF value of 59 ± 11 ml/min/100 g for gray matter is somewhat on the low side as compared to the literature value of 60–80 ml/min/100 g (Ingvar and Risberg, 1967; Obrist et al., 1967; Yamamoto et al., 1977; Frackowiak et al., 1980; Baron et al., 1981). This slightly lower value is believed to be due mainly to the partial volume effect of imaging structures that have a size smaller than the imaging resolution (Hoffman et al., 1979). The lCBF values listed in Table 1 for gray and white matter are the average values over many regions of various structural sizes, most of which are smaller than the imaging resolution (1.2 cm), whereas the literature values of 60–80 ml/min/100 g were obtained either by methods that are independent of imaging resolution (Ingvar and Risberg, 1967; Obrist et al., 1967) or from structures that are large enough to have a recovery coefficient close to

unity (Frackowiak et al., 1980). We chose to report values that are averaged over many regions because they are less sensitive to the exact brain cross sections imaged, are less sensitive to the image noise level, and are realistic in terms of applying the technique.

As compared to the results of Frackowiak et al. (1980), who used a constant infusion technique, the higher value of their results could also be due partly to their assumption that the distribution volume of water was equal to 1. In other words, their results can be viewed as flow per unit distribution volume of water. With the values of 0.85 ml/g (gray) obtained in this study for distribution volume, the lCBF value of 65.3 ml/min/100 ml of water distribution volume in gray matter as reported by Frackowiak et al. (1980) is equal to 55.5 ml/min/100 g of gray matter, which is in the same range of values reported in Table 1.

Another source of possible underestimation of lCBF by the present technique is its intrinsic characteristic of underestimating the flow and distribution volume when there is admixture of gray and white matter within the space of an imaging resolution element (Huang et al., 1982; Lammerstma et al., 1981). For the resolution that can be achieved by the present PCT scanners (1.2 cm FWHM in plane × 1.3 cm FWHM in thickness), this tissue admixture problem is unavoidable. However, as shown by simulation studies (Huang et al., 1982), the underestimation due to this source is about 5–6%.

In spite of the problems discussed above, the lCBF values and the gray-to-white matter ratio (2.9) that were obtained in this work are in agreement with the values obtained by other methods, especially when one considers the wide differences in technique, ranging from tracer and instrumentation to data analysis (Kety and Schmidt, 1948*a;* Ingvar and Risberg, 1967; Obrist et al., 1967; Yamamoto et al., 1977; Frackowiak et al., 1980).

The variability of flow values among the subjects studied is, however, rather large (about 19% SD). The blood P_{CO_2} values of these subjects have a standard deviation of about 7%, which may have caused some of the variability in blood flow but is probably not responsible for all the variations. The correlation of the flow values with age was also found to be insignificant (correlation coefficient = 0.4). Some of the variation could be due to the different brain levels that were measured in different subjects. Also, the subjects that have the largest deviation from the average values are the early studies, when only one scan was obtained for each subject and the experimental procedure was still in the early developmental stage. As a comparison, the standard deviation of the flow values in the last four studies is only about 10%, quite consistent with the CBF variation predicted from the 7% variation in P_{CO_2} (Grubb et al., 1974). This reduction in variation is believed to be due to (1) an improvement in skill of personnel in performing the experiments and (2) a better averaging of the partial volume effect by taking a larger number of brain sections. The use of a different tracer administration method (i.v. injection of water versus inhalation of CO_2) in the later studies could also be a possible cause for the reduction in variability, although there is no apparent reason to explain it. More studies are being planned to investigate and improve the accuracy of the technique.

Quantitative values of lCWV

The distribution volume of water obtained in this work is 0.85 ± 0.03 and 0.76 ± 0.03 ml/g for gray and white matter, respectively. The gray-to-white matter ratio of 1.13 ± 0.05 is quite consistent with the ratio reported in the literature (McIlwain and Bachelard, 1971). However, with a water content of blood of 79%, the distribution volumes of 0.85 and 0.76 ml/g would imply that the water contents in gray and white matter should be 67% and 60%, respectively. These water contents are about 15% lower than the chemically analyzed values of 83% and 70% reported in the literature for gray and white matter (McIlwain and Bachelard, 1971). The discrepancy could be due to a number of factors, among which random error probably can be ruled out because the variation in lCWV among the studied subjects (~3%) is significantly smaller than the discrepancy in question (15%).

As mentioned earlier, the technique employed in the present work could underestimate the lCWV values if there is admixture of tissues within an image resolution element. The amount of underestimation was found through computer simulations to be about 5% when the admixture was 50% gray and 50% white matter (Huang et al., 1982). For other mixture ratios, the amount of underestimation would be even smaller. Thus, the admixture problem cannot fully account for the discrepancy found above.

Another aspect that needs to be examined is that the tracer ^{15}O-water is only about 95% freely diffusible across the BBB in primates (Eichling et al., 1974; Raichle et al., 1976), and the single compartment in the model assumes a value of 100%. Whether the low lCWV value is due to this approximation can be examined by comparing the tracer concentration in tissue to that in blood at late

times (~9 min) when the blood curve varies very slowly. At these times, the tissue concentration is gradually approaching its equilibrium value, which only depends on the distribution volume and not on the diffusion limitation of the tracer. In the present studies, because a high concentration of tracer was delivered initially to tissue with a subsequently small and decreasing delivery (Fig. 4), a net tissue clearance of tracer occurred after the initial phase. Thus, at late times, the tissue-to-blood concentration ratio should be larger than (before equilibrium is reached) or equal to (after equilibrium) the distribution volume of water.

Using computer simulations and assuming a model that includes diffusion limitation of water across BBB (Huang et al., 1979*a*), we have found that, for the normal CBF ranges and for the blood curves measured in the present work, the ratio of tissue to blood concentrations at 9–10 min is about 15% higher than the equilibrium value if tracer is 100% freely diffusible, and the ratio is larger if tracer is less than 100% diffusible. In other words, the true value of lCWV is expected to be at least 15% lower than the ratio of tissue to blood concentration at 9–10 min. In our studies, the ratio of tissue to blood concentration over the whole brain at 9 min is shown in Table 2 to be 0.97, which would correspond to an lCWV value of <0.84 ml/g, consistent with the value based on the model in this work (Table 1). This consistency suggests that the model is not responsible for the low lCWV obtained in this study.

Regardless of whether a model is used or not, lCWV values are basically derived from the ratio of the labeled water concentration in tissue (measured by PCT scanner) to that in blood (measured by a well counter). Any error in the PCT measurements or in the calibration between the two measuring devices can be reflected directly in the calculated lCWV values. Many physical factors and reconstruction parameters, such as scattering, random coincidence, dead time, calibration, and sampling and attenuation correction, could affect the measurements of PCT (Hoffman et al., 1979, 1981*a,b;* Huang et al., 1979*b,* 1980*a*). In the present study, all these factors had been carefully considered in order to minimize their possible adverse effects. For example, transmission measurements were used for attenuation correction. A headholder was used to reduce subject movements. The "septa in" option was chosen to reduce scattering and randoms (subtracted from data), but shadow shields were "out" to increase detection efficiency (and thus reduce noise) and to match the NeuroECAT's medium sampling distance, which was chosen to improve the temporal resolution and to reduce processing time. Although it is not exactly known whether these considerations have completely eliminated all the possible systematic errors, the PCT measurements were done as carefully as possible. Also, the same PCT measurement technique has been quite successful in providing accurate measurements of other physiological parameters, like blood volume, lCMRGlc, and flow (Phelps et al., 1979*a,b;* Huang et al., 1980*b;* Wisenberg et al., 1981). Therefore, it is unlikely that a systematic error of >15% could be due to the PCT measurements.

A possible hypothesis that can explain the discrepancy is that, during the time course of these studies, not all the water in tissue is freely exchangeable with water in blood. A relatively small fraction of water molecules could be tightly bound to other large molecules in tissue (i.e., water of hydration) and normally have a very slow exchange rate with the freely exchangeable water molecules. Using *in vitro* experiments, Ginsberg et al. (1982) have recently determined the tissue-to-blood ratio of ^{15}O-water in rat brain to be 0.956 ml/g at 10 min after tracer injection. Like the results of the present study, the value of 0.956 ml/g is also lower than the ratio of total water content, tissue-to-blood, which is about 1.05 ml/g (because rat brain contains mostly gray matter, and assuming water content in gray matter and blood of rat are the same as in humans). The result is consistent with the hypothesis that not all of the tissue water is freely exchangeable within the duration of this study. However, more *in vitro* studies that would measure the tissue-to-blood ratio at later and multiple times are needed to investigate the hypothesis.

Procedure of the present technique

For the present technique, tracer can be introduced through i.v. injection of ^{15}O-water or through single breath inhalation of ^{15}O-carbon dioxide. Both methods are easy to use. However, the single breath inhalation method requires some cooperation from the subject that may be difficult for certain patients or undesirable for certain stimulation studies. No significant difference in radiation dose is expected between the two techniques, although the inhalation method may give a slightly higher dose because of a longer resident time of ^{15}O-carbon dioxide in the lung.

The measurement time of 10 min was chosen because the ^{15}O radioactivity at 10 min had dropped to about 3% of its initial value. After 10 min, the photon counting noise is too large to give more information. However, in this work, no attempt was

made to adjust this measurement time to optimize the signal-to-noise ratio of the lCBF and lCWV images. Neither have the other parameters (like temporal sampling times, duration of tracer introduction, processing time, etc.) been optimized in the studies reported here. Work is being done in our laboratory to examine these parameters for optimization of the technique.

The most invasive step in the procedure is the sampling of arterial blood to give the ^{15}O-water input function. Less invasive methods are being examined to replace this step. It is hoped that the whole procedure can be further improved and the technique made more convenient.

Labeled water as a flow tracer

It is generally believed that the tracer used in the clearance methods for CBF studies should be inert and 100% freely diffusible into tissue. Labeled water is known to be less than 100% diffusible across the BBB (Eichling et al., 1974; Bolwig et al., 1975; Raichle et al., 1976; Go et al., 1981). This has raised some doubts about whether labeled water is an appropriate tracer for CBF studies. The main reason that a 100% diffusible tracer is preferred is to avoid any flow dependence on the tracer's extraction fraction. This dependence would cause the relationship between tracer uptake and flow to be nonlinear, with the degree of nonlinearity directly related to the degree of the flow dependence. For labeled water, the extraction fraction is larger than 95% in brain tissue of primates within the physiological flow range, and the nonlinearity between tracer uptake and flow is not expected to be serious. Also, if necessary, the finite permeability of water across the BBB can be taken into account by modification of the model (Huang et al., 1979*a*). The requirement that the permeability surface product be constant for simple modeling is also well satisfied by labeled water (Go et al., 1981). Thus, the <100% free diffusibility of water across the BBB should not cause problems for its use as a flow tracer for measuring lCBF.

The potential variability of its distribution volume is another possible source of error for using a diffusible tracer as a flow tracer. For the measurement techniques that require an assumed value of the distribution volume that can also vary greatly (e.g., xenon), particularly in different abnormal tissues, this variability certainly is a concern. However, with the present technique, lCBF and lCWV are measured at the same time, and the technique does not assume any advance knowledge about the size of distribution volume. Also, the variation in distribution volume of water is not expected to vary much, even in pathological cases (Tower, 1976). Therefore, the variability of distribution volume for water will not be a problem, especially when the present technique is used.

The advantages of using ^{15}O-water for CBF studies are many. The short half-life of ^{15}O gives low radiation dosage to the subject, and studies can be repeated in sequence with minimal delay. Water is chemically inert in tissue and does not have any potential side effects. There are other tracers that can be used for lCBF studies with PCT (Ginsberg et al., 1981*a;* Holden et al., 1981). However, their overall advantages and disadvantages relative to ^{15}O-water still need to be shown.

The general approach presented in this work for using PCT to collect fast dynamic information and for estimating flows from dynamic information is also expected to be applicable for other diffusible tracers.

Acknowledgment: The authors would like to thank Dr. Eberhard Henze for his proficiency and skill in performing the arterial sampling procedures; Dr. John Mazziotta for consultations on subject selection and study protocol; Carl Selin, Ron Sumida, Francine Aguilar, and Larry Pang for technical assistance in carrying out the human studies; the UCLA medical cyclotron staff for preparation of ^{15}O-carbon dioxide and ^{15}O-water; the chemistry staff for analyzing the water contents of blood samples; Lee Griswold for illustration; and Robin Townsend for typing the manuscript. This work was supported by DOE contract DE-AM03-76-SF-0012, NIH grant R01-GM-24839-01, USPH grant 515654-01, and donations from the Will's Foundation, Houston, Texas; Fritts Family Foundation, Bakersfield, California; the Hereditary Disease Foundation, Los Angeles; and Jennifer Jones/Simon Foundation, Los Angeles.

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