INVESTIGATIVE NUCLEAR MEDICINE

Brain Blood Flow Measured with Intravenous $H_2{}^{15}O$. I. Theory and Error Analysis

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The tissue autoradiographic method for the measurement of regional cerebral blood flow (rCBF) in animals was adapted for use with positron emission tomography (PET). Because of the limited spatial resolution of PET, a region of interest will contain a mix of gray and white matter, inhomogeneous in flow and in tracer partition coefficient (λ). The resultant error in rCBF, however, is less than 4%. Although the tissue autoradiographic method requires a monotonically increasing input function to ensure a unique solution for flow, the PET adaptation does not, because of an additional integration in the operational equation. Simulation showed that the model is accurate in the presence of ischemia or hyperemia of the gray matter. Inaccuracy in timing of the arterial input function will result in large errors in rCBF measurement. Propagation of errors in measurement of tissue activity is largely independent of flow, reflecting the nearly linear flow compared with activity relationship.

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Positron emission tomography (PET) makes possible the safe and accurate quantification of the regional concentration of positron-emitting radionuclides in vivo. Using mathematical models to describe the biological behavior of specific radiotracers, one can determine regional cerebral blood flow (rCBF) and metabolism from the radioactivity concentrations of blood and local tissue. The soundness of physiological measurements made with PET depends not only on accurate radiotracer quantification by the tomographic scanner, but also on the validity of assumptions inherent in the physiological model and the sensitivity of the model to errors in the measurements of tissue and blood radioactivity.

We have proposed that the tissue autoradiographic method for the measurement of rCBF in animals, originally developed by Kety and his colleagues (*1*,*2*) can be adapted for in vivo rCBF determination with PET (*3*). This report describes in detail such a PET adaptation and examines its accuracy in relation both to deviations from model assumptions and to errors in measurement of tissue and blood radiotracer. A subsequent report (*4*) discusses the implementation and validation of this method using O-15-labeled water as the radiotracer.

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THEORY

The tissue autoradiographic method for the measurement of rCBF, based on the principles of inert gas exchange between blood and tissues developed by Kety (*5*), has been widely used in laboratory animals (*1*,*6*). A freely diffusible, biologically inert radiotracer is infused intravenously for a brief time period, T, followed by decapitation of the animal. rCBF is obtained by numerically solving the following equation for f, the flow per unit weight of tissue:

$$C_i(T) = f \int_0^T C_a(t) \exp[-f/\lambda(T - t)]dt$$

$$= fC_a(T)^* \exp[-(f/\lambda)T], \quad (1)$$

where $C_i(T)$ is the instantaneous local tissue radiotracer concentration (cps/unit weight) after an infusion time of T seconds, derived from a quantitative autoradiogram of a brain slice; $C_a(t)$ is the measured concentration of radiotracer in arterial blood as a function of time; and λ is the brain:blood equilibrium partition coefficient for the tracer. The asterisk denotes the operation of convolution. The derivation of Eq. (1) is based on a one-compartment model in which flow and λ are considered homogeneous in a region of interest. It is assumed that rCBF remains constant during the period of measurement.

Current PET scanners cannot measure the instantaneous tissue count rate, $C_i(T)$. A scan must be performed over many seconds, essentially summing the decay events occurring during the scan. One obtains an image of local counts collected during the scan, not of instantaneous count rate. Therefore, to adapt the tissue autoradiographic technique for in vivo studies with PET, we have modified the operational Eq. (1) of this model by an integration of the instantaneous count rate, $C_i(T)$, over the time of the scan, T_1 to T_2, as follows:

$$C = \int_{T_1}^{T_2} C_i(T)dT$$

$$= f \int_{T_1}^{T_2} C_a(T)^* \exp[-(f/\lambda)T]dT \qquad (2)$$

Here, C is the local number of counts per unit weight of tissue recorded by the tomograph from a region of brain during the scan. The arterial activity curve $C_a(t)$ is determined by frequent arterial blood sampling, and both the PET scan data and the blood curve are corrected for the decay of radiotracer that occurs following its intravenous injection. Once a value of λ is specified (see below), Eq. (2) can be solved numerically for flow for any specific region in the tomographic image. Alternatively, a look-up table calculated from Eq. (2) may be used to relate local tissue counts to rCBF (*7*).

Several potential sources of error have been identified for the tissue autoradiographic method, and their impact must be considered in this PET adaptation. These difficulties include inhomogeneity of tissue with respect to flow (*8*), uncertainty in the exact value of λ, the partition coefficient for the radiotracer (*8*), restrictions on the shape of the arterial concentration input function $C_a(t)$ (*9*), and uncertainty in the timing of $C_a(t)$ (*10*). The PET adaptation of the autoradiographic method might introduce further errors in flow measurement related to the limited spatial resolution of the scanner (*11*), to the performance of the model when applied to disease conditions, and to the impact of error in the measurement of local tissue radioactivity with the scanner. These potential sources of inaccuracy in the PET autoradiographic method, and a computer simulation to study their impact, will now be discussed.

METHODS OF ERROR ANALYSIS

Our approach to rCBF measurement with PET is based on a one-compartment model that assumes that the tissue in which the local radioactivity measurement is made is homogeneous with respect to flow and λ. However, because of the limited spatial resolution of PET—currently in the range of 1–1.5 cm (*12,13*)—a region of interest (ROI) will contain a mix of gray and white matter inhomogenous in both flow and λ. Thus an average λ must be selected for use in the operational equation, Eq. (2), and the resultant measured flow will reflect some nonlinear combination of the gray and white matter flows in the ROI.

A computer simulation was developed to study the effect of tissue inhomogeneity and other possible sources of error. The simulation is based on the following principles. A tissue ROI may be considered to contain varying fractions, w_g, and w_w, of gray and white matter respectively, where $w_g + w_w = 1$. One may specify the flow, f, and the known λ for gray or white matter, and an arbitrary arterial radiotracer time-activity curve, $C_a(t)$, and then apply Eq. (2) to calculate the tissue counts, C_g or C_w that would be obtained if the ROI consisted only of gray or white matter. The following relations are obtained for gray and white matter, respectively:

$$C_g = f_g \int_{T_1}^{T_2} C_a(T)^* \exp[-(f_g/\lambda_g)T]dT \qquad (3)$$

$$C_w = f_w \int_{T_1}^{T_2} C_a(T)^* \exp[-(f_w/\lambda_w)T]dT \qquad (4)$$

Then, for relative weights, w_g and w_w, of gray and white matter in the ROI, the regional tissue counts that would be obtained with a PET scan for these weights is

$$C = w_g C_g + w_w C_w. \qquad (5)$$

This weighted count value, C, is then used in Eq. (2) along with the specified arterial time-activity curve and an average brain λ to calculate the "measured" flow. This is to be compared with the "true" flow in the ROI, that is the weighted sum of gray and white flows

$$f_{true} = w_g f_g + w_w f_w \qquad (6)$$

Any difference between these two flow values reflects an error in rCBF measurement due to the specified degree of tissue inhomogeneity in the ROI.

In addition, this computer simulation can be used to investigate a wide variety of other possible sources of error in rCBF measurement. The shape of the arterial time-activity input function, $C_a(t)$, may affect the performance of the autoradiographic method. Ginsberg (*9*) has noted that the tissue autoradiographic method requires a monotonically increasing input function $C_a(t)$. Otherwise, a situation can develop in which different flows can give rise to the same local tissue radioactivity, and a unique flow result will not be obtained from Eq. (1). The effect of the input function in the PET adap-

tation of this method [Eq. (2)] is examined with the simulation by specifying various shapes for $C_a(t)$ in Eqs. (3) and (4).

Abnormal conditions, such as ischemia or neoplasm, can alter both the regional partition coefficient for the tracer and the degree of flow inhomogeneity. Performance of the PET autoradiographic method in such cases can be studied by specifying flows and/or λ in Eqs. (3) and (4) to simulate tissue disease, and then comparing the resultant "measured" flow with the true weighted regional flow.

Inaccuracy in the measurement of the tissue or arterial activity concentrations used in Eq. (2) will result in errors in flow calculation. Several inaccuracies are possible. In practice, the arterial blood curve is obtained by sampling from a peripheral artery. Since the distance from the heart to a peripheral artery (e.g., the femoral or radial) may be greater than the distance from heart to brain, the data points on the sample-derived curve can be delayed in time with respect to the true input function. In addition, difficulties in rapidly sampling arterial blood do lead to a less-than-perfect definition of the arterial input curve. Finally, error in measuring tissue activity with the PET system is propagated in the calculation of flow. The effect of these various measurement inaccuracies can be simulated. Equations (3) to (5) are used to calculate the true or expected tissue activity for a specified arterial input curve in a ROI. The calculated flow as affected by one of the above measurement errors is obtained by inserting the specific measurement error—either in tissue counts, C, or arterial activity, $C_a(t)$—in Eq. (2) before the flow is calculated, and then comparing this calculated flow with the true weighted regional flow from Eq. (6).

To facilitate these simulation studies, which involved manipulation of the arterial input function, $C_a(t)$ was approximated by the function $A \cdot t \cdot \exp(-t/t_p)$. This yields a rising, then falling curve with its peak value at time t_p. The arbitrary constant, A, can be adjusted such that the area under the input curve, which corresponds to the total decay-corrected activity injected, is held constant. A low value of t_p (e.g., 10 sec) results in an input waveform similar in shape to that obtained in practice with an intravenous bolus injection, whereas for long t_p, the rising part of the curve simulates an infusion input (see Fig. 3, upper left).

All of these simulation studies are based on a scan length of 40 sec ($T_2 - T_1$, Eq. 2), which is in keeping with the original measurement time of 1 min or less proposed by Kety and his colleagues (*1,2,6,7*). Unless otherwise specified, the value for average brain λ for water used in Eq. (2) is 0.95 ml · g^{-1}, and the arterial input is a bolus waveform reaching its peak at 10 sec.

RESULTS

The effect of tissue inhomogeneity in an ROI containing varying proportions of gray and white matter is shown in Fig. 1. The respective values of flow and λ used in Eqs. (3) and (4) were 80 ml · min^{-1} · hg^{-1} and 1.04 ml · g^{-1} in gray matter (*14*), and 20 ml · min^{-1} · hg^{-1} and 0.88 ml · g^{-1} in white matter (*14*). The arterial input function had a bolus waveform reaching its peak at 10 sec. The calculated rCBF from the one-compartment PET autoradiographic model is very close to the true weighted flow over the whole range of possible tissue mixes, with the maximum error of −3.7% occurring in an ROI containing 70% white matter, using an average λ in Eq. 2 of 0.95 ml · g^{-1}. The calculated values for flow were relatively insensitive to the choice of the value for the average λ for the model, for example, 0.90, 0.95, or 1.00 ml · g^{-1}, as illustrated. In addition, the error in rCBF determination due to tissue inhomogeneity is affected little by the shape of the input function, as seen in Table 1.

The relationship between the tissue counts in an ROI and its true weighted flow was examined using Eqs. (3)–(6). In Fig. 2 this relationship is plotted for an 80% gray ROI, with gray flow varying from 10 to 100 ml · min^{-1} · hg^{-1}, and a ratio of gray-to-white flow of 4:1. Over the range of flow likely to be seen in humans, the number of local tissue counts is almost linearly related to flow. This has been found true regardless of the shape of the arterial input function, and of the weights and flows of gray and white matter in the ROI.

The effect of the shape of the arterial time-activity input curve on the solution of the original autoradiographic equation [Eq. (1)] for flow is illustrated in Fig. 3. Two inputs were used, a bolus input and a slowly changing infusion (Fig. 3, upper left). As seen in Fig. 3, upper right, for certain infusion times, a bolus input can

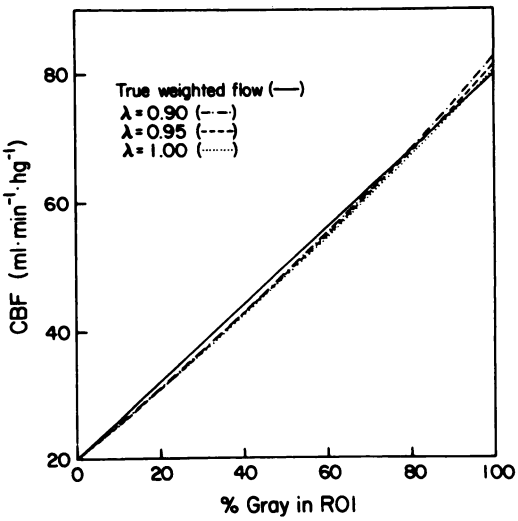

FIG. 1. Calculated flow for regions of interest with varying mixes of gray and white matter, for model with average partition coefficients of 0.90, 0.95, and 1.00 ml · g^{-1}. Solid line represents true weighted flow of the tissue mix. Arterial input function is bolus waveform reaching its maximum at 10 sec.

TABLE 1. EFFECT OF THE SHAPE OF THE ARTERIAL INPUT FUNCTION ON CALCULATED rCBF

% Gray in ROI	True flow in ROI	Calculated rCBF*			
		Step	10-sec peak	40-sec peak	60-sec peak
0	20	20.0	19.9	19.9	19.9
20	32	31.0	30.9	31.0	31.1
40	44	42.6	42.5	42.6	42.8
60	56	54.8	54.7	54.7	55.0
80	68	67.7	67.7	67.3	67.7
100	80	81.4	81.4	80.6	81.1

* Calculations made using a model λ of 0.95 ml · g^{-1} and a scan length of 40 sec. Flows are given in ml · min^{-1} · hg^{-1}. The input functions consisted (a) of a step function, and (b) of waveforms of shape $A \cdot t \cdot \exp(-t/t_p)$, with peak values reached at the times listed.

give rise to the same tissue activity in regions that have different flows. The infusion times at which these multiple solutions occur depend upon the shape of the input function. With a bolus input reaching its peak in 10 sec, the first such time is at 84 sec, while a faster-rising bolus peaking in 5 sec leads to multiple solutions appearing earlier, at 71 sec. Thus, there is a potential for multiple solutions in the calculation of flow from a given tissue activity with the tissue autoradiographic method. This problem does not arise with a slowly changing infusion input. However, since the PET autoradiographic approach, as embodied in Eq. (2), involves an integration of tissue activity over time, this problem of multiple solutions with a bolus input does not arise over the equivalent time period (Fig. 3, lower left); in fact, the curves in tissue counts as a function of time continue to remain separated at 140 sec.

The effects of simulated abnormal tissue on rCBF determination are shown in Figs. 4 and 5. Cerebral ischemia or hyperemia was modeled by using as values for pure gray-matter flow 40, 60, 80, and 100 ml · min^{-1} · hg^{-1} in the calculation of regional gray-matter counts with Eq. (3). As seen in Fig. 4, the largest errors occur with the highest gray flow, with the maximum error being −6% in a 30% gray ROI. As gray flow decreases,

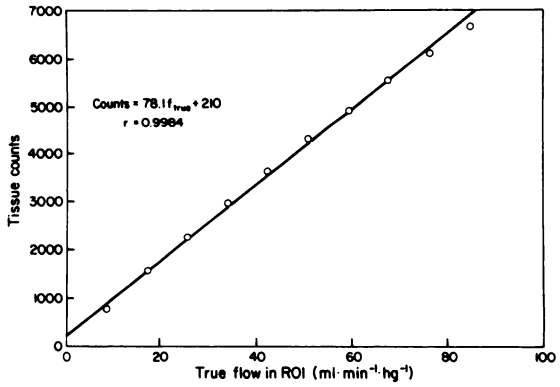

FIG. 2. Relationship between true weighted flow and tissue counts in ROI that is 80% gray matter (see text).

the error in calculated flow decreases as well, since the inhomogeneity in the ROI with respect to flow is less. The ability of the PET autoradiographic method to quantify incremental changes in rCBF accurately is illustrated in Table 2. The changes in flow that would be measured with incremental changes in gray-matter flow of 20 ml · min^{-1} · hg^{-1} are listed for various gray:white tissue mixes. These measured changes closely reflect the true weighted flow change in the ROI.

To simulate abnormal tissue such as a brain tumor in which λ may vary widely, flows were calculated for an ROI containing varying proportions of white matter and tissue, with abnormal λs of 0.90 and 1.05 ml · g^{-1}. The calculated flows that would be obtained in practice are very close to the true weighted regional flows, with the errors shown in Fig. 5. This is not surprising, given the relative insensitivity of the model to the value of average λ used in the operational Eq. (2), as noted above.

Inaccuracy in the timing of the arterial activity curve can cause large errors in rCBF measurement, as shown in Fig. 6. A moderate 2-sec delay in the sampled arterial activity curve with respect to the true arterial brain input causes a 4–10% over estimation of rCBF with a bolus input, while with a larger 5-sec delay, errors of up to +24% are obtained. Of note, for the same degree of delay, larger errors are obtained with a slowly changing infusion input than with a bolus input. The effect of the frequency of sampling of the arterial activity curve, $C_a(t)$, on calculated flow was studied. In practice, discrete arterial samples are rapidly drawn at an interval of about every 5 sec. We compared calculated blood flow for this 5-sec and for a rapid 1-sec sampling frequency, using the bolus input function in Fig. 3, (upper left), in ROI with varying mixes of gray and white matter. The flows calculated from the less frequently sampled input differed no more than 3.6% from those calculated using the rapidly sampled input.

The effect of error in the measurement of regional tissue activity with PET on the resultant calculated rCBF is shown in Fig. 7. The percent error in activity

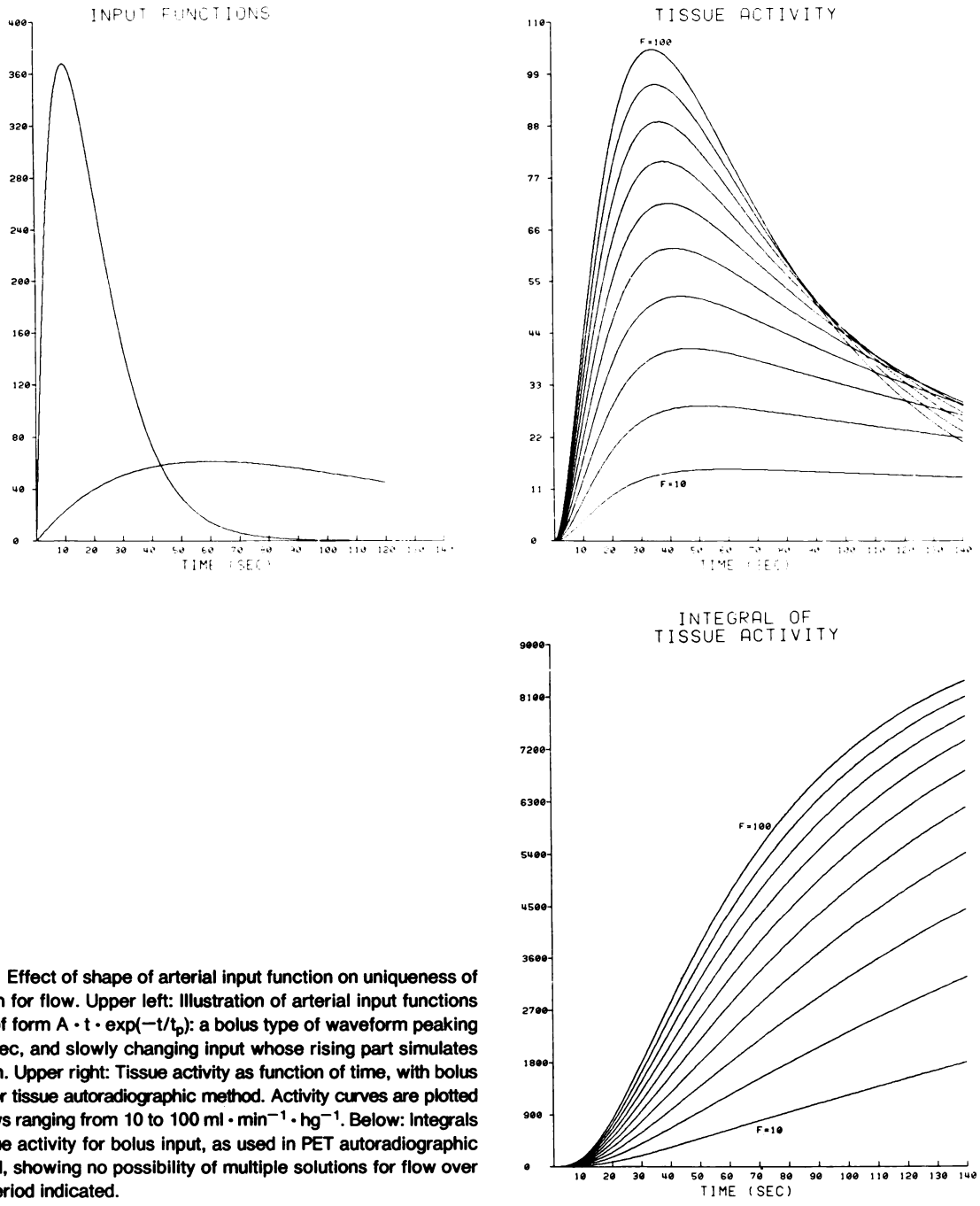

FIG. 3. Effect of shape of arterial input function on uniqueness of solution for flow. Upper left: Illustration of arterial input functions used, of form $A \cdot t \cdot \exp(-t/t_p)$: a bolus type of waveform peaking at 10 sec, and slowly changing input whose rising part simulates infusion. Upper right: Tissue activity as function of time, with bolus input for tissue autoradiographic method. Activity curves are plotted for flows ranging from 10 to 100 ml $\cdot$ min^{-1} $\cdot$ hg^{-1}. Below: Integrals of tissue activity for bolus input, as used in PET autoradiographic method, showing no possibility of multiple solutions for flow over time period indicated.

measurement is propagated as an approximately equivalent percent error in rCBF. In addition, the propagation of error in tissue activity measurement is essentially independent of flow rate.

DISCUSSION

The ability to measure cerebral blood flow is critical for an understanding of the pathophysiology of cerebrovascular and other neurological disorders. PET makes possible, for the first time, the safe and accurate in vivo quantification of rCBF in man. However, for reliable rCBF quantification with PET, the strengths and limitations of the physiological model used to calculate flow from blood and local tissue radiotracer measurements must be understood.

Although the tissue autoradiographic method, as well as its PET adaptation, is based on a one-compartment model, which assumes regional tissue homogeneity, the limited spatial resolution of PET will result in an ROI containing a mix of gray and white matter that is heterogeneous in both flow and λ. However, this study demonstrates that the rCBF measured in such a region will be very close to the true weighted gray and white flows in the region. Eklof (*8*) has demonstrated that the

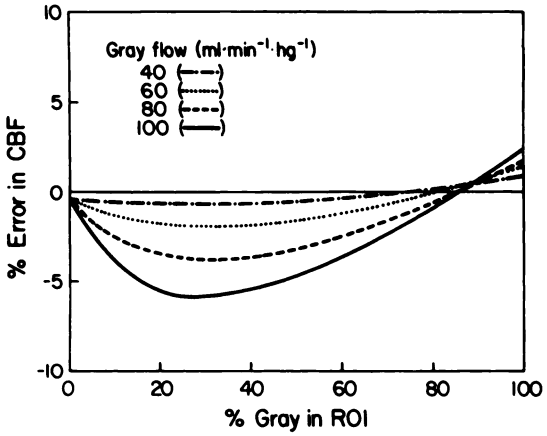

FIG. 4. Percentage errors in calculated rCBF with various gray-matter flows simulating hyperemia (100 ml · min^{-1} · hg^{-1}) or ischemia (60 and 40 ml · min^{-1} · hg^{-1}), for varying gray:white mixes. White-matter flow is 20 ml · min^{-1} · hg^{-1}.

tissue autoradiographic method accurately reflects the true weighted flow in a gray-matter region that is heterogeneous in flow. Ginsberg et al. (*15*) used an autoradiographic strategy with an external probe system to measure global cerebral blood flow in the rat. Their model predicted reliable estimates of rCBF in simulated gray:white mixtures heterogeneous only in flow provided the white component was less than 25%. The analysis of our PET autoradiographic approach indicates that the rCBF measured in an ROI that is heterogeneous in both flow and λ will be within 4% of the true weighted flow regardless of the gray:white proportion.

The finding that rCBF and local tissue radioactivity are almost linearly related in the flow range likely to be encountered in human studies is of practical importance. Firstly, the image of tissue counts will linearly reflect relative differences in flow in different regions of the brain during the scan. Thus, for certain applications, such as functional mapping of the brain, where only relative changes in rCBF are sought, arterial blood sampling might not be required. Secondly, as seen in Table 2, the technique will accurately reflect changes in regional gray-matter flow in a linear fashion, although the change will be lessened by a factor equal to the fraction of gray matter in an ROI. Finally, the propagation of error in tissue radioactivity measurement in the calculation of flow will be approximately linear (see below).

The calculated blood flow was shown to be quite insensitive to the choice of average λ used in the PET operational equation. Eklof (*8*) reported a similar behavior for the tissue autoradiographic method with infusion times less than 60 sec and flows less than 100 ml · min^{-1} · hg^{-1}. This is a very useful property, since it is not, possible in general to use a λ weighted to the gray:white proportions in the ROI, as these proportions are not known in practice. In addition, although the λ in abnormal tissue, such as tumor, will generally be unknown, the routine use of an average λ results in little error. Thus, although it is based on a one-compartment model, the PET autoradiographic method will accurately quantify rCBF in inhomogeneous regions of tissue in both normal brain and in conditions that may change regional flow or λ.

The finding that a bolus input may be used in the PET method without the risk of multiple solutions for flow (as occurs in the tissue autoradiographic method) has important practical implications. Our PET method has been implemented using as the diffusible tracer water labeled with O-15, which has a 123-sec half-life. Thus, the use of a slow infusion of radiotracer during the length of the scan would result in considerable decay of the tracer during its infusion, with less activity being delivered to the brain than is desirable for reliable PET images.

It is important to understand the effects of inaccuracy in tissue and arterial activity measurements on the calculation of rCBF, and then to minimize the impact of these inaccuracies if possible. A mismatch in timing between the sampled peripheral arterial activity curve and the arterial input to the brain was shown to cause large errors in the calculated rCBF. This finding provides a motive for strategies to correct for these timing errors. One approach that has been implemented is to measure the difference in arrival times of the radiotracer bolus between the brain and the peripheral sampling site. This time difference is used to shift the peripheral-artery activity curve appropriately in time before using it for rCBF calculation. Relatively infrequent sampling of the arterial blood curve, e.g., every 5 sec, introduced rather small errors in rCBF. However, these errors might be reduced by using an automated method of blood sampling to obtain a more nearly continuous curve, as has been done in animal experiments (*7*).

Errors in measurement of tissue activity were found to result in approximately equivalent errors in rCBF. Thus, improvements in PET scanner accuracy will be directly reflected in the rCBF calculations. Furthermore,

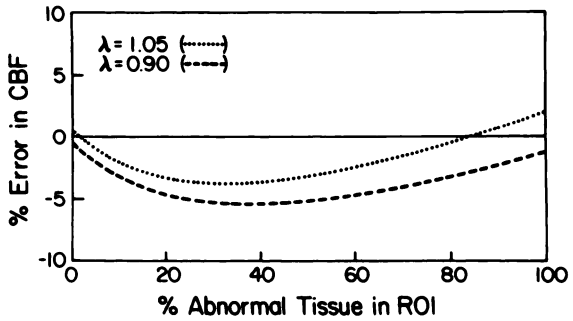

FIG. 5. Percentage errors in calculated rCBF for ROI containing white matter with flow of 20 ml · min^{-1} · hg^{-1} and λ_w = 0.88 ml · g^{-1}, and varying proportions of abnormal tissue, with flow of 80 ml · min^{-1} · hg^{-1} and with partition coefficients of 0.90 and 1.05 ml · g^{-1}.

TABLE 2. MEASURED CHANGES IN rCBF WITH INCREMENTAL CHANGES IN GRAY MATTER FLOW OF 20 ml · min^{-1} · hg^{-1}

% Gray in ROI	True change in rCBF in ROI	Measured changes in rCBF* for indicated changes in gray flow			
		100–80	80–60	60–40	40–20
100	20	21.0	20.6	20.5	20.2
90	18	18.2	17.9	18.2	18.1
80	16	15.4	15.7	15.9	16.0
70	14	13.1	13.3	13.7	14.0
60	12	10.8	11.2	11.6	11.9

* Calculations made using the same simulated conditions as in Table 1. White matter flow is 20 ml · min^{-1} · hg^{-1}.

the nature of error propagation with the autoradiographic method is more acceptable than with the equilibrium inhalation method using O-15 carbon dioxide, which is also currently in use to measure rCBF with PET (*16,17*). In the latter method, because of a very nonlinear relationship between regional flow and tissue activity, errors in activity measurement are amplified in the calculation of rCBF, and this error propagation changes with local flow rates (*18*). These problems do not occur with the PET autoradiographic method.

This simulation study did not address the issue of the limitation of water as a freely diffusible tracer (*19*). It has been proposed to modify the operational equation of the tissue autoradiographic method by inclusion of the factor m = 1 − exp(−PS/f), where PS is the product of capillary permeability and surface area (*9*). However, when Eckman et al. (*20*) calculated the value of m in a simulation study, they found it was in fact not a constant, but merely approached the value of 1 − exp(−PS/f) asymptotically with time. Therefore, an appropriate modification of the tissue autoradiographic method to account for diffusion limitation of the tracer is lacking, and this complex issue was not included in our extension of the method to PET. We have chosen to study this problem experimentally by comparing blood flow measured with O-15-labeled water in our PET autoradiographic method to blood flow measured with the intracarotid injection of $H_2{}^{15}O$. The details of these experiments in baboons are reported in the subsequent paper in this series (*4*).

In conclusion, this study of the adaptation of the Kety autoradiographic method shows that it is well suited for the measurement of rCBF in man with PET. An appreciation of the validity of assumptions in the model and of its accuracy will lead to more precise quantification of regional cerebral blood flow with positron emission tomography.

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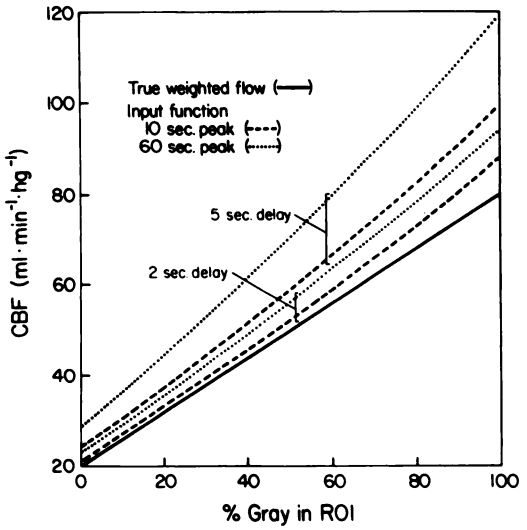

FIG. 6. Effect of delay between curve for peripheral arterial samples and actual arterial input to brain. Resultant calculated flows are shown for 2-sec and 5-sec delays, for bolus input (10-sec peak) and infusion (60-sec peak).

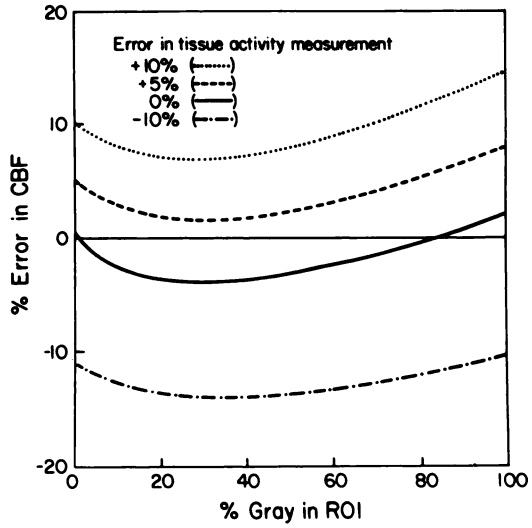

FIG. 7. Effects of error in measurement of regional tissue activity on error in calculated flow.

REFERENCES

1. LANDAU WM, FREYGANG WH JR, ROWLAND LP, et al: The local circulation of the living brain; values in the uanesthetized and anesthetized cat. *Trans Am Neurol Assoc* 80:125-129, 1955
2. KETY SS: Measurement of local blood flow by the exchange of an inert, diffusible substance. *Meth Med Res* 8:228-236, 1960
3. RAICHLE ME: Quantitative in vivo autoradiography with positron emission tomography. *Brain Res Rev* 1:47-68, 1979
4. RAICHLE ME, MARTIN WRW, HERSCOVITCH P: Brain blood flow measured with intravenous $H_2{}^{15}O$. II. Implementation and validation. *J Nucl Med* 24:790-798, 1983
5. KETY SS: The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev* 3:1-41, 1951
6. SAKURADA O, KENNEDY C, JEHLE J, et al: Measurement of local cerebral blood flow with iodo[^{14}C]antipyrine. *Am J Physiol* 234:H59-H66, 1978
7. REIVICH M, JEHLE J, SOKOLOFF L, et al: Measurement of regional cerebral blood flow with antipyrine-^{14}C in awake cats. *J Appl Physiol* 27:296-300, 1969
8. EKLÖF B, LASSEN NA, NILSSON L, et al: Regional cerebral blood flow in the rat measured by the tissue sampling technique; a critical evaluation using four indicators C^{14}-antipyrine, C^{14}-ethanol, H^3-water and xenon^{133}. *Acta Physiol Scand* 91:1-10, 1974
9. GINSBERG MD: Autoradiographic measurement of cerebral blood flow. In *Cerebral Metabolism and Neural Function.* Baltimore, Williams and Wilkins, 1980, pp 161-169
10. MEYER MW, WERTH LJ: Error analysis of a convolution integral approach to estimate local blood flow. *J Appl Physiol* 35:631-634, 1973
11. MAZZIOTTA JC, PHELPS ME, PLUMMER D, et al: Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *J Comput Assist Tomogr* 5:734-743, 1981
12. TER-POGOSSIAN MM, FICKE DC, HOOD JT JR, et al: PETT VI: A positron emission tomograph utilizing cesium fluoride scintillation detectors. *J Comput Assist Tomogr* 6: 125-133, 1982
13. HOFFMAN EJ, PHELPS ME, HUANG SC, et al: A new tomograph for quantitative positron emission computed tomography of the brain. *IEEE Trans Nucl Sci* NS-28:99-103, 1981
14. TER-POGOSSIAN MM, EICHLING JO, DAVIS DO, et al: The determination of regional cerebral blood flow by means of water labeled with radioactive oxygen 15. *Radiology* 93: 31-40, 1969
15. GINSBERG MD, LOCKWOOD AH, BUSTO R, et al: A simplified in vivo autoradiographic strategy for the determination of regional cerebral blood flow by positron emission tomography: theoretical considerations and validation studies in the rat. *J Cereb Blood Flow Metabol* 2:89-98, 1982
16. SUBRAMANYAM R, ALPERT NM, HOOP B JR, et al: A model for regional cerebral oxygen distribution during continuous inhalation of $^{15}O_2$, $C^{15}O$, and $C^{15}O_2$. *J Nucl Med* 19:48-53, 1978
17. FRACKOWIAK RSJ, LENZI G-L, JONES T, et al: Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *J Comput Assist Tomogr* 4:727-736, 1980
18. JONES SC, GREENBERG JH, REIVICH M: Error analysis for the determination of cerebral blood flow with the continuous inhalation of ^{15}O-labeled carbon dioxide and positron emission tomography. *J Comput Assist Tomogr* 6:116-124, 1982
19. EICHLING JO, RAICHLE ME, GRUBB RL JR, et al: Evidence of the limitations of water as a freely diffusible tracer in brain of the Rhesus monkey. *Circ Res* 35:358-364, 1974
20. ECKMAN WW, PHAIR RD, FENSTERMACHER JD, et al: Permeability limitation in estimation of local brain blood flow with [^{14}C]antipyrine. *Am J Physiol* 229:215-221, 1975