Simplified Nonlinearity Correction of Oxygen-15-Water Regional Cerebral Blood Flow Images without Blood Sampling

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A noninvasive method, the double-integration method, was developed to estimate regional cerebral blood flow (rCBF) by using ^{15}O-water and PET. It relies on the acquisition of images with a correction of nonlinearity of brain tissue counts and can produce rCBF images on a pixel-by-pixel basis. **Methods:** Oxygen-15-water PET studies were performed on five normal human volunteers, and continuous sampling from the radial artery was conducted to generate functional CBF images according to the invasive catheterization method. The method centers on a computer-based program elaborated to calculate an arterial input function with an assumption of the whole brain blood rate of 50 ml/dl/min and consequently does not require arterial catheterization or arterial input function sampled from other studies. **Results:** The results indicate a good correlation between this method and the invasive method ($r > 0.966$, $p < 0.001$). **Conclusion:** This noninvasive method was demonstrated to provide an accurate estimation of rCBF and may simplify the activation studies.

Key Words: regional cerebral blood flow; oxygen-15-water; PET; noninvasive method

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The measurement of regional cerebral blood flow (rCBF) was established with PET and ^{15}O-water. Several methods have been described to measure rCBF, such as a combination of dynamic and integral methods (*1,2*), the integrated projection technique (*3*), weighted-integration technique (*4*), the steady-state method (*5*) and the autoradiographic method (*6–8*). These methods take into account functional information derived from tissue counts and appropriate arterial blood samples. At the same time, a correction for delay and dispersion within an arterial counting device has to be determined to avoid errors in the calculated rCBF (*9,10*). On the other hand, the use of arterial catheterization to collect blood samples is an undesirable procedure, especially in studies that require repeated measurements (e.g., activation studies), because discomfort and pain may affect the real flow values (*11*). Furthermore, patient complaints and pain may result in some inconvenience for both the patients and examiners. Therefore, arterial catheterization has had to be abandoned in some studies. In these cases, a standard input function has been used to calculate rCBF. However, this procedure has the pitfall of increasing the nonlinearity in the corrected flow because this standard input function can be different from the true individual input function.

In the present article, a noninvasive method, the double-integration method (DIM), is proposed to linearize brain activity without arterial blood sampling. This method assumes the whole brain blood rate to be 50 ml/dl/min, and double integration is done of the tissue activity curve to calculate the input function. The ^{15}O-water kinetic data obtained with a PET scanner were processed for the calculation of the rCBF. The method has the ability to produce a pixel-by-pixel image of the rCBF. The principles of the theoretics and the computational scheme are presented. Computer simulations were realized to validate the results. In this study, both this method and the invasive method were performed, and the results achieved by both procedures were correlated to assess the accuracy of this noninvasive method.

THEORY

According to the principle of inert gas exchange between capillary blood and tissue, in a single-compartment model for the CBF measurement using ^{15}O-labeled water developed by Ketty (*12*), the tissue radiotracer concentration is expressed with the rate constant of K_1 (influx or clearance) and k_2 (efflux or rate) as follows:

$$\frac{dC_t(t)}{dt} = K_1C_a(t) - k_2C_t(t), \qquad \text{Eq. 1}$$

where $K_1 = f$ (flow), $k_2 = f/Vd$ (Vd = volume of distribution of water for brain tissue) and $C_a(t)$ and $C_t(t)$ are decay-corrected arterial and tissue concentrations, respectively.

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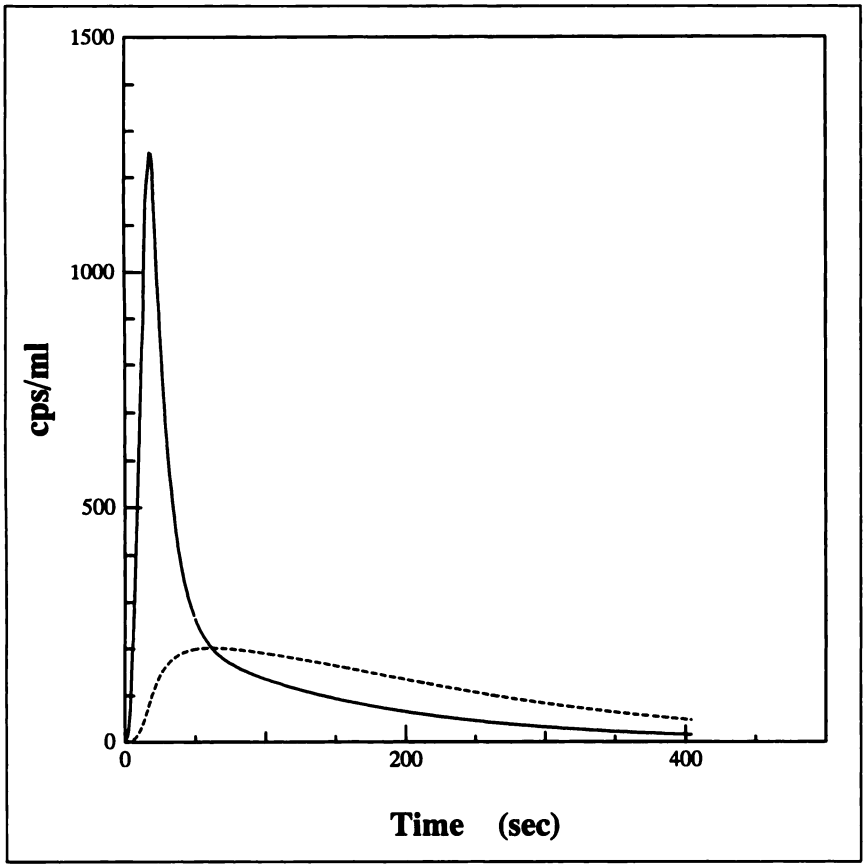

FIGURE 1. Arterial radioactivity curve set following the intravenous injection of ^{15}O-water (solid lines). This curve was utilized in the present study to generate tissue count (broken lines).

By integrating Equation 1 twice from time 0 to T, the following is obtained:

$$\int_0^T C_t(t)\,dt = \frac{K_1}{V_d}\left(V_d \int_0^T dt \int_0^t C_a(u)\,du - \int_0^T dt \int_0^t C_t(u)\,du\right). \quad \text{Eq. 2}$$

With a whole-brain region of interest (ROI) or $C_w(t)$ and if $K_1 = f_0$ for the average whole brain was assumed to be 50 ml/dl/min, the integrations of $C_a(t)$ can be estimated as follows:

$$\int_0^T dt \int_0^t C_a(u)\,du = \frac{1}{V_d}\int_0^T dt \int_0^t C_w(u)\,du + \frac{\int_0^T C_w(t)\,dt}{f_0} = A. \quad \text{Eq. 3}$$

Then the regional blood flow was calculated with Equations 2 and 3 as follows:

$$K_1 = \frac{\int_0^T C_t(t)\,dt}{A - \frac{1}{V_d}\int_0^T dt \int_0^t C_t(u)\,du}, \quad \text{Eq. 4}$$

where V_d was assumed to be unity. $C_t(t)$ for each pixel was determined by dynamic data acquisition. In the application of this model, values of $\int_0^T C_w(t)$ were obtained by a measurement of the integral concentration of ^{15}O-water in the whole brain which is defined on the summated images. Instead of values of $C_a(t)$, "A" was calculated from the double-integration function of $C_w(t)$. Hence, the rCBF for each pixel was estimated.

Simulation Studies

The simulations were designed with either measured or noise-free fitted curves of the arterial input function, which were obtained from the measured beta detecter count of a single subject (Fig. 1). First, the tissue activity function was generated as follows:

$$C_t(T) = \exp^{-\left(\frac{f}{V_d}\right)T_f} \int_0^T C_a(t) \exp\left(\frac{f}{V_d}\right)t\,dt, \quad \text{Eq. 5}$$

where V_d was fixed at unity. If f_0 = 50 ml/dl/min is assumed, the whole-brain tissue activity, $C_w(t)$, was gener-

ated (Fig. 1). The tissue activity for other brain regions was similarly generated with different flow values, e.g., 20 and 80 ml/dl/min. Finally, according to Equation 4, K_1 was calculated for each simulated tissue activity as described earlier.

Regions of white and gray matter were simulated by assuming the flow to be 20 and 80 ml/dl/min, respectively.

MATERIALS AND METHODS

PET Studies and Data Processing

The study was performed on five normal volunteers (age range 23–32 yr, mean ± s.d. 27 ± 3 yr). All subjects included in this study participated in an activation study protocol. Two control states were studied. Cerebral blood flow was measured with ^{15}O-water and the ECAT 931 (CTI, Knoxville, TN). The system has an image resolution in reconstructed transaxial and axial dimensions of 8 and 7.5 mm, respectively. A transmission scan was performed to correct tissue attenuation with a ^{68}Ge-^{68}Ga external ring source. For the measurement of CBF, 40 mCi of ^{15}O-water was injected in a period of 20 sec through the antecubital vein. Four ^{15}O-water scans were collected; each scan was started simultaneously with the ^{15}O-water injection. Here only the results of the first and last scan performed under resting baseline conditions will be given. Sequential images were obtained at the same levels of the brain with the center of the axial field of view at 50 mm above the Deutch horizontal line. Each study included the following protocol: a 30-sec background scan followed by 18 consecutive frames of 5 sec each (scan frame time) during 90 sec (scan time). After image reconstruction, dynamic image data were transferred to a work station for image processing.

The arterial radioactivity concentration was monitored with a beta counter set along a blood draining line. With a draining pump, blood was withdrawn from the radial artery by a cannula at a flow rate of 4 ml/min, and radioactivity was counted with a counter that consisted of a plastic scintillator and counting electronics to yield the arterial input function. The concentration of radioactivity in the arterial line was measured in a well counter for the calibration between the beta detector and the well counter.

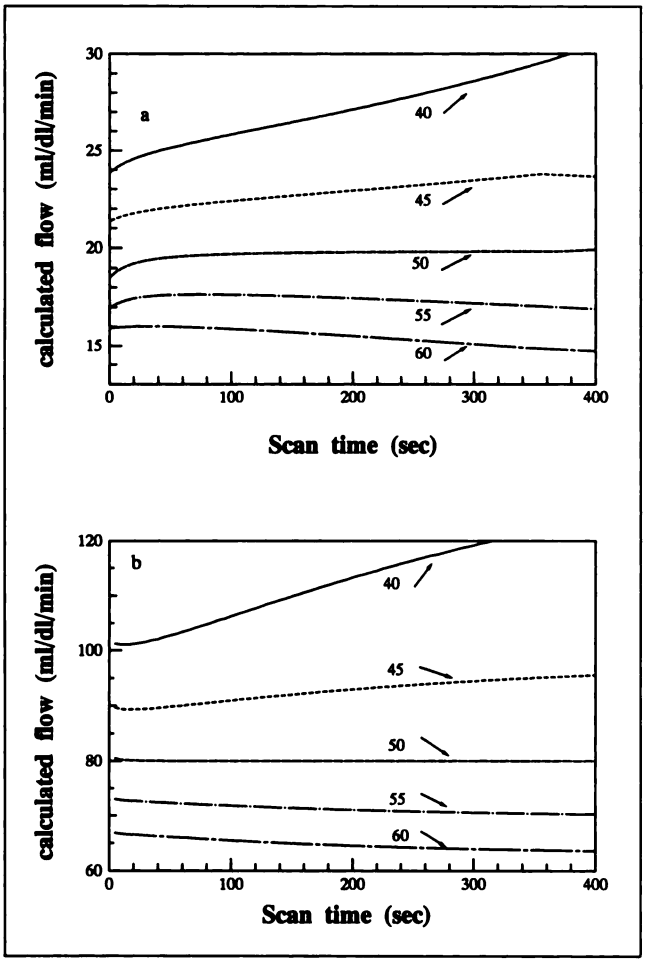

FIGURE 2. Effect of whole-brain curve with CBF not equal to 50 ml/dl/min on estimation of flow values. CBF was obtained by assuming CBF = 50 ml/dl/min in the calculation of a by using a fitted input function.

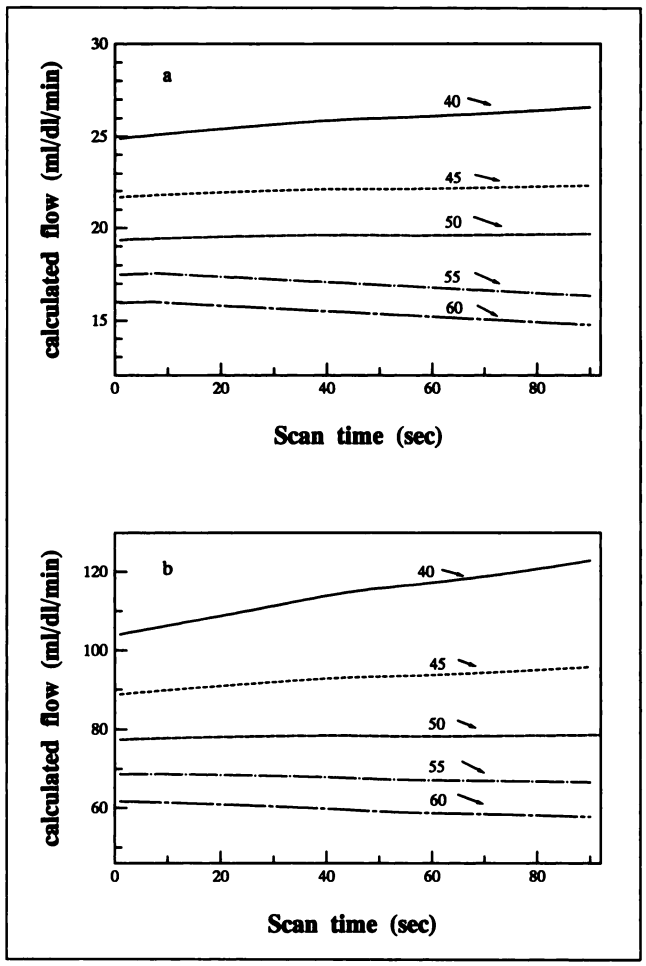

FIGURE 3. Effect of whole-brain curve with CBF not equal to 50 ml/dl/min on estimation of flow values. CBF was obtained by assuming CBF = 50 ml/dl/min in the calculation of a by using a measured input function.

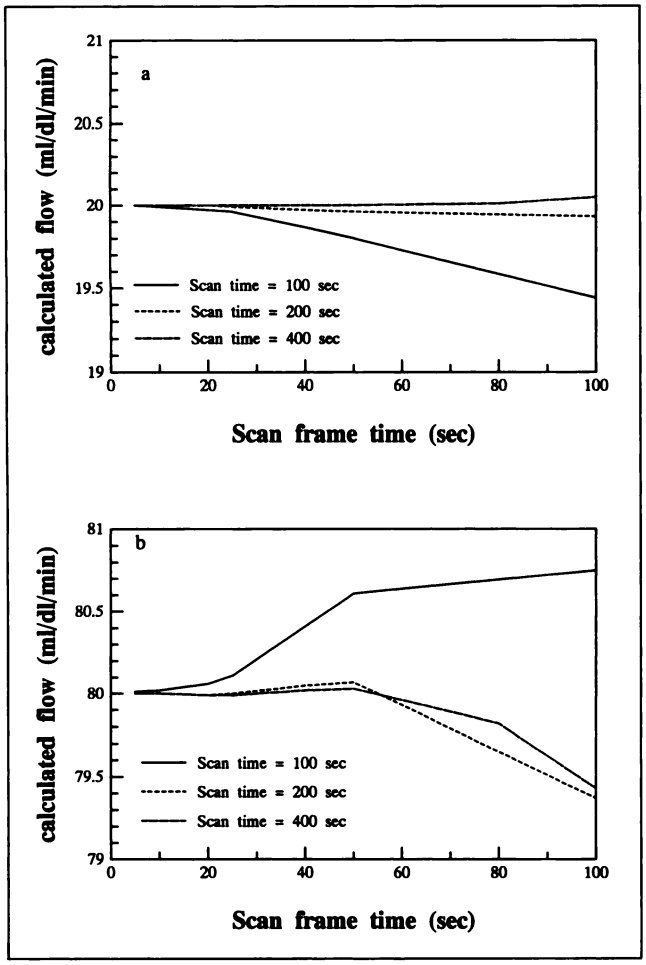

FIGURE 4. Effect of interval scan time on a 5–100-sec interval was considered with a different total scan time from 100, 200 and 400 sec by using a fitted input function.

With these images and the arterial radioactivity curve, CBF was calculated. Values of the delay time were estimated (*13*) from the least-squares fit between the initial slope of the total counts of the PET system and those of the estimated brain activity curve that was generated from the arterial curve with a dispersion time constant of 25 sec, according to the method of Lammertsma et al. (*1*). Standard rCBF images were generated according to the autoradiographic technique with an individual arterial input function and a standard input function (*7*). However, a program was elaborated to calculate pixel-by-pixel rCBF images, according to the method described. The whole-brain ROIs were set manually on the summated images.

Several elliptic ROIs were defined on the functional images generated by the autoradiographic method and projected with the same location on those generated by the current method for comparison, including the whole brain, the frontal cortex and the frontal white matter. Similarly, images generated by the autoradiographic method were compared with those generated with a standard input function.

RESULTS

Simulation

The rCBF was correctly calculated by this method when the whole-brain flow was 50 ml/dl/min in either a low- (20 ml/dl/min) or high-flow region (80 ml/dl/min) for any scan time (Fig. 2). When the real whole-brain flow was higher or lower than 50 ml/dl/min, the regional flow was under- or overestimated. This situation is not affected by using the measured arterial curve (Fig. 3) or a fitted noise-free curve (Fig. 2).

Figure 4 depicts the effect of scan frame time (abscissa) as a function of the scan time from 100, 200 and 400 sec for high- (80 ml/dl/min) and low-flow (20 ml/dl/min) regions. The calculated flow showed some divergence; however, the CBF values shifted only slightly. For example, in a low-flow region, the underestimation was approximately 3% (Fig. 4a), whereas in the high-flow region, the overestimation was approximately 1.5% (Fig. 4b) on the total scan time selected at 100 sec.

The effect of fixing V_d at unity was evaluated by generating $C_t(t)$ with various V_d values, as shown in Figure 5. It

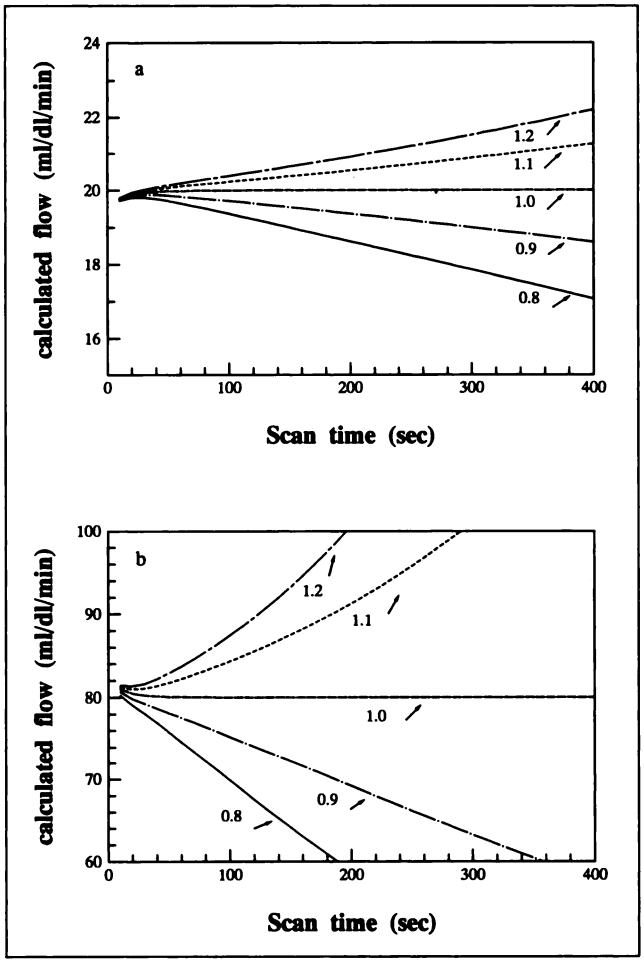

FIGURE 5. Error due to an incorrect V_d of water (arrows). CBF values were plotted for varying V_d from 0.8 to 1.2 in increments of 0.1 by using a fitted input function.

can be seen that V_d values less than 1.0 produce a systematic underestimation in the calculated flow and a systematic overestimation with V_d values more than 1.0, especially when flow was high. For example, more than 10% of error in CBF resulted from a 20% overestimation of V_d at a scan time of 100 sec (Fig. 6). Statistical random noise was introduced into tissue activities (*14*), including the whole brain (Fig. 7). It was noted that the calculated flow was rather stable with a shorter scan time; 20% of tissue noise induced less than 5% CBF error.

Human Studies

Figure 8 shows the corresponding CBF images by the autoradiographic method and by the current method in one subject. Comparisons of flow values of the whole brain, cortical regions and white matter are shown for each patient in Table 1. Note that the CBF values for the whole brain in the current method are comparable with those in the autoradiographic method. The correlation between these images was evaluated by a pixel-by-pixel plot of all image pixels, as shown in Figure 9 for a typical case. A significant correlation was obtained. The correlation was also tested between images obtained with individual arte-

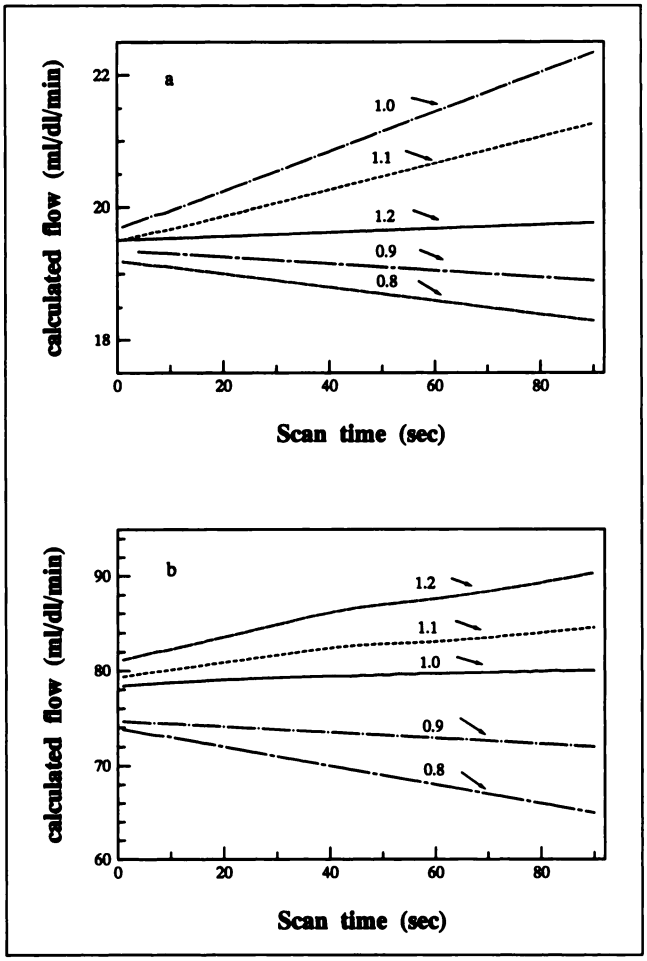

FIGURE 6. Error due to an incorrect V_d of water (arrows). CBF values were plotted for varying V_d from 0.8 to 1.2 in increments of 0.1 by using a measured input function.

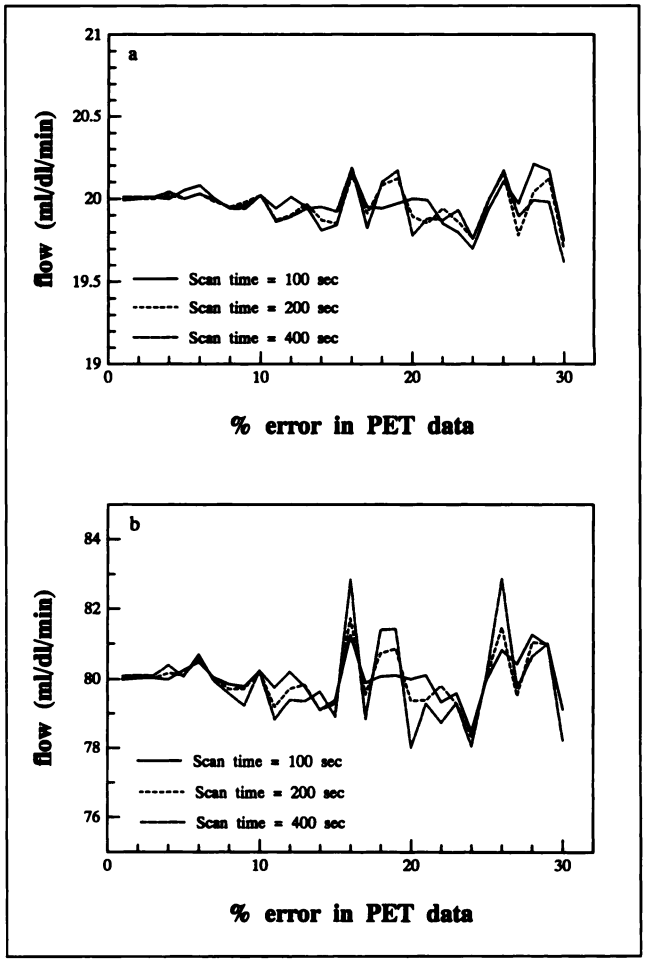

FIGURE 7. Percentage of error in noise scan level was plotted using 100-, 200- and 400-sec total scan time with flows of 20 and 80 ml/dl/min.

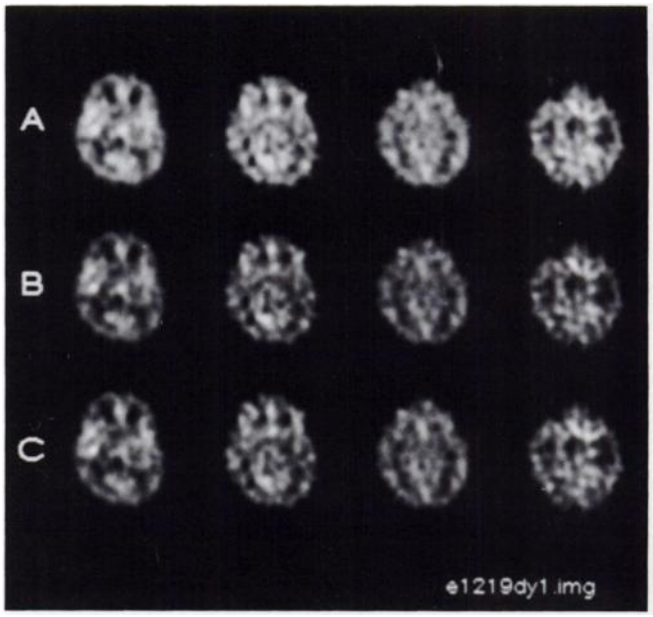

FIGURE 8. Raw images and quantitatives images. Two original images were processed according to the invasive method and DIM. This corresponds to one study.

TABLE 1
Autoradiographic Method Versus Double-Integration Method Comparison*

		Study 1		Study 2		Study 3		Study 4		Study 5	
		Run 1	Run 2	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
Whole brain	ARM	49.5 ± 2.3	52.0 ± 3.4	50.0 ± 1.1	47.6 ± 2.0	50.1 ± 3.2	47.7 ± 2.7	47.9 ± 2.7	49.6 ± 3.6	53.3 ± 1.2	50.6 ± 0.7
	ARM	69.1 ± 4.1	68.6 ± 5.3	61.8 ± 4.6	67.0 ± 8.3	61.2 ± 6.5	61.4 ± 9.7	61.0 ± 6.6	64.0 ± 6.6	68.8 ± 9.6	69.7 ± 6.7
Gray matter	DIM	67.1 ± 4.3	64.7 ± 4.5	62.5 ± 4.6	71.4 ± 9.4	62.0 ± 8.3	58.5 ± 8.7	63.6 ± 6.7	69.4 ± 6.7	63.5 ± 9.2	67.0 ± 7.8
	ARM	24.8 ± 0.6	30.2 ± 1.7	26.4 ± 1.6	26.0 ± 0.2	29.0 ± 2.0	31.4 ± 2.0	25.6 ± 2.1	28.1 ± 2.7	31.5 ± 1.6	25.2 ± 0.6
White matter	DIM	23.3 ± 0.7	26.5 ± 1.5	28.7 ± 2.3	25.4 ± 1.0	30.0 ± 2.0	29.5 ± 1.1	25.3 ± 1.1	26.3 ± 2.7	27.6 ± 2.0	28.6 ± 4.0

*Values are expressed as mean ± s.d.
ARM = autoradiographic method; DIM = double-integration method.

rial input function and those obtained with a standard input function (Fig. 10). Although a good correlation was observed, distortion of the linearity was found in the higher-flow regions. On the other hand, the mean and s.d. on the frontal cortex by the autoradiographic method with a standard input function were significantly larger than those from the noninvasive method (76.42 ± 11.6). The accuracy of the letter method is clearly demonstrated.

DISCUSSION

The goal of this study was to estimate rCBF with ^{15}O-water and PET noninvasively. Such measurement of rCBF requires serial arterial blood sampling to determine the input function. Because arterial blood sampling is stressful to subjects, simplified semiquantitative methods have been used, such as using the tissue activity alone or substituting individual blood activity by the average standardized arterial curve (*15,16*). In either case, regional flow was normalized by assuming a whole-brain flow rate of a certain value, such as 50 ml/dl/min. However, the nonlinearity between normalized brain counts and real flow are not solved because individual true input functions are not known. The present method is an attractive approach to the estimate of rCBF by the use of ^{15}O-water. It also assumes a fixed whole-brain flow value not only to normalize flow but also to cancel out arterial input function. The method was based on the dynamic approach and has the advantage of avoiding arterial data from other studies. If the whole brain flow is assumed to be 50 ml/dl/min and the V_d to be unity, the method generates flow images in a short time.

In the computer simulations with an ideal input curve, free from noise, with short scan times (such as 10 sec), CBF was accurately calculated. These simulations suggest any scan protocol may be applicable as long as noise-free tissue function is obtained. When a measured (with statistical noise) curve for input function was used, the simulation corroborated the results by a fitted curve. However, as shown in Figure 5, flow values become more labile with longer scan times because of the effects of tissue heterogenity. There is a potential problem of the sampling pitch in

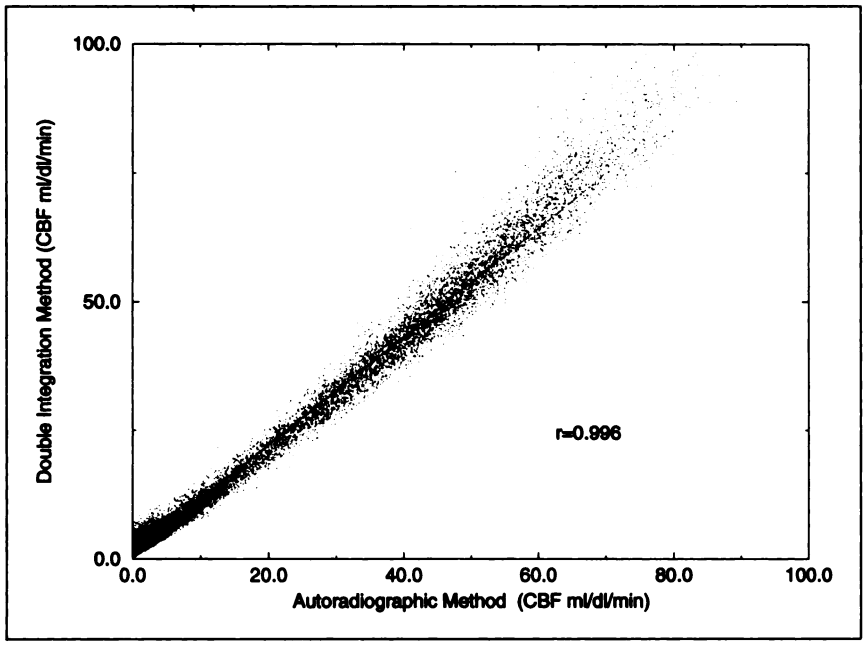

FIGURE 9. Comparison of rCBF values measured by DIM and the autoradiographic method on a pixel-by-pixel basis, corresponding to a study. The solid line represents the linear-regression line.

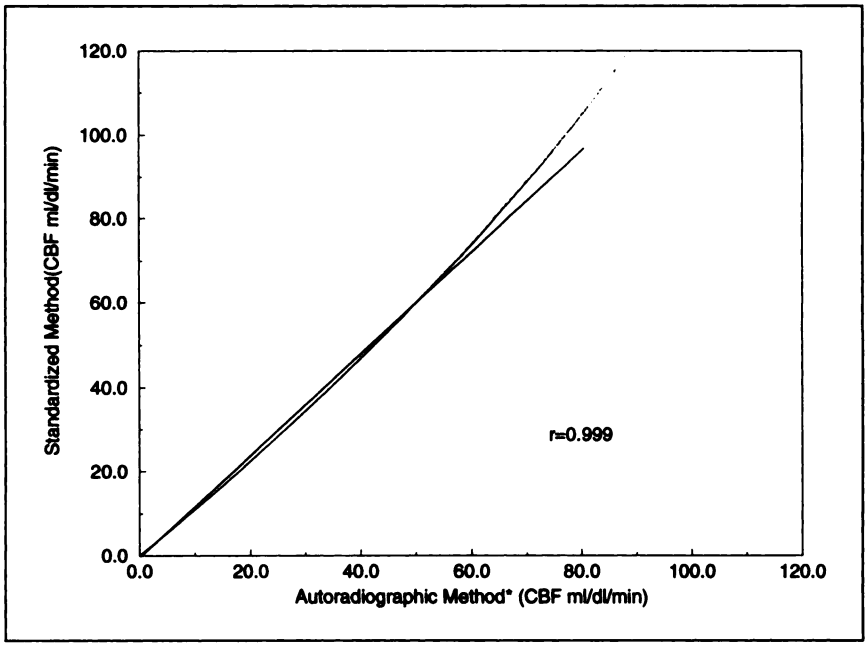

FIGURE 10. rCBF values measured by the autoradiographic method using both a real arterial input function* and a standard input function. The solid line represents the linear-regression line.

the DIM. This effect was tested by changing the scan frame time from 5 to 100 sec. It was found that the estimation of flow by the DIM was relatively stable. Although the optimum scan frame time was not clearly defined here for noisy data, in the ideal situation, any scan frame time yielded a good estimation of flow (Fig. 4). This implies that single-scan data may be processed to solve tissue count nonlinearity by these equations.

Error in the V_d of water was found to be most critical and produced an almost similar effect as in other CBF techniques (*5,7*). As shown in Figure 4, more than 10% of error in the CBF resulted from a 20% overestimation of the V_d at a scan time of 100 sec. However, the authors did not study this issue further because their aim was not to calculate the absolute flow.

A good correlation was found between the results of DIM and the autoradiographic method (Fig. 9 and Table 1). The resulting rCBF of the DIM values and those of the autoradiographic method were compared, and a correlation was established on pixel-by-pixel basis (Fig. 9). Included in this analysis was a comparison between the autoradiographic method achieved by either on-line detection of the arterial concentration (with correction for delay and dispertion) or by the use of a standard input function (with a correction for delay and dispersion using standard values). The results of CBF were overestimated, especially in higher-flow regions, in a simplified method with a standard input function (Fig. 10). Thus, nonlinearity is not completely eliminated by using a standard input function.

Disadvantages of the present method are estimates of CBF which are obtained by taking the ROI to get whole-brain tissue counts and the program assumed that the flow average in the whole brain is 50 ml/dl/min. It is possible to derive wrong values if the assumed flow in the whole brain is not close to the real flow, especially in pathologic states. However, DIM may be applicable to brain activation studies that require standardization of flow values with the least linearity distortion.

In conclusion, a noninvasive (i.e., without arterial puncture) calculation method to determine relative flow was developed. Preliminary simulations revealed satisfactory linearization of values relative to the absolute flow, which may be substantial in comparison with those of the autoradiographic method using a standard input function.

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