

Noninvasive Measurement of Regional Cerebral Blood Flow Change with $H_2^{15}O$ and Positron Emission Tomography Using a Mechanical Injector and a Standard Arterial Input Function

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Abstract—To estimate changes in regional cerebral blood flow (rCBF) without arterial sampling in the study of functional-anatomical correlations in the human brain, using ^{15}O -labeled water and PET, a standard arterial input function was generated from the input function in 10 normal volunteers with dose calibration and peak time normalization. The speed and volume of injection were precisely controlled with a mechanical injector. After global normalization of each tissue activity image, the standard arterial input function was applied to obtain estimated CBF images. Relative changes in estimated rCBF to whole brain mean CBF (ΔF_{est}) and those in regional tissue activity (ΔC) were compared with true relative rCBF changes (ΔF) in 40 pairs of images obtained from 6 normal volunteers. ΔF_{est} correlated well with ΔF , whereas ΔC consistently underestimated ΔF . This noninvasive method simplifies the activation studies and provides the accurate estimation of relative flow changes.

I. INTRODUCTION

POSITRON emission tomographic (PET) measurements of regional cerebral blood flow (rCBF) with intravenously administered ^{15}O -labeled water are well suited to the study of functional-anatomical correlations within the human brain [1], [2]. Quantification of the change in rCBF from an initial resting state is important for the expression of regional neuronal activation [3]. The measurement of rCBF with PET usually requires serial arterial blood sampling to accurately determine the arterial input function of the tracer. For functional brain mapping, however, the calculation of absolute blood flow values may not be required. Instead, relative changes in rCBF can provide substantial information about the cerebral responses to neurobehavioral tasks [3]. Therefore, the measurement of relative changes in cerebral blood flow without arterial sampling would be preferable.

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For wide clinical application, noninvasive and simplified techniques for quantifying relative changes in rCBF have been sought by other investigators [1], [3]. The near-linear relation between radiotracer concentration and rCBF implies that the distribution of radiotracer concentration closely approximates the rCBF distribution [2]. However, relative changes in simple radiotracer concentration underestimate relative rCBF changes in the gray matter, which is the main concern of activation studies [2], [3]. Fox *et al.* [1] proposed a method for correcting the underestimation of rCBF for a region of interest, but not on a pixel-by-pixel basis. In the present paper, we show that correction for the nonlinear relationship between radiotracer concentration and rCBF is essential for quantification of relative changes in CBF. We present a method that can account for this nonlinearity in estimating relative CBF changes over the whole brain without arterial sampling. The technique utilizes a standard arterial input function and a reference table for the calculation of blood flow [4].

II. THEORY

A. CBF Measurement

Measurement of CBF was performed by an adaptation of Kety's diffusible autoradiographic method [4]-[6]. The regional change in cerebral radiotracer concentration is described as

$$\frac{dC_T(t)}{dt} = EFC_a(t) - EF\frac{C_T(t)}{\mu} - \lambda C_T(t) \quad (1)$$

where $C_T(t)$ is the tissue concentration of $H_2^{15}O$ measured by PET, $C_a(t)$ is the arterial concentration of $H_2^{15}O$ measured by blood sampling, F is the regional blood flow, μ is the partition coefficient of water between brain and blood, and λ is the physical decay constant of ^{15}O . E is the extraction fraction of the tracer between capillaries and tissues [5], [6].

PET value C obtained by the scan from $t = t_1$ to $t = t_2$ is

$$C = \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} FC_a(t) * \exp[-(F/\mu + \lambda)t] dt \quad (2)$$

where * indicates convolution. Here, we assumed the extraction fraction was equal to unity [5]. The "look-up" reference

table function $F = G(C)$ was generated to relate F to C [4], and applied to the PET images of radioactivity pixel-by-pixel to calculate rCBF.

B. Measurement of Relative Change in rCBF

Global Normalization: In an activation study, the primary concern is to locate and quantitate rCBF changes induced by the activation paradigm [7], because global (whole-brain) CBF is not significantly affected by passive sensory stimulation [8], [9] or motor tasks [10], [11]. The fluctuation of global CBF (gCBF) between successive scans in the current study (the mean within-subject coefficient of variation was 5.1%) was similar to that observed in previous studies [8]-[11]. The fluctuation could be caused by technical problems such as insufficient temporal sampling of arterial blood, or by failure to correct the delay and dispersion of the input function [6], [12], [13]. Physiological factors, such as the variation of P_aCO_2 , might also have contributed [11]. The effect of fluctuation of gCBF was effectively abolished by multiplying each pixel by a correction factor calculated as the scan gCBF divided by the true mean gCBF [1], [7]-[10]. This method, global normalization, has been proved to allow quantitative comparison of the relative regional increase in radiotracer concentration and blood flow induced by selective stimulation [1]. This process assumes that scan-to-scan fluctuation equally affects every pixel used for calculation of gCBF and that the contribution of the activated region to the variation in gCBF is small relative to that of gCBF [9].

C. Relative Change in rCBF

In the neurobehavioral task batteries, we consider state 1 (control) and state 2 (activation) of the same subject. The reference tables of each state are $G_1(C)$ and $G_2(C)$, respectively. The simple radiotracer concentrations at one pixel are C_1 and C_2 . The corresponding rCBFs F_1 and F_2 are $F_1 = G_1(C_1)$, $F_2 = G_2(C_2)$. The global means of CBF in each state are F_{1g} and F_{2g} . Using F_{1g} and F_{2g} , F_1 and F_2 are expressed as

$$\begin{aligned} F_1 &= yF_{1g} \\ F_2 &= (y + \Delta y)F_{2g} \end{aligned} \quad (3)$$

where variable y represents the CBF of state 1 relative to F_{1g} , and $y + \Delta y$ of state 2. The relative change in CBF, ΔF , is expressed with radiotracer concentrations and reference table functions of each state as follows:

$$\Delta F = \frac{\Delta y}{y} = \frac{gF_2}{F_1} - 1 = \frac{gG_2(C_2)}{G_1(C_1)} - 1 \quad \text{where } g = \frac{F_{1g}}{F_{2g}}. \quad (4)$$

Similarly, C_1 and C_2 can also be expressed as

$$\begin{aligned} C_1 &= xC_{1g} \\ C_2 &= (x + \Delta x)C_{2g} \end{aligned} \quad (5)$$

where variable x represents the radiotracer concentration relative to the global concentration in state 1. With (5), (4) is

expressed as

$$\Delta F = \frac{gG_2((x + \Delta x)C_{2g})}{G_1(xC_{1g})} - 1. \quad (6)$$

A fractional increase propagation function $H(C)$ is defined as

$$H(C) = \frac{dG/G}{dC/C} \quad (7)$$

which is the ratio of the fractional increase in the CBF to the fractional increase in the measured radiotracer concentration. For a small ΔC ,

$$\begin{aligned} G(C + \Delta C) &= G(C) + G(C) \frac{\Delta C}{C} H(C) \\ &= G(C) \left(1 + \frac{\Delta C}{C} H(C)\right). \end{aligned} \quad (8)$$

Therefore, if Δx is small, this relationship may be applied to the numerator of (6):

$$\begin{aligned} G_2((x + \Delta x)C_{2g}) &= G_2(xC_{2g} + \Delta(xC_{2g})) \\ &= G_2(xC_{2g}) + G_2(xC_{2g}) \frac{\Delta(xC_{2g})}{xC_{2g}} H_2(xC_{2g}) \end{aligned} \quad (9)$$

where H_2 is the fractional increase function at state 2.

Using this expression for the numerator of (6), ΔF can be expressed with a fractional increase propagation function H_2 as

$$\Delta F = \frac{gG_2(xC_{2g})}{G_1(xC_{1g})} \left(1 + \frac{\Delta x}{x} H_2(xC_{2g})\right) - 1 \quad (10)$$

noting that

$$\frac{\Delta(xC_{2g})}{xC_{2g}} = \frac{\Delta x}{x}$$

since C_{2g} is constant. Moreover, C_{1g} and C_{2g} are considered to be constant, $G_1(xC_{1g})$, $G_2(xC_{2g})$, and $H_2(xC_{2g})$ are the functions of x . Thus

$$\begin{aligned} G_1(xC_{1g}) &= \hat{G}_1(x), \quad G_2(xC_{2g}) = \hat{G}_2(x) \\ &: \text{systematic normalized reference table function} \\ H_2(xC_{2g}) &= \hat{H}_2(x) \\ &: \text{normalized increase propagation function.} \end{aligned}$$

Using this notation, ΔF is expressed as

$$\begin{aligned} \Delta F &= \frac{g\hat{G}_2(x)}{\hat{G}_1(x)} \left(1 + \frac{\Delta x}{x} \hat{H}_2(x)\right) - 1 \\ &= J(x) \left(1 + \frac{\Delta x}{x} \hat{H}_2(x)\right) - 1 \end{aligned} \quad (11)$$

where

$$J(x) = \frac{g\hat{G}_2(x)}{\hat{G}_1(x)} = \frac{\hat{G}_2(x)}{\hat{G}_1(x)} \frac{F_{2g}}{F_{1g}}. \quad (12)$$

$J(x)$ is the ratio of the relative blood flow of consecutive scans to the corresponding relative concentration of radiotracer (x). If G_1 and G_2 are linear,

$$\frac{\hat{G}_1(x)}{F_{1g}} = \frac{\hat{G}_2(x)}{F_{2g}} = x$$

then $J(x) = 1$. If, in addition, $\hat{H}_2(x) = 1$, then $\Delta F = \frac{\Delta x}{x}$. This is not the case, however, as washout of the radiotracer causes nonlinearity between C and F . When the relative change in CBF, ΔF , is estimated by the relative change in radiotracer concentration, $\Delta C = \frac{\Delta x}{x}$, the systematic error is

$$\Delta C - \Delta F = \frac{\Delta x}{x}(1 - \hat{H}_2(x)J(x) + (1 - J(x))). \quad (13)$$

In this paper, we propose a standard reference table function $G_s(C)$, which was derived from the standard arterial input function obtained from measured arterial curves in 10 normal subjects. In this method, radiotracer concentration images are globally normalized to C_s , which is the standard global mean of radiotracer concentration determined independently. $G_s(C)$ was then applied to the normalized images. Estimated relative change in rCBF is then expressed as

$$\Delta F_{\text{est}} = \frac{G_s(\alpha_2 C_2) - G_s(\alpha_1 C_1)}{G_s(\alpha_1 C_1)}$$

where

$$\alpha_1 = \frac{C_s}{C_{1g}} \quad \alpha_2 = \frac{C_s}{C_{2g}}. \quad (14)$$

Using the definitions of C_1 and C_2 given in (5), (14) may be expanded as

$$\begin{aligned} \Delta F_{\text{est}} &= \frac{G_s((x + \Delta x)C_s) - G_s(xC_s)}{G_s(xC_s)} \\ &= \frac{G_s((x + \Delta x)C_s)}{G_s(xC_s)} - 1. \end{aligned} \quad (15)$$

If Δx is relatively small, $G_s((x + \Delta x)C_s)$ may be approximated in terms $H_s(xC_s)$ using a derivation and notation similar to those used in simplifying $G_2((x + \Delta x)C_{2g})$ in (6)–(8):

$$\Delta F_{\text{est}} = \left(1 + \frac{\Delta x}{x} H_s(xC_s)\right) - 1 = \frac{\Delta x}{x} \hat{H}_s(x) \quad (16)$$

The systematic error in estimating ΔF by ΔF_{est} is expressed as follows using (11):

$$\Delta F_{\text{est}} - \Delta F = \frac{\Delta x}{x} (\hat{H}_s(x) - \hat{H}_2(x)J(x)) + (1 - J(x)). \quad (17)$$

This error is small when $\hat{H}_2(x)$ is well approximated by $\hat{H}_s(x)$ and when $J(x)$ is close to unity. Since delay and dispersion of the arterial input function affect the shape of the reference table [5], strict control of the speed and volume of injection was attempted to increase the reproducibility of the input functions. In that situation, $J(x)$ would be near unity, because relative blood flow of consecutive scans corresponding to the same relative concentration of radiotracer (x) is expected to be the same. In addition, variability in $\hat{H}_2(x)$ would be small, because the shapes of the reference tables

are probably similar, even interindividually. A standard input function can be generated by averaging the input functions after dose calibration and peak time normalization. Using the standard input function, a standard reference table $\hat{G}_s(x)$ can be calculated, where C_s is selected to fit $\hat{H}_s(x)$ to the mean $\hat{H}_2(x)$ at each x . To quantitate the relative change in rCBF noninvasively, tissue activity images are globally normalized with $\alpha = C_s/C_g$, then the standard reference table $F = G_s(C)$ is applied to generate normalized CBF images of states 1 and 2. The activation-induced change in rCBF is then obtained by pixel-by-pixel subtraction of the normalized CBF images of state 1(control) from that of state 2(activated).

III. MATERIALS AND METHODS

A. Tomograph Characteristics

The PCT-3600W system (Hitachi Medical Co., Japan) was employed for PET scanning [14]. This system simultaneously acquires 15 slices with a center-to-center interslice distance of 7 mm. All scans were performed at a resolution of 9 mm full width at half maximum (FWHM) in the transaxial direction and 6.5 mm in the axial direction. Field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively. Tomographic transmission data, using a standard Ge-68/Ga-68 plate source, was obtained before all emission measurements.

B. Subject Preparation

Ten normal volunteers (all men, aged 20–25 years) were studied. Six of them participated in an activation study involving a finger-movement paradigm and PET. The remaining four participated in other activation studies, and their arterial radiotracer activity curves were used only to obtain the standard arterial input function. Written informed consent was obtained from each subject using forms and procedures approved by the Ethics Committee of Kyoto University Faculty of Medicine.

A catheter was placed in the cubital vein of the subject's right arm and the brachial artery of the left arm. The subject lay in a resting state, with eyes closed, and the room was quiet and dimly lit. No attempt was made to control the subject's thought content. During scanning, the head was immobilized with an individually molded head-holder.

C. Behavioral States

Two scans were acquired while the subjects were at rest; no stimulation was given and no task was performed (state 1, control). Two to four scans were performed while the subjects moved the fingers in the right hand (state 2, activation). A total of 31 measurements were performed, including 12 control states and 19 activation states.

D. Tracer Techniques

Scan acquisition of 90 seconds was initiated at the start of tracer injection. Data were collected on six consecutive frames of 15 seconds each. The sinograms were added to make one static PET image.

$H_2^{15}O$ was injected into the right cubital vein (6 ml in 15 seconds) with an automatic injector. Arterial blood samples were obtained manually from the left brachial artery every 3 to 5 seconds after the radiotracer was injected until scanning was completed to obtain the arterial input curve. The volume and activity of residual radiotracer in the syringe were measured and corrected for decay to obtain the injected dose.

E. Data Analysis

Reference Table: The reference table function $G(C)$ was calculated from (2), using the measured arterial input function. The arterial activity curve $Ca(t)$ was determined by multiple blood samplings starting from $t = 0$ with linear interpolation between measured points. For each CBF value from $F = 0$ to 130 ml/min/100 g in steps of 0.2 flow units, the average tissue activity, C , was calculated from (2). The relation between blood flow and tissue radiotracer concentration (reference table) was approximated by a 4th-order polynomial equation for each scan. $J(x)$ and $H(x)$ were obtained from $G(C)$, global CBF, and global radiotracer concentration. Global radiotracer concentration (C_g) and global CBF (F_g) were determined for each scan. First, a template for each subject was obtained from the tissue activity image of the initial resting state. The template consisted of all pixels having 30% or more of the maximum activity in the 15 slices. This 30% cut-off method can effectively eliminate nonbrain structures, such as the cranium and ventricles. This was confirmed by direct comparison of the template and the magnetic resonance images of the brain in each subject. F_g and C_g were then calculated for each scan by averaging the values of all pixels in the template.

Standardization of Arterial Input Function

Arterial input function data were obtained from all ten subjects, including the six involved in the finger-movement paradigm. Two series of arterial samplings were performed while subjects were in a resting state, during which no stimulation was given and no task was performed.

The arterial input function was normalized to correspond to an injected dose of 10 mCi of $H_2^{15}O$. Each dose-normalized arterial input function was shifted to the mean peak time. These shifted curves were averaged to obtain the standard input function. A standard reference table was calculated as, described earlier.

Determination of C_s and $G_s(C_s)$

While $H_s(C)$ is determined by $G_s(C)$, $\hat{H}_s(x)$ depends on C_s . For accurate estimation of the mean $\hat{H}(x)$ by $\hat{H}_s(x)$ in a wide range of x , C_s was chosen to minimize the mean absolute error in the range of x (0–1.5). The standard global mean of blood flow (F_s) was defined as $F_s = G_s(C_s)$.

Calculation of Relative Change in rCBF with Standard Reference Table (ΔF_{est})

To determine the systematic errors in relative changes of rCBF (ΔF) by the relative changes in radiotracer concen-

TABLE I
INCREASE PROPAGATION FACTORS AT TISSUE CONCENTRATION OF
RADIOTRACER RELATIVE TO GLOBAL MEAN FROM STANDARD
REFERENCE TABLE ($\hat{H}_s(x)$) VS. FROM REFERENCE TABLES
CALCULATED WITH MEASURED ARTERIAL INPUT FUNCTION ($\hat{H}(x)$)

100×(%)	$\hat{H}_s(x)^*$	$\hat{H}(x), (N = 31)$		
		mean	SD	% Coeff. var. (SD/mean × 100)
10	1.02	1.02	0.005	0.494
20	1.04	1.04	0.008	0.776
30	1.06	1.06	0.011	1.013
40	1.08	1.08	0.013	1.164
50	1.10	1.10	0.016	1.451
60	1.12	1.12	0.019	1.681
70	1.14	1.14	0.022	1.977
80	1.16	1.16	0.027	2.311
90	1.19	1.19	0.032	2.712
100	1.21	1.21	0.040	3.309
110	1.24	1.24	0.048	3.859
120	1.28	1.28	0.057	4.442
130	1.31	1.32	0.077	5.814
140	1.35	1.36	0.079	5.809
150	1.39	1.40	0.091	6.512

*When $C_s = 237$ nCi/ml.

tration (ΔC) and by the relative changes estimated with the standard reference table method (ΔF_{est} , ΔC , ΔF , and ΔF_{est} were calculated using the following equations:

$$\Delta C = \frac{\alpha_2 C_2 - \alpha_1 C_1}{\alpha_1 C_1}$$

$$\Delta F = \frac{\beta_2 G_2(C_2) - \beta_1 G_1(C_1)}{\beta_1 G_1(C_1)}$$

$$\Delta F_{est} = \frac{G_s(\alpha_2 C_2) - G_s(\alpha_1 C_1)}{G_s(\alpha_1 C_1)}$$

where

$$\alpha_1 = C_s / C_{1g}, \alpha_2 = C_s / C_{2g}$$

Since measured CBF images were globally normalized to 50 ml/min/100 g,

$$\beta_1 = 50 / F_{1g}, \beta_2 = 50 / F_{2g}.$$

IV. RESULTS

Mean value of $J(x)$, the ratio of relative CBF to the corresponding relative tissue radiotracer activity x , overall within-subject control-activation study pairs, was distributed in the range of 0.992 to 1.006 with a coefficient of variation less than 1.678% over a range of x from 0.1 to 1.5. Figure 1 and Table I show the reproducibility of $\hat{H}(x)$ over a range of x from 0.1 to 1.5. The increase propagation factor at the global mean of radiotracer concentration ($\hat{H}(1)$) was 1.21 ± 0.04 (mean ± SD).

The standard arterial input function obtained from the 10 subjects is shown in Fig. 2. Peak time of this curve was 36 seconds, peak value 3133 nCi/ml, and delay time 20 seconds.

The standard reference table was calculated from the standard arterial input function and (2), and was fit to a 4th-order polynomial,

$$G_s(C) = 3.1454 \times 10^{-2} + 0.17082C + 1.7565 \times 10^{-4}C^2 - 1.5639 \times 10^{-7}C^3 + 5.2443 \times 10^{-10}C^4.$$

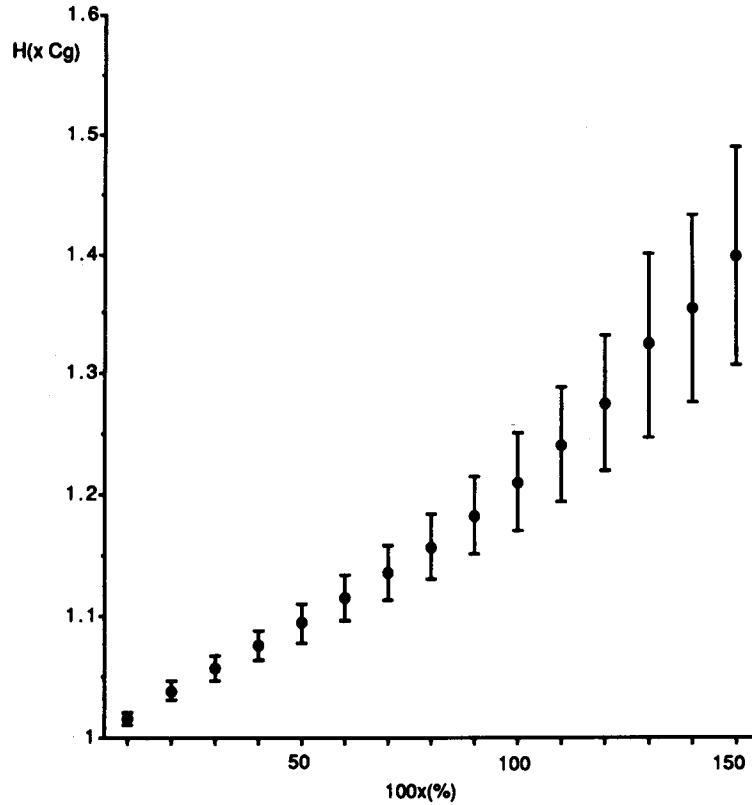


Fig. 1. Distribution of increase propagation factors $\hat{H}_2(x)$. Variable x is the radiotracer concentration relative to the global mean of each measurement. Values are mean \pm 1SD of 31 measurements.

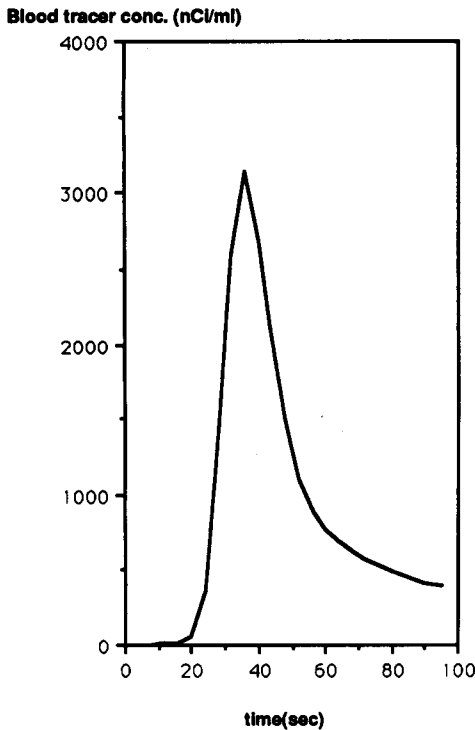


Fig. 2. Standard arterial input function obtained from 10 normal volunteers with dose calibration and peak time normalization.

Maximum and mean error in terms of absolute value in the range of G_s (0 - 130 ml/min/100 g) were 0.26 and 0.09 ml/min/100 g, respectively.

TABLE II
SYSTEMATIC ERROR OF ΔF_{est} AND ΔC AT VARIOUS VALUES OF CBF (ml/min/100 g) WHERE $\Delta F = 0.3$

CBF	$\Delta F_{est} - \Delta F$	$\Delta C - \Delta F$
30	0.53 ± 1.62	$-3.97 \pm 1.36^*$
50	0.00 ± 1.17	$-6.66 \pm 0.96^*$
70	-0.58 ± 2.13	$-9.19 \pm 1.59^*$

* $p < 0.01$ (ANOVA) for comparison with $\Delta F_{est} - \Delta F$.

$\hat{H}(x)$ was well fit to the mean of $\hat{H}(x)$ over a range of x from 0.1 to 1.5 when C_s was 237 nCi/ml (Table I). The standard global mean of CBF, $F_s = G_s(C_s)$, was 50 ml/min/100 g, which was almost equal to the mean of gCBF calculated with the measured input function (49.5 ± 7.9 , mean \pm S.D.).

Table II shows a systematic underestimation of ΔF by ΔC ($p < 0.01$; ANOVA), as reported by Fox *et al.* [1]. This underestimation was observed in the low, middle, and high flow range ($F = 30, 50, 70$ ml/min/100 g). The underestimation increased as ΔF and F increased. The ΔF_{est} was an accurate estimate of the true ΔF without the systematic underestimation found with ΔC over a range of ΔF from 0 to 40% at variable flow values ($F = 30, 50, 70$ ml/min/100 g) (Tables II and III).

V. DISCUSSION

The present method permits accurate estimation of changes in rCBF with H₂¹⁵O and PET noninvasively using a standard input function. Fox *et al.* [2] and Herscovitch *et al.* [12]

reported that the nearly linear relation between C (regional tissue radioactivity) and F (regional CBF) inherent in the PET/autoradiographic model indicates that changes in rCBF will be closely approximated by changes in C . Fox *et al.* [1] expressed the relation between C and F as:

$$F = a(C)^2 + b(C)$$

where a and b are constants determined for each scan using a reduced polynomial regression. They further showed that when changes are expressed as fractional changes from initial control measurement, relative changes in rCBF (ΔF) can be calculated with those in tissue activity (ΔC) with the equation

$$\Delta F = \Delta C + \Delta C(\Delta C + 1)\alpha$$

where

$$\alpha = 1 + b \left(\frac{b - \sqrt{b^2 + 4af_c}}{2af_c} \right)$$

and f_c is the rCBF within the region of interest (ROI) during the control state.

Therefore, α should depend on the scan, the subject, and the flow values in each ROI. Fox *et al.* [1] showed that α is relatively constant across the subjects in the ROI taken in the striate cortex. For estimation of relative blood flow change, they used the mean value of $\alpha(\bar{\alpha})$ from the initial control scans from 8 normal volunteers, and estimated flow change as

$$\Delta F_{\text{est}} = \Delta C + \Delta C(\Delta C + 1)\bar{\alpha}.$$

Since $\bar{\alpha}$ is still flow-dependent, to estimate the CBF changes in the ROI other than striate cortex, one should know the value of f_c , regional CBF in the control state [1]. This process makes it impossible to apply their method on a pixel-by-pixel basis to the whole image. The estimation of relative change of rCBF must be restricted to the specific ROI whose resting blood flow is already known.

In this study, we deduced a more general expression of the relation between ΔF and ΔC , (10), without any need for knowing f_c :

$$\Delta F = J(x)(1 + \Delta C\hat{H}_2(x)) - 1$$

As our results show, $J(x)$ is quite close to unity. Since unity of $J(x)$ means that in each individual the same relative radio-tracer concentration will accompany the same relative CBF values in the consecutive sessions, this result is reasonable. This is probably because intra-subject reproducibility of shape and delay of input functions between control and activation states is high, and in turn, the normalized reference tables $\hat{G}_1(x)$ and $\hat{G}_2(x)$ are similar in each individual. The similarity could be due to the strict control of speed and volume of injection provided by a mechanical injector. In this case, we can simplify (10) as

$$\Delta F = \hat{H}_2(x)\Delta C. \quad (18)$$

Comparing (18) with (16) shows that the utility of the proposed method for estimating ΔF_{est} depends on the accuracy with which $\hat{H}_2(x)$ is estimated when arterial samples are not

obtained. As shown in Table I, the coefficient of variation of $\hat{H}_2(x)$ among subjects is small over a wide range of relative radiotracer concentration (0.1–1.5). Therefore, to quantify relative CBF changes, the nonlinear relationship between C and F can be systematically corrected with a standard reference table. This is in contrast to the fact that absolute quantification of CBF and CBF changes need individual arterial input function, because they are quite sensitive to the shape of the input function [5], [13], [15].

To substitute $\hat{H}_2(x)$ with $\hat{H}_s(x)$, we planned to obtain the standard arterial input function and the standard reference table $G_s(C)$, which in turn can generate $\hat{H}_s(x)$, which was best fit to the mean $\hat{H}(x)$ by selecting proper C_s . If the method of radiotracer injection is constant across the subjects, the delay and the shape of the arterial input function are expected to be similar, even interindividually for normal subjects. Mazziotta *et al.* [3] reported that by examining the arterial blood time-activity curves in over 10 normal subjects after a bolus injection of H_2^{15}O , both the shape and the tracer appearance time were found to be very similar [3]. In our study, however, the tracer appearance time varied from subject to subject. On the basis of these findings, we obtained a standard arterial input function from normal volunteers using mechanical injection with exact dose measurement. We averaged arterial input functions after dose calibration and peak time normalization, to preserve the shape of the input function.

As C_s was selected just to fit $\hat{H}_s(x)$ to the mean value of $\hat{H}(x)$, $F_s = G(C_s)$ is not necessarily the global mean of each scan calculated with the standard reference table. If intersubject averaging is attempted, global normalization of each scan calculated with a standard reference table should be performed. This will not affect our results, as global normalization is a linear transformation. Similarly, $G_s(\alpha_1 C_1)$ is not necessarily equal to $\beta_1 G_1(C_1)$. We used the normalized CBF value calculated from the measured arterial input of state 1 ($\beta_1 G_1(C_1)$) for comparison of systematic error of ΔF by ΔF_{est} at different blood flows (Table II).

At $\Delta F = 0.3$, there was no systematic error for estimation of ΔF by ΔF_{est} at a wide range of CBF values (Table II). As relative changes in regional blood flow of 0.3 to 0.5 are not readily achieved [1], most ΔF measurements are less subject to error.

The nonlinear count-flow relationship increases as scan time is prolonged, because of increased tracer washout. This has a particularly greater effect on the higher flow region [3]. To avoid underestimation of relative flow changes by the tissue activity changes in the gray matter, scanning for less than 60 seconds from the arrival of the tracer to the brain was recommended [2], [3], although even with 40-second scanning, ΔC underestimated ΔF [1]. In this study, underestimation of ΔF by ΔC was greater than that reported by Fox *et al.* [1], because our protocol used a longer scanning time.

Although a shorter scanning time is better to detect relative flow change, longer imaging time might be favored as a compromise between statistical noise and detection sensitivity [3]. If the injected dose is reduced or the detection sensitivity of the tomograph is lower, application of a standard reference table serves to preserve detectability of flow changes. Quantification

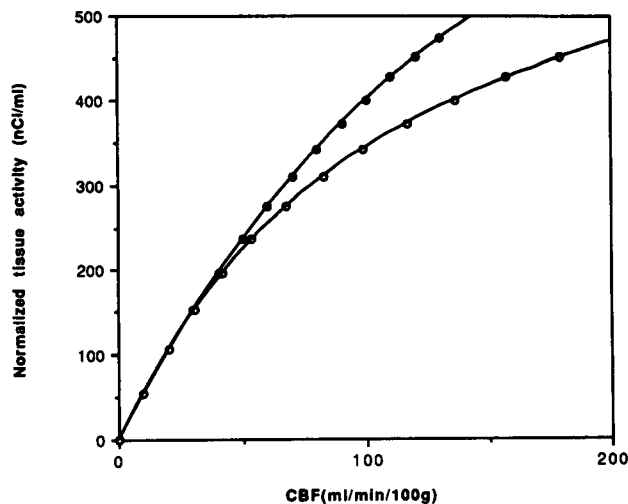


Fig. 3. Standard reference table with correction (open circles) and without correction (closed circles) of incomplete extraction of water. $PS = 133$ ml/min/100 g [19] was used.

of relative flow changes is particularly important when the images are analyzed with ROIs because of partial volume effect.

Correction of delay and dispersion of the arterial input function is essential for accurate estimation of CBF [13]. In this study, however, the correction was not performed for the following reasons. First, we adopted manual arterial sampling, in which external delay and dispersion were negligible. Second, it is impossible to measure the internal delay time and dispersion constant with the single-frame autoradiographic method. With the dynamic method, mean internal dispersion time is estimated at 5 seconds if blood is sampled at the radial artery [13], and differences of arrival time ("head-to-hand" time lag) are 3 seconds [16]. However, the correction is not practical, as internal delay and dispersion depend on the site of arterial sampling (radial artery vs. brachial artery) and on the location of the brain region [17]. Finally, the failure to correct the delay and dispersion may be acceptable because of the relatively long scan acquisition time used [13].

Incomplete extraction of water is another cause of the nonlinear count-flow relationship [6], [18], [19]. Unfortunately, the different values for the permeability-surface area product of water obtained under varying conditions indicated its variability and the difficulty in choosing a value for general use [6], [18], [19]. Nevertheless, an extraction correction may still be beneficial for an activation study to enhance the flow changes in the higher flow region, which is our primary concern. The relationship between values for CBF measured by PET (F) and the extraction-fraction-corrected CBF (F_{corr}) is known as

$$F_{corr} = F/[1 - \exp(-PS/F_{corr})] \quad (19)$$

where PS is the permeability-surface area product of water [6]. Thus, there is no way to algebraically solve for F_{corr} in terms of F . However, Berridge *et al.* [19] compared ¹⁵O-labeled butanol which has $E = 1$ [18] and ¹⁵O-labeled water in the identical normal volunteers. Instead of (19), they used

TABLE III
SYSTEMATIC ERROR OF ΔF_{est} AND ΔC AT VARIOUS
VALUES OF ΔF (%) WHERE $F = 50$ ml/min/100gr

ΔF	$\Delta F_{est} - \Delta F$	$\Delta C - \Delta F$
0.1	0.14 ± 1.71	$-1.96 \pm 0.84^*$
0.2	-0.07 ± 0.88	$-4.24 \pm 0.79^*$
0.3	0.00 ± 1.17	$-6.66 \pm 0.96^*$
0.4	-0.26 ± 1.34	$-9.58 \pm 1.46^*$

* $p < 0.01$ (ANOVA) for comparison with $\Delta F_{est} - \Delta F$.

TABLE IV
INCREASE PROPAGATION FACTORS AT TISSUE CONCENTRATION OF RADIOTRACER
RELATIVE TO GLOBAL MEAN, WITH AND WITHOUT PS CORRECTION

100×(%)	$\hat{H}_s(x)^*$	$\hat{H}_s(x)$ PS corrected ⁺
10	1.02	0.99
20	1.04	1.03
30	1.06	1.06
40	1.08	1.10
50	1.10	1.14
60	1.12	1.18
70	1.14	1.23
80	1.16	1.29
90	1.19	1.36
100	1.21	1.44
110	1.24	1.53
120	1.28	1.63
130	1.31	1.74
140	1.35	1.85
150	1.39	1.97

* When $C_s = 237$ nCi/ml.

+ With assumption that gCBF value is 50 ml/min/100 g, correction for incomplete extraction was performed. Mean PS value = 133 ml/min/100 g [19].

the equation

$$F_{corr} = F/[1 - \exp(-PS/F)]. \quad (20)$$

They calculated PS by a nonlinear regression fit of the corrected data of ¹⁵O-labeled water with (19) to the measured butanol, resulting in $PS = 133$ ml/min/100 g. With (20), the corrected standard reference table $G_{scorr}(C)$ is expressed as

$$G_{scorr}(C) = \frac{G_s(C)}{1 - \exp\left[-\frac{PS}{F}\right]} : \begin{array}{l} \text{Extraction-corrected standard} \\ \text{reference table} \end{array}$$

where $F = G_s(C)$.

This approach may not be strictly precise, because a PS correction based on (20) should be applied to the absolute CBF value. However, with the assumption that intrasubject and intersubject variability of global CBF is relatively small, and considering that F_s (50 ml/min/100 g) is close to the mean of the measured F_g (49.5 ± 7.9 ml/min/100 g), the correction might be justified.

In the corrected standard reference table $G_{scorr}(C)$ and its increase propagation factors (Fig. 3 and Table IV), the PS value was assumed to be 133 ml/min/100 g [19]. Much more amplification of ΔC is achieved with the PS corrected standard reference table than with the uncorrected one. As this amplification is larger in the higher flow range, this correction would be of great help in detecting activated foci, which are expected to occur in the high flow region.

Our method cannot assess the changes in global CBF common to the non-invasive methods proposed previously [1],

[3]. Our approach requires strict control of the volume and speed of tracer injection. Further, a series of arterial sampling and injected dose measurements should be performed on normal subjects to acquire the standard arterial input function before any noninvasive studies are performed.

In conclusion, the standard arterial input function method is feasible for correcting the underestimation of relative changes in CBF in neurobehavioral task batteries. This method is particularly useful when the scanning time is relatively long, and when the analysis of the data is based on regional analysis.

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