
Noninvasive Estimation of FDG Input Function for Quantification of Cerebral Metabolic Rate of Glucose: Optimization and Multicenter Evaluation

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The aims of this study were to determine whether body weight or body surface area (BSA) should be used for noninvasive measurement of the cerebral metabolic rate of glucose (CMRGl_c) by FDG PET with a standardized input function (SIF) and an autoradiographic method and to validate the procedure in a large population from different PET centers. **Methods:** Plasma input functions measured by intermittent arterial blood sampling after intravenous injection of FDG, in 101 patients from 1 institution who were fasting for at least 4 h, were used to generate the SIF. The SIF was generated by averaging over 101 patients the input function normalized with the net injected dose and initial distribution volume (DV) of FDG estimated by the formula $c \times H^a \times W^b$, where H is body height and W is body weight. To evaluate the estimation of DV by BSA or body weight, the coefficient of variation (CV) of the ratio of $H^a \times W^b$ to the measured DV was calculated by changing a and b independently. Estimation of the CMRGl_c with SIF based on the formula for DV was validated with an additional 192 subjects from 3 institutions who underwent FDG PET while fasting. The result of simulation was compared with the results of 4 previously published formulas for BSA and body weight. **Results:** The optimal set of parameters, in which a was 0.80 and b was 0.35, minimized the CV. The averaged percentage error of the CMRGl_c based on the optimal set of parameters for DV estimation and SIF was 8.9% for gray matter and 10.6% for white matter. Four BSA formulas brought about a similar error, which was significantly smaller than that based on body weight ($P < 0.001$, ANOVA). **Conclusion:** Noninvasive estimation of CMRGl_c is made possible by careful measurement of the net injected dose and BSA.

Key Words: FDG PET; initial distribution volume; standardized input function; glucose metabolism; brain

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The autoradiographic method in which FDG PET is used for measurement of the regional cerebral metabolic rate of

glucose (CMRGl_c) has been well established in humans with static scans (1–4). This method requires the measurement of arterial plasma FDG concentration as an input function and thus necessitates repeated arterial blood sampling. Because frequent arterial blood sampling may not be feasible in clinical settings, several methods have been proposed to simplify the procedure. Techniques to estimate the input function from a population-based standard arterial input curve for FDG have been attempted with calibration using 2-point arterial blood sampling (5) or 2-point arteriovenous sampling (6). These methods calibrate the population-based standard input function to the individual input function using the measured plasma FDG concentration, assuming that the shape of the input function is the same across subjects. With the same assumption of constant shape of the input function, Tsuchida et al. (7) proposed a calibration method using injected dose per body weight or per body surface area (BSA), assuming they are parallel with the initial distribution volume (DV) of FDG. Because the distribution of FDG is much less in fatty tissues than in lean body mass (8) and the BSA is a better indicator of lean body mass than is body weight (9), an estimation of CMRGl_c based on BSA was expected to be better than that based on body weight. However, Tsuchida et al. failed to detect a difference in the accuracy of CMRGl_c estimation by body weight and BSA, possibly because of the formula of BSA, the limited number of subjects who had a relatively constant body habitus, or both. First, considering that many formulas exist for calculating BSA (10–13), it is not known whether the formula Tsuchida et al. used, which was proposed by Fujimoto and Watanabe (10), is the best for estimating the DV. Second, Tsuchida et al. validated their method with relatively few subjects from a single institute. To be used, the method must be validated with a larger population from multiple centers. Hence, the purpose of this study was 2-fold: to determine whether body weight or BSA should be used for the method of Tsuchida et al. and to validate the procedure in a large population from 3 PET centers in Japan.

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MATERIALS AND METHODS

Institutions

The 3 independent PET centers participating in this retrospective study were the Biomedical Imaging Research Center of Fukui Medical University (Fukui), the Tokyo Metropolitan Institute of Gerontology (Tokyo), and the Hyogo Institute for Aging Brain and Cognitive Disorders (Hyogo). The protocol was approved by the ethical committee or its equivalent at each institution, and written informed consent was obtained from each subject before the PET study. All institutions performed FDG PET with repeated arterial blood sampling in fasting subjects.

Subjects

In all, 293 subjects participated in the study. Data from 101 subjects who underwent FDG PET studies with arterial sampling in Fukui were included in the analysis of the DV of FDG (group A). The data from the other 192 subjects who underwent FDG PET studies with arterial sampling at 3 institutions (56 in Fukui, 81 in Tokyo, and 55 in Hyogo) were analyzed to validate the estimation of input function by the standardized input function (SIF) (group B). The participants' age, body height, body weight, body mass index (BMI), and plasma glucose concentration are summarized in Table 1. The BMI, a measure of body habitus, was calculated from the equation $BMI = [\text{body weight (kg)} / (\text{height (m)})^2]$.

FDG was prepared by electrophilic fluorination of triacetylglucal with [^{18}F]acetylhypofluorite followed by HCl hydrolysis using an automated FDG synthesis system (NKK, Tokyo, Japan) and a small cyclotron (Oscar 2,3; Oxford Instruments, Abingdon, Oxfordshire, UK) in Fukui and Hyogo. An automated FDG synthesis system and Cypris 370 compact cyclotron (Sumitron Heavy Industries, Ltd., Tokyo, Japan) were used in Tokyo.

Arterial Sampling Procedure

Small plastic catheters were placed in the radial artery of 1 arm for arterial sampling and in the antecubital vein of the other arm for the radiotracer injection. Plasma glucose concentrations were measured during or after the PET scan.

In Fukui, 92–532 MBq FDG were injected manually over a period of 30 s, and the residual FDG in the syringe and catheters was flushed with saline. In Tokyo, 104–273 MBq FDG were injected by an infusion pump for a period of approximately 2 min; a large part of the tracer was injected for 10 s, and saline flushing followed. In Hyogo, 173–330 MBq FDG were injected for a period of 60 s at a constant infusion rate by an infusion pump, and residual FDG in the catheter was flushed with saline.

After the start of infusion, arterial blood was sampled frequently from the radial artery. Samples were taken every 15 s for the first 2 min; the interval was then gradually prolonged, up to 60 or 70 min (Fukui: 3, 5, 7, 10, 15, 20, 30, 45, and 60 min; Tokyo: 3, 5, 7, 10, 15, 20, 30, 45, and 60 min; Hyogo: 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, and 70 min). To minimize the interinstitute inconsistencies caused by sampling interval, the Hyogo data at 2.5, 3.5, 4.5, 8, 9, 12, 14, 16, 18, 25, and 70 min were not used in the further analysis. For a similar reason, the radioactivity concentration at 5 min and 45 min was obtained by averaging the radioactivity concentration at 4 and 6 min and at 40 and 50 min, respectively.

The sampled blood was centrifuged, and the plasma was collected from each tube. Plasma radioactivity was measured by a scintillation counter at each institution. The dose of FDG in the syringe was measured with a radionuclide dose calibrator before and after injection to obtain the net injected dose (nID). Dose calibration was performed with a CRC-712 radioisotope calibrator (Capintec, Ramsey, NJ) in Fukui and Tokyo and with a CRC-12 radioisotope calibrator (Capintec) in Hyogo. The scintillation well counter was the Autowell Gamma System ARC-2000 (Aloca, Tokyo, Japan) in Fukui, the blood sampling system BSS-1 (Shimadzu, Kyoto, Japan) in Tokyo, and the Well Stand type FS (Shimadzu, Kyoto, Japan) in Hyogo. All institutions performed cross-calibration between the scintillation well counter and the radionuclide dose calibrator. Approximately 100–300 MBq FDG were measured with the radionuclide dose calibrator used for measuring the injected dose of FDG. The decayed radioactivity (in hertz) of the same FDG was counted by the scintillation counter approximately 24 h later, when the scintillation counter could correctly measure the decayed FDG. A cross-calibration factor (in becquerels per hertz) was obtained as the ratio of the decay-corrected values.

Data Analysis

Calculation of DV. The nID was calculated by subtracting the decay-corrected doses of FDG in the syringe before and after injection. Semilogarithmic recordings of plasma input functions were graphically extrapolated from the data between 5 and 30 min to obtain the y-intercept or initial plasma concentration ($C_p(0)$), assuming that in this period the intravascular and extravascular FDG pool of the whole body had reached a steady state (14). The measured initial DV of FDG for a subject i was defined as (15):

$$DV_i = nID_i / C_{p_i}(0). \quad \text{Eq. 1}$$

TABLE 1
Summary of Subjects in the 3 Institutions

Group	No. of subjects	Age (y)	Body height (cm)	Body weight (kg)	Body mass index (kg/m ²)	Plasma glucose (mg/dL)
A						
Fukui	101 (76 M/25 F)	63.4 ± 13.7	160.7 ± 8.0	56.7 ± 8.8	21.9 ± 2.8	96.3 ± 13.5
B						
Fukui	56 (36 M/20 F)	62.2 ± 11.0	159.9 ± 8.4	56.0 ± 10.5	21.7 ± 2.8	97.7 ± 14.1
Tokyo	81 (43 M/38 F)	57.4 ± 15.2	158.7 ± 9.6	52.2 ± 11.5	20.6 ± 3.5	96.2 ± 18.1
Hyogo	55 (21 M/34 F)	67.5 ± 8.5	155.7 ± 8.0	52.7 ± 11.1	21.6 ± 3.4	92.4 ± 6.5

Values are mean ± SD.

TABLE 2
BSA Formulas Analyzed

Reference	Parameter	
	a	b
Du Bois and Du Bois (11)	0.725	0.425
Gehan and George (12)	0.42246	0.514565
Mosteller (13)	0.5	0.5
Fujimoto and Watanabe (10)	0.444	0.663

BSA = C × H^a × W^b, where H is body height, W is body weight, and C is a constant.

Estimation of DV by Body Weight and Height. To establish a formula to estimate DV by body weight and height, the following function, R_i(a, b), for each subject i was introduced:

$$R_i(a, b) = H_i^a \times W_i^b / DV_i, \quad \text{Eq. 2}$$

where H_i is body height, W_i is body weight, and a and b are independent variables. The coefficient of variation (CV) of R_i among 101 subjects in group A was computed with varying a and b values in the ranges of 0–2 and of 0–1, respectively and independently. The constants of a₀ and b₀ that minimize the CV of R_i among subjects in group A (optimal set) were determined. Assuming that R_i(a₀, b₀) is constant across subjects, a formula for estimated DV (EDV) can be expressed as:

$$EDV = c_0 \times H^{a_0} \times W^{b_0}, \quad \text{Eq. 3}$$

where:

$$\frac{1}{c_0} = \frac{1}{101} \times \sum_{i=1}^{101} \frac{H_i^{a_0} \times W_i^{b_0}}{DV_i}. \quad \text{Eq. 4}$$

SIF. The EDV of each subject in group A was calculated with Equation 3 with the optimal set (a₀, b₀). To obtain DV estimated by BSA or body weight, the optimal set was replaced with the sets for the BSA formulas (Table 2), and the set for body weight (0, 1). Input functions of group A were linearly interpolated with a 15-s interval. The input function of each subject i, Cp_i(t), was normalized with his or her EDV and nID_i and averaged over group A to generate the SIF:

$$SIF(t) = \frac{\sum_{i=1}^n \frac{EDV_i}{nID_i} \times Cp_i(t)}{n}, \quad n = 101. \quad \text{Eq. 5}$$

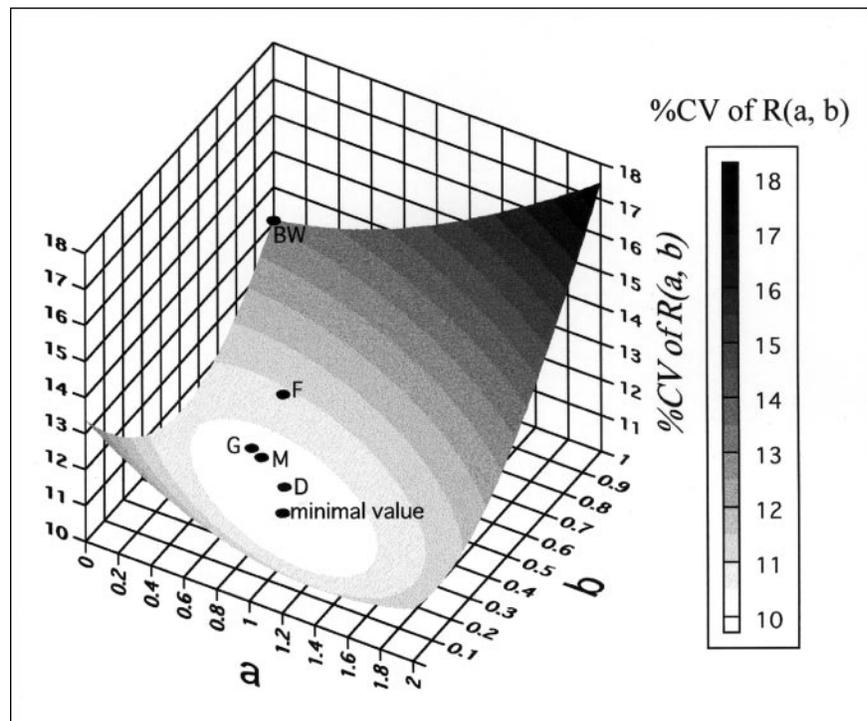
The similarity between the shape of the SIF generated by the optimal set of a and b and the shape of the SIF proposed by Tsuchida et al. (7) was evaluated by semilogarithmic plottings of 2 SIFs.

Estimated Individual Input Function. The estimated individual input function in group B, Cp.sim(t), was calculated with the following equation (7):

$$Cp.sim(t) = \left(\frac{nID}{EDV} \right) \times SIF(t). \quad \text{Eq. 6}$$

The area under the curve (AUC), which indicates the time integral of the plasma input function from 0 to 60 min, was used to compare the estimated input function with the measured one. This comparison was done because CMRGlc values calculated by the autoradiographic method (1–4) depend on the AUC instead of on its rate of change (5,16,17). The AUC (in Bq/mL/min) was calculated using a simple trapezoid algorithm. The percentage error of estimation of the AUC was calculated with the following

FIGURE 1. Relationship between CV of R(a, b) and (a, b) in group A (n = 101). Parameters, (a, b) = (0.80, 0.35), minimized CV of R(a, b). BW = body weight correction; D = Du Bois and Du Bois (11); G = Gehan and George (12); M = Mosteller (13); F = Fujimoto and Watanabe (10).



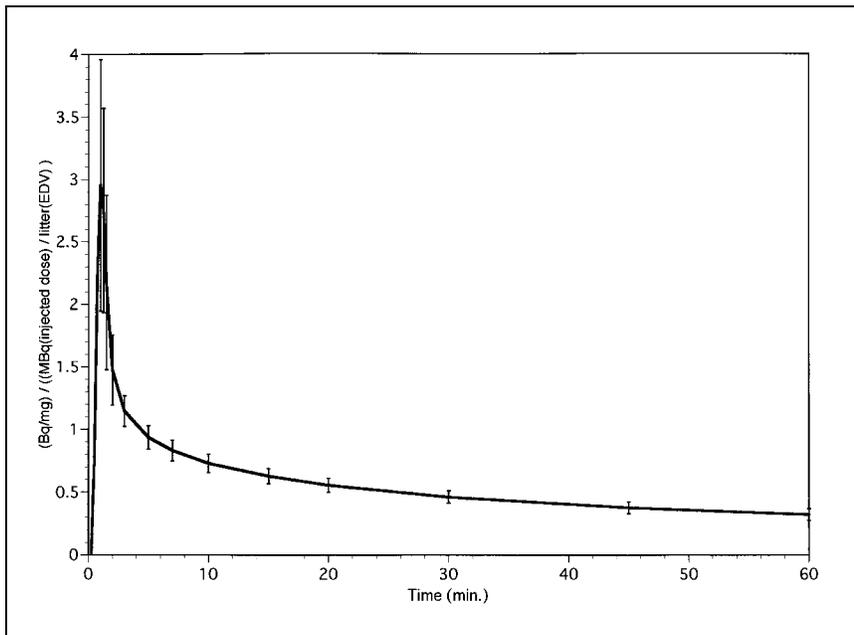


FIGURE 2. SIF corrected with nID per EDV. Error bar shows SD.

equation:

% error of estimation of AUC =

$$\left| \frac{AUC_{sim} - AUC_{real}}{AUC_{real}} \right| \times 100, \quad \text{Eq. 7}$$

where AUC_{real} is the AUC obtained from the measured input function and AUC_{sim} is the AUC obtained from the simulated input function. The percentage error of estimation of the AUC is expressed as the mean \pm SD.

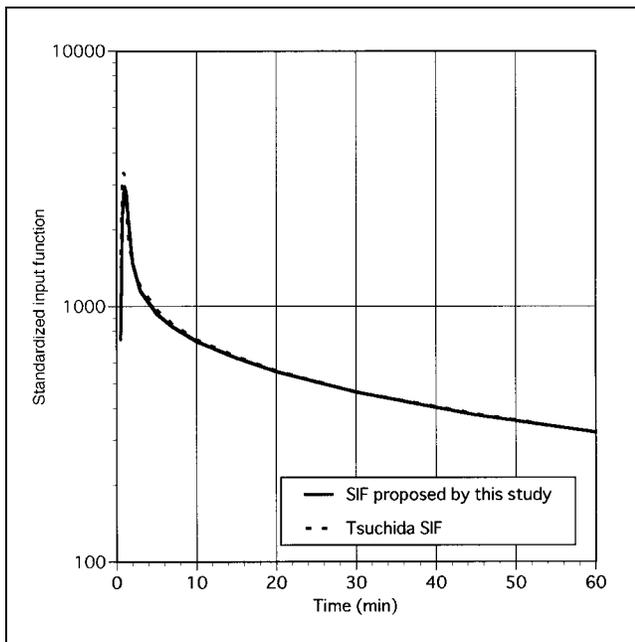


FIGURE 3. SIF proposed by this study and by Tsuchida et al. (7). For direct comparison, latter SIF was normalized to former SIF using values obtained at 60 min.

Influence of the Estimated Input Function on CMRGlc. A simulation study was performed to evaluate the error of the estimation of CMRGlc with the autoradiographic method and the simulated input function. CMRGlc (y) calculated by the autoradiographic method is linearly related to tissue radioactivity (x), and its slope and y -intercept are determined by the input function only:

$$y = M(x), y = S(x), \quad \text{Eq. 8}$$

where M is a linear function determined by the measured input function and S is that determined by the simulated input function. For a given CMRGlc value y_0 , the estimated CMRGlc is $S(M^{-1}(y_0))$. Hence, the percentage error of estimation is calculated without tissue activity:

$$\% \text{ error of CMRGlc} = \frac{|S(M^{-1}(y_0)) - y_0|}{y_0} \times 100. \quad \text{Eq. 9}$$

The details of the procedure are described in the Appendix. The error of the estimation of CMRGlc in group B for typical normal gray matter (7.3 mg/min/100 g) and white matter (3.4 mg/min/100 g) (4) was reported as the mean \pm SD.

RESULTS

The relationship between the CV of R and (a, b) is presented in Figure 1. The coordinates used in the 4 BSA formulas as exponent constants, (0.725, 0.425) by Du Bois and Du Bois (11), (0.422, 0.515) by Gehan and George (12), (0.5, 0.5) by Mosteller (13), and (0.444, 0.663) by Fujimoto and Watanabe (10), were plotted graphically. They are close to the line of $a + 3 \times b = 2$, whereas the coefficients of Fujimoto and Watanabe were shown to be more distant from the line, with a larger percentage CV than other formulas. The coordinate (0, 1), indicating the body weight correction, was also plotted. The CV at $(a, b) = (0, 1)$ was larger than the CV at the coordinates used in the BSA formulas as

TABLE 3
Percentage Error in Estimation of AUC and CMRGlc by
Optimal Set of Parameters in the 3 Institutions

Institution	No. of subjects	AUC (%)	CMRGlc	
			Gray matter (%)	White matter (%)
Fukui	56	7.7 ± 6.0	9.3 ± 7.4	11.1 ± 9.3
Tokyo	81	7.5 ± 6.1	10.1 ± 8.1	12.0 ± 9.8
Hyogo	55	6.1 ± 4.9	6.9 ± 5.6*	7.9 ± 6.8*
Total	192	7.2 ± 5.7	8.9 ± 7.3	10.6 ± 9.0

**P* < 0.05 (1-way ANOVA, with post hoc Scheffé test).

exponent constants. The combination of parameters, (a, b) = (0.80, 0.35), minimized the CV. The formula for estimating the initial DV proposed by the study was:

$$EDV(\text{mL}) = 39.0 \times H_{(\text{cm})}^{0.80} \times W_{(\text{kg})}^{0.35} \quad \text{Eq. 10}$$

The shape of the EDV-corrected SIF with the optimal set of parameters (0.80, 0.35) (Fig. 2) was close to the shape of the SIF proposed by Tsuchida et al. (7), although the peak location was slightly different. For direct comparison, their SIF was normalized to the SIF proposed in this study, using the values obtained at 60 min (Fig. 3).

Percentage error of estimation of the AUC with the optimal set of a and b in group B was 7.2% ± 5.7% (Table 3). No significant difference was found among the 3 institutions in the percentage error of the AUC, although Hyogo showed a tendency toward a smaller percentage error. The percentage error of estimation of CMRGlc was 8.9% ± 7.3% for gray matter and 10.6% ± 9.0% for white matter (Table 3). The percentage error of estimation of CMRGlc was smaller in Hyogo than in Fukui or Tokyo.

Compared with the optimal set of a_0 and b_0 , corrections with the BSA formulas proposed in the other studies (10–13) showed a similar percentage error in estimation of the AUC and CMRGlc (Table 4). Body weight correction gave a

significantly larger percentage error in estimating the AUC and CMRGlc (*P* < 0.001, ANOVA).

DISCUSSION

This study suggests that normalization by BSA is more accurate than by body weight. Figure 1 clearly shows that the CV at (a, b) = (0,1) was larger than the CV at the 4 coordinates used in the BSA formulas. The reasons are that the distribution of FDG is much less in fatty tissues than in lean body mass (8) and that the BSA is a better indicator of lean body mass than body weight (9). Actually, the set of optimal coefficients, (a_0, b_0) = (0.80, 0.35), was obtained from the initial DV of FDG, whereas those of the other 4 previously published BSA formulas were obtained from the measured BSA. Nevertheless, (0.80, 0.35) was close to the coefficients obtained by the 4 different BSA formulas near the line (a + 3 × b = 2) indicating the dimension of BSA (11). Coefficients more distant from this line, as those of body weight (0, 1) or of Fujimoto and Watanabe (10) (0.444, 0.663), were shown to be a less efficient estimation of the DV (Fig. 1). Hence, the DV of FDG is better estimated by the combination of body weight and body height with the constraint of the dimension of area, rather than body weight only (9). The rationale is related to the century-old “law of surface area,” with which estimates of BSA are widely used in physiology and clinical medicine to normalize measures of biologic function and to calculate drug dosage (18).

The shape of the EDV-corrected SIF was close to the shape of the SIF proposed by Tsuchida et al. (7), but the peaks were slightly different from each other (Fig. 2). This difference is because group A of this study for generating SIF is different from the group of Tsuchida et al., although the injection regimen and sampling scheme are identical. The peak difference may be caused by intermittent arterial samplings, which may augment the group difference. The shape around the peak of the input function varied across subjects for up to 5 min because of a fluctuation between the intra- and extravascular components of the FDG pool (7).

TABLE 4
Percentage Error in Estimation of AUC and CMRGlc by Various Formulas

Formula	Parameter		Percentage error of estimation			
	a	b	CV of R (%) (n = 101)	AUC (%) (n = 192)	CMRGlc (%) (n = 192)	
					Gray matter	White matter
Optimal set of parameters	0.80	0.35	10.09	7.2 ± 5.7	8.9 ± 7.3	10.6 ± 9.0
BSA correction						
Du Bois and Du Bois (11)	0.725	0.425	10.12	7.3 ± 5.8	9.0 ± 7.6	10.6 ± 9.3
Gehan and George (12)	0.42246	0.514565	10.30	7.3 ± 5.9	9.0 ± 7.4	10.7 ± 9.1
Mosteller (13)	0.5	0.5	10.26	7.3 ± 5.9	9.0 ± 7.5	10.7 ± 9.1
Fujimoto and Watanabe (10)	0.444	0.663	10.87	8.7 ± 6.3	10.4 ± 7.6	12.2 ± 9.3
Body weight correction	0	1	13.09	12.1 ± 9.2*	13.8 ± 10.1*	16.2 ± 12.4*

**P* < 0.001 (1-way ANOVA, with post hoc Scheffé test) for comparison with optimal set of parameters.

The difference in the shape of the peak only slightly affects calculation of CMRGlc with the autoradiographic method (5,17).

In this study, the percentage error of estimation of AUC was $7.2\% \pm 5.7\%$, whereas in the study of Tsuchida et al. (7), the averaged percentage error of AUC was $3.5\% \pm 2.2\%$ with BSA correction and $3.7\% \pm 2.9\%$ with body weight correction. The difference may be caused by a wider variety of body habitus, interinstitute differences in measuring arterial input function, or both. We evaluated the procedure using 192 subjects from 3 different institutes. This population had a wide variety of body types (height, 138–178 cm; weight, 31–105 kg; BMI, 15.4–35.5 kg/m²), whereas the population studied by Tsuchida et al. was 10 subjects from 1 institute and did not include an extreme body habitus (height, 145–169 cm; weight, 48–67 kg; BMI, 18.2–24.5 kg/m²).

Given the retrospective nature of our analysis, it is subject to many possible sources of error. For example, errors could be introduced by mismeasurement of FDG dose, plasma radioactivity, body weight, or body height. Accurate measurement of the dose of FDG in the syringe before and after injection is essential to obtain the nID. In Fukui, the ratio of the residual dose to the nID was $1.5\% \pm 1.3\%$.

Different injection schemes may introduce potential errors for estimation of SIF and, hence, AUC. But the potential error from different injection styles is thought to be small, because CMRGlc values calculated by autoradiographic methods depend primarily on the time integral of input function (AUC) instead of its rate of change (5). CMRGlc obtained from a slow FDG injection (for 3 min) and from a bolus injection agreed well (19), supporting the insensitivity of injection style (6).

The percentage CV of the CMRGlc given by the autoradiographic method and arterial samplings was approximately 11% in gray matter and approximately 14% in white matter (4). In this article, we have evaluated the error caused by the standard input function instead of by the measured input function, to see if replacement of the latter with the former is reasonable. The error intrinsic to the procedure with the measured input function and the error caused by replacement with the standard input function are different. Assuming that the errors are orthogonal, an expected total error is the square root of the sum of the square of each error, or approximately 17.6% ($= (14^2 + 10.6^2)^{0.5}$). Hence, the noninvasive measurement cost an approximately 3.6% increase in error compared with the invasive method. Considering the relatively large intrinsic error and the clinical merit, we concluded that this degree of increase in error is acceptable.

CONCLUSION

Careful measurement of the dose of FDG, body height, and body weight and the use of an appropriate formula for BSA make possible the noninvasive estimation of CMRGlc.

APPENDIX

Simulation Study for Estimation of Input Function on Calculation of CMRGlc with an Autoradiographic Method

The operational equation established by Phelps et al. (1) for calculating CMRGlc is expressed as follows:

$$\text{CMRGlc} = \frac{C_g}{LC} \times \frac{\left[\text{Ci}(T) - \frac{k_1}{\alpha_2 - \alpha_1} \times \left\{ (k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)e^{-\alpha_2 t} \right\} \otimes \text{Cp}(t) \right]}{\frac{k_2 + k_3}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes \text{Cp}(t)}$$

$$\alpha_1 = \frac{1}{2}[k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}]$$

$$\alpha_2 = \frac{1}{2}[k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}], \quad \text{Eq. 11}$$

where C_g is the plasma glucose level (in mg/dL), LC is the lumped constant, $\text{Ci}(T)$ is the radioactivity of FDG in the brain at time T , and $\otimes \text{Cp}(t)$ denotes the convolution of plasma activity of FDG; k_1 , k_2 , k_3 , and k_4 are the rate constants for carrier-mediated transport of FDG from plasma to tissue, for carrier-mediated transport back from tissue to plasma, for phosphorylation by hexokinase, and for FDG-6-phosphate hydrolysis by glucose-6-phosphatase, respectively.

This equation indicates that CMRGlc calculated by the autoradiographic method is linearly related to the radioactivity of FDG in the brain and that the slope and y-intercept are determined by the input function only.

If the simulated input function, or $\text{Cp.sim}(t)$, is adopted, instead of the measured input function, or $\text{Cp}(t)$, CMRGlc is simulated as follows:

$$\text{CMRGlc.sim} = \frac{C_g}{LC} \times \frac{\left[\text{Ci}(T) - \frac{k_1}{\alpha_2 - \alpha_1} \times \left\{ (k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)e^{-\alpha_2 t} \right\} \otimes \text{Cp.sim}(t) \right]}{\frac{k_2 + k_3}{\alpha_2 - \alpha_1} (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes \text{Cp.sim}(t)}, \quad \text{Eq. 12}$$

where CMRGlc.sim is the simulated CMRGlc using a simulated input function, or Cp.sim(t).

Combining Equations 11 and 12:

$$\begin{aligned} \text{CMRGlc.sim} &= \frac{L(t) \otimes C_p(t)}{L(t) \otimes C_{p,\text{sim}}(t)} \times \\ &\quad \text{CMRGlc.real} - \frac{C_g}{LC} \times \\ &\quad \frac{M(t) \otimes C_{p,\text{sim}}(t) - M(t) \otimes C_p(t)}{L(t) \otimes C_{p,\text{sim}}(t)} \\ L(t) &= \frac{k_2 + k_3}{\alpha_2 - \alpha_1} \times (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \\ M(t) &= \frac{k_1}{\alpha_2 - \alpha_1} \times \\ &\quad [(k_4 - \alpha_1)e^{-\alpha_1 t} - (\alpha_2 - k_4)e^{-\alpha_2 t}]. \quad \text{Eq. 13} \end{aligned}$$

Equation 13 indicates that CMRGlc.sim is linearly related to CMRGlc.real within a subject using the autoradiographic method.

Hence, the percentage error of estimation of CMRGlc was obtained from the following equation:

$$\begin{aligned} \% \text{ error of} \\ \text{estimation} \\ \text{of CMRGlc} &= \left| \frac{\text{CMRGlc.sim} - \text{CMRGlc.real}}{\text{CMRGlc.real}} \right| \times 100 \\ &= \left| A + \frac{B}{\text{CMRGlc.real}} - 1 \right| \times 100 \\ A &= \frac{L(t) \otimes C_p(t)}{L(t) \otimes C_{p,\text{sim}}(t)} \\ B &= -\frac{C_g}{LC} \times \\ &\quad \frac{M(t) \otimes C_{p,\text{sim}}(t) - M(t) \otimes C_p(t)}{L(t) \otimes C_{p,\text{sim}}(t)}. \quad \text{Eq. 14} \end{aligned}$$

All the error can be estimated for the entire spectrum of the CMRGlc. For simplicity of presentation, we have chosen representative values of CMRGlc for the gray matter and white matter (7.3 and 3.4 mg/min/100 g) (*I*) for calculating the error, assuming that a single PET scan was obtained at 60 min. The *k* values were fixed as follows: $k_1 = 0.102/\text{min}$, $k_2 = 0.13/\text{min}$, $k_3 = 0.062/\text{min}$, and $k_4 = 0.0068/\text{min}$ (*I*). The LC was also fixed at 0.42 (*I*).

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