Simplification for Measuring Input Function of FDG PET: Investigation of 1-Point Blood Sampling Method

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The current method for quantitative FDG PET study requires application of multiple arterial blood sampling for measuring the input function, but the procedure is invasive and complicated. The purpose of this study was to establish a 1-point blood sampling technique that gives data comparable with the data of more elaborate serial arterial sampling. **Methods:** We established a time point for 1-point arterial sampling that exhibited the highest correlation between plasma radioactivity at the time point and the real integrated value (IV) of the measured input function obtained by multiple arterial sampling in 120 patients and the smallest coefficient of variation of the real IV divided by plasma radioactivity at the time point in 120 patients. Scaling factors for estimation at each sampling point were determined, and a reference table was established to make the supposed input function. **Results:** The optimal time for 1-point arterial sampling was 12 min after FDG injection. A good correlation was observed between the real IVs and those estimated from 1-point arterial blood sampling at 12 min using the supposed input function ($n = 120$; $P < 0.001$). The time point at which the difference between values of arterial and venous blood disappeared was 40 min after FDG injection. The percentage errors of IV estimation by 1-point sampling were 1.70% ($n = 120$) for arterial blood at 12 min and 3.64% ($n = 10$) for venous blood at 40 min. **Conclusion:** We conclude that the simplified 1-point sample method works in a manner that is comparable with serial arterial sampling and should be useful for clinical PET.

Key Words: PET; glucose metabolic rate; FDG; input function; blood sampling; clinical PET

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Clinical PET is becoming a routine procedure in health care, and the recent development of FDG PET has facilitated the diagnosis of brain disorders such as Alzheimer's disease, heart disease, and cancer at a relatively early stage. The cerebral glucose metabolic rate (CMR_{glc}) is currently measured in humans using PET on the basis of the method proposed by Sokoloff et al. (*1–4*). Tissue FDG concentration after injection is a convolution integral of the arterial input function with the tissue weight function by serial arterial sampling. To obtain an input function (Cp), multiple arterial blood sampling is usually first performed and then integrated. However, this method is invasive, and the required procedure is complicated for clinical PET. A skilled worker performs 20 consecutive arterial blood samplings with intervals between 5 s and 5 min during a 40-min period to obtain the real input function at Nishijin Hospital (*5*). However, this procedure is inconvenient because arterial catheter placement and consecutive arterial blood sampling must be performed at short intervals. Some efforts have been made to solve these problems, but several arterial samplings still remained in practical use (*6,7*). In this study, we tested a simple noninvasive method of obtaining an input function equivalent to that calculated by the current method using data from 1-point arterial or venous blood sampling at an early time point after intravenous FDG injection. For comparison, we also examined a nonblood sampling method.

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MATERIALS AND METHODS

Study Population

The study group consisted of 120 patients (70 males, 50 females; age range, 16–81 y; average [mean ± SD] age, 46.1 ± 17.9 y) with cerebral disease or suspected cerebral disease (brain tumor, cerebrovascular injury, epilepsy, moyamoya disease, and other diseases). Informed consent was obtained from all patients. The blood glucose level ranged from 60 to 367 mg/dL. None of the patients had significant heart or respiratory disease. Dynamic PET data were collected continuously for 1 2-min period and 10 4-min periods, for a total of 11 periods and 42 min. The spatial resolution of the positron camera was 8.2 mm in full width at half maximum in-plane resolution, whereas the average axial resolution was 12.8 mm (Headtome Set-120W; Shimadzu, Kyoto, Japan).

Blood Sampling

In 120 patients, 111–666 MBq FDG in 10 mL were injected over 40 s into the anconeal cutaneous vein with each patient resting in the supine position. Twenty seconds after initiation of intravenous injection (the time point at which PET begins to count activity over the baseline), PET dynamic scanning was started, and 20 consecutive arterial blood samples were obtained over a 40-min period (5,

10, 15, 20, 30, 60, 90, 120, 150, 180, 240, 300, 420, 540, 720, 900, 1200, 1500, 1800, and 2400 s). Seven consecutive venous blood samples were also obtained after PET scanning was started (120, 300, 720, 900, 1800, 2100, and 2400 s). Two milliliters of arterial and venous blood were sampled. Arterial blood was sampled using a 20-gauge Surflow needle catheter (TERUMO, Tokyo, Japan) placed in the opposite brachial artery, and venous blood was sampled through a 22-gauge Surflow needle catheter used for FDG injection (the catheter was immediately flushed with physiologic saline to prevent sample contamination). Arterial and venous blood samples were aliquoted into tubes containing anticoagulant (ethylenediaminetetraacetic acid, disodium salt), left in ice water, and then centrifuged (3000 rpm, 2000*g*, 4°C) for 10 min to separate the plasma. The radioactivity in the plasma samples was then measured with an autowell γ counter (ARC-400; Aloka, Tokyo, Japan). Calculation of the CMR_{glc} was performed using the methods of Phelps et al. (*2*) and Huang et al. (*3,4*).

1-Point Blood Sampling Method

Establishment of Time Point for 1-Point Arterial Sampling. Correlation between the blood radioactivity (counts per second [cps]/g) and the integrated value (IV) obtained for 40 min (real IV) of the real input function (from 0 to 40 min), at a given time point, was determined for the 120 patients to select the optimal time point for 1-point blood sampling for the study population. The time point that exhibited the highest correlation between blood radioactivity and real IV was selected (Fig. 1). To obtain reliable results, the coefficient of variation (CV) of the real IV divided by the plasma radioactivity for each time point was calculated in 120 cases. The time point at which the smallest CV was obtained was considered the optimal time point for blood sampling.

Determination of Scaling Factors for Estimation at Each Blood Sampling Point. The measured value for the arterial blood sample at each of the 20 time points was divided by the measured value at the optimal sampling time point (the value at 12 min was selected on the basis of results) for the 120 patients, and the mean value at each time point was calculated.

Reference Table to Estimate Input Function. The value for the arterial blood sample collected 12 min after intravenous FDG injection was multiplied by a scaling factor (mean value) using a reference table to estimate the input function (Fig. 2).

Establishment of Time Point for 1-Point Venous Blood Sampling. The ratio of the venous plasma value to the arterial plasma value was calculated over the 40-min period after intravenous FDG injection. The time point at which the difference between values of

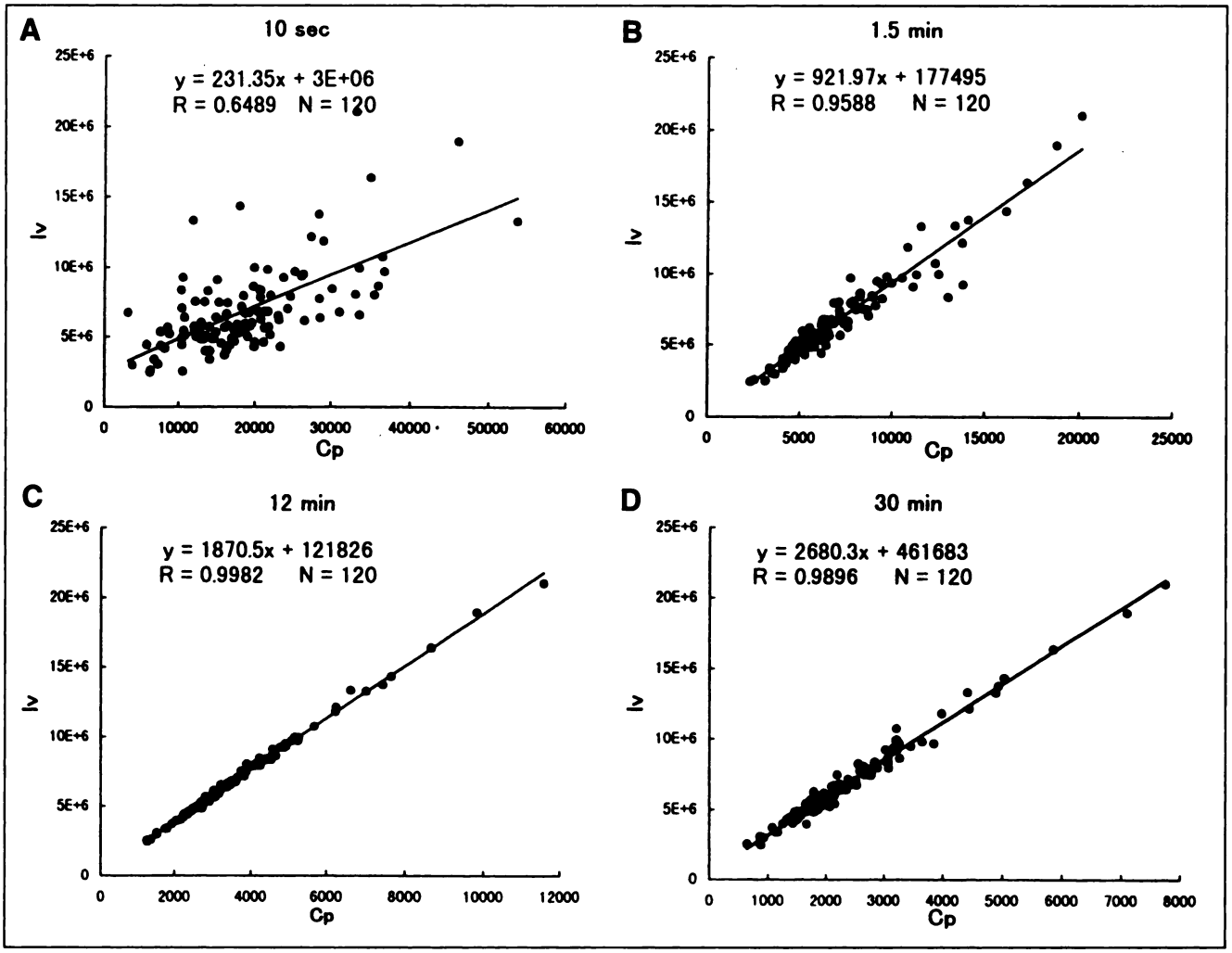

FIGURE 1. Correlation analysis between each arterial plasma radioactivity (Cp in cps/g) and real IV (in cps/g × s) obtained by multiple arterial blood sampling is shown. Graphs show 4 of 20 blood sampling points: A, 10 s; B, 1.5 min; C, 12 min; D, 30 min.

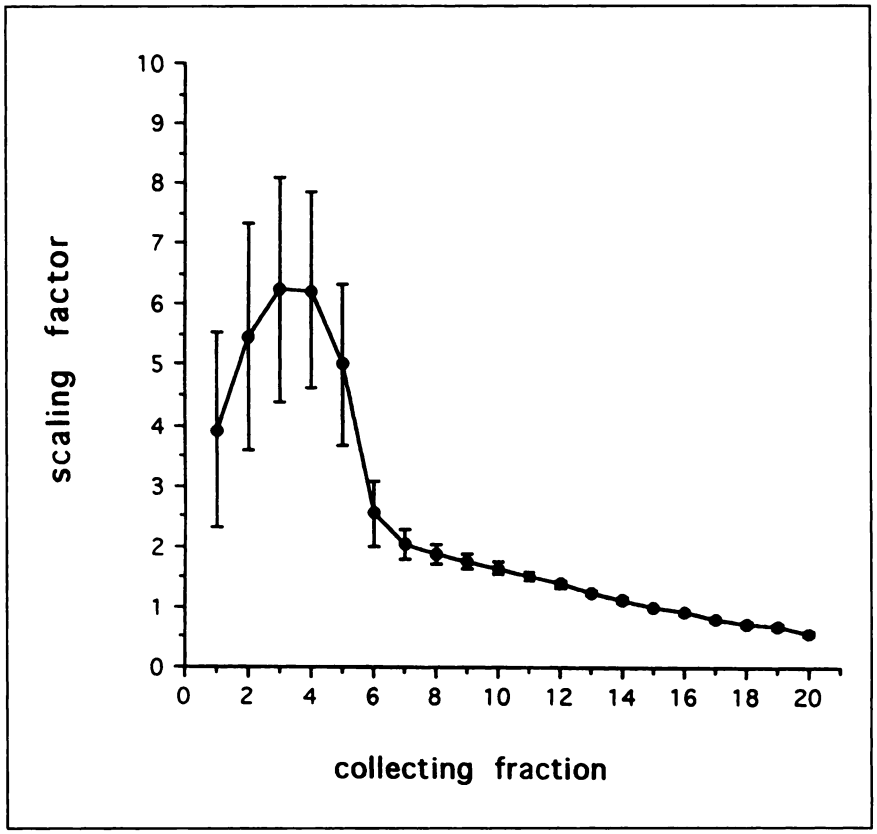

FIGURE 2. Collecting fractions and scaling factors. After time point for use in 1-point blood sampling was determined to be 12 min, measured values at each time point were divided by value at 12 min (collecting fraction no. 15), and means for 120 patients were calculated (Table 1).

arterial and venous blood disappeared was the optimal time point for sampling venous blood (Fig. 3). The arterial blood value at 12 min was estimated from the measured value for venous blood sampled at 40 min (Table 1).

Correlation Between Real IV and Estimated IV by 1-Point Sampling Method. Figure 4 shows the estimated IV by 1-point arterial sampling, and Figure 5 shows the estimated IV by 1-point venous sampling. The percentage error of estimation between the

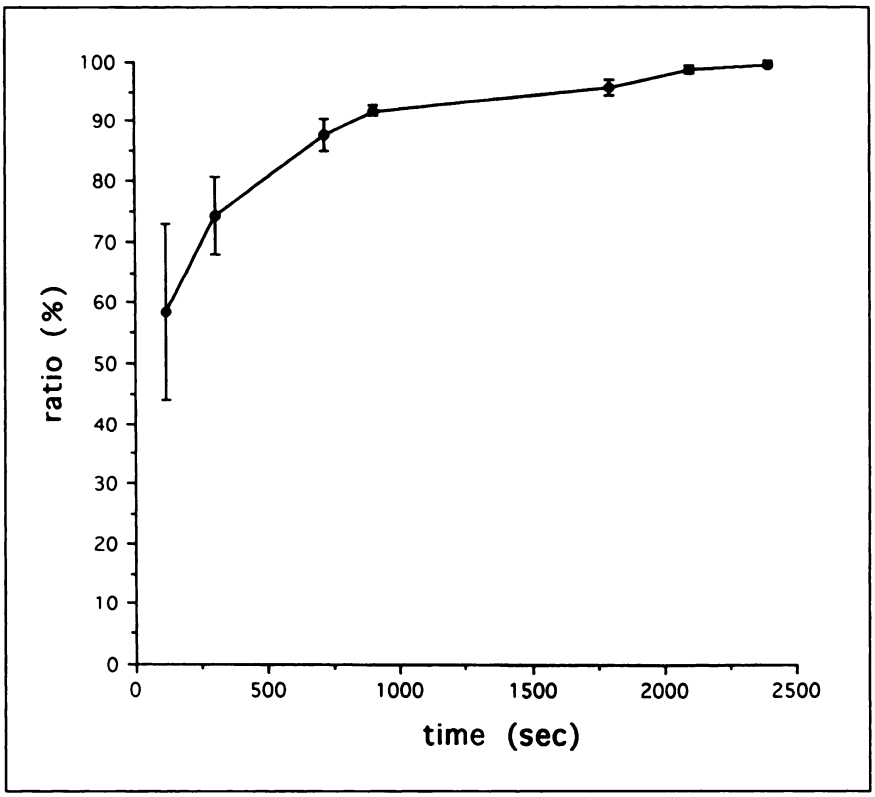

FIGURE 3. Ratios of venous plasma radioactivity to arterial plasma radioactivity at 40 min after FDG injection.

TABLE 1
Reference Table of Scaling Factors

No.	Blood collecting time (s)	Scaling factor (mean)	SD	Fluctuation counting (CV)
1	5	3.92	1.60	40.8
2	10	5.46	1.88	34.5
3	15	6.24	1.84	29.4
4	20	6.23	1.60	25.7
5	30	5.00	1.32	26.3
6	60	2.54	0.54	21.6
7	90	2.02	0.24	12.0
8	120	1.87	0.15	8.0
9	150	1.75	0.12	6.9
10	180	1.65	0.11	6.4
11	240	1.50	0.08	5.0
12	300	1.38	0.06	4.2
13	420	1.23	0.04	3.1
14	540	1.12	0.03	2.3
15	720	1.00	0	0
16	900	0.91	0.02	2.3
17	1200	0.80	0.03	3.5
18	1500	0.72	0.04	5.5
19	1800	0.66	0.04	6.1
20	2400	0.56	0.04	6.8

Scaling factors (arterial plasma radioactivity at each sampling point divided by 12-min arterial plasma radioactivity) were calculated in 120 cases and averaged.

real IV and the estimated IV is presented as Equation 1:

$$\% \text{ error of IV estimation} = \frac{|\text{estimated IV} - \text{real IV}|}{\text{real IV}} \times 100. \quad \text{Eq. 1}$$

Investigation of Nonblood Sampling Method. Ten microliters of FDG solution were counted in triplicate using an autowell γ counter, and the values were averaged. The total injected count was calculated from this average as follows: Counts in 10 μL × 1000 = total counts of injected FDG (10 mL). On the basis of the total counts of injected FDG and the surface area of the body, an equation to estimate IVs of the standard input function was formulated.

RESULTS

A time point for 1-point arterial sampling was established. Figure 1 shows that the 1-point blood radioactivity (cps/g) and the real IV were well correlated 5 min after intravenous FDG injection and suggests that 1-point blood radioactivity is a good indicator of real IV under the nonfixed FDG dose conditions. The CV of the real IV divided by arterial plasma radioactivity at each time point was 3.2 at 9 min, 2.2 at 12 min, 3.2 at 15 min, and 4.6 at 20 min. The CV at 12 min after FDG injection was the smallest and it was most stable at 12 min. On the basis of these results, 12 min after injection was considered the optimal time point for 1-point sampling of arterial blood.

Scaling factors for estimation at each blood sampling time point were determined (Table 1). The estimated input function was obtained by multiplying the mean value (scaling factor) calculated by the arterial blood value at 12 min gotten by 1-point sampling. Table 1 is the reference table used to estimate the input function. After intravenous FDG injection, the venous blood value was initially lower than the arterial blood values, but the difference between those valves decreased gradually, and they were equal after 40 min (Fig. 3). This finding indicated that 40 min after injection was the best time point for 1-point venous blood sampling.

IVs of the estimated input function obtained by the 1-point arterial blood sampling method correlated with the real IV, with $r = 0.997$ and $P < 0.001$ (n = 120) (Fig. 4).

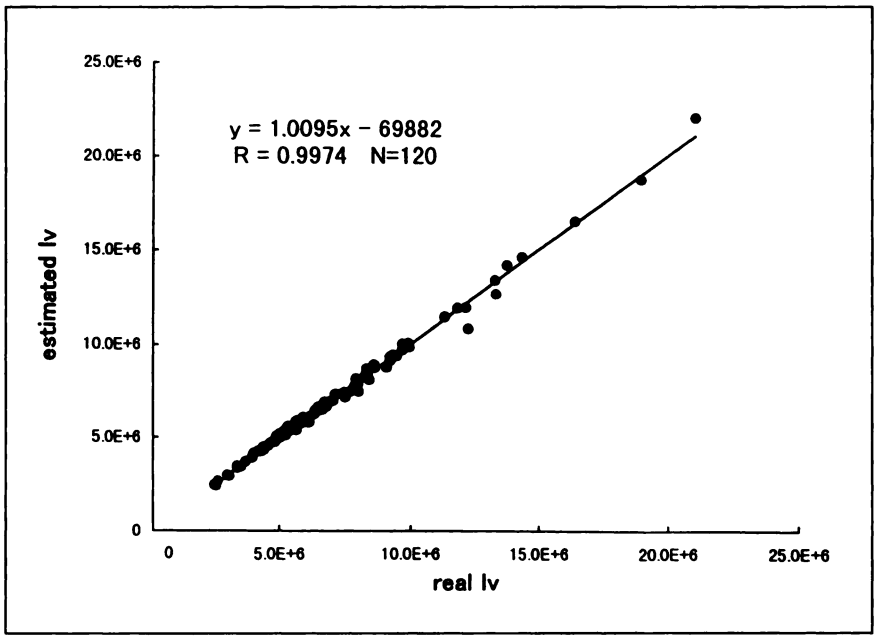

FIGURE 4. Estimated IV by 1-point arterial sampling. Correlation and variation between real IV (cps/g × s) and estimated IV (cps/g × s) obtained by 1-point arterial sampling are shown.

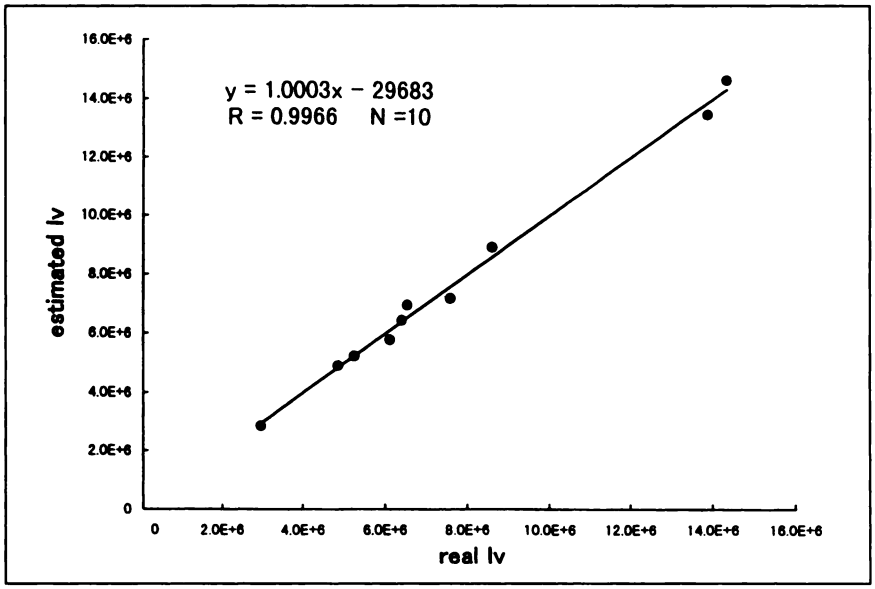

FIGURE 5. Estimated IV by 1-point venous sampling: Correlation and variation between real IV (cpm/g × s) and estimated IV (cpm/g × s) obtained by 1-point venous sampling are shown.

The value of arterial blood sampled 12 min after injection could be estimated by dividing the venous plasma value at 40 min by the scaling factor 0.56 calculated in Table 1. The estimated IV by the 1-point venous blood sampling method correlated with the real IV, with $r = 0.997$ and $P < 0.001$ (n = 10) (Fig. 5). Thus, there was very good correlation for each method. As a result, the percentage errors of IV estimation by 1-point sampling were 1.70% (n = 120) for arterial blood at 12 min and 3.64% (n = 10) for venous blood at 40 min. Figure 6 summarizes the results.

With regard to the nonsampling method of estimating IVs of the input function, the CV for the mean value of 30 cases calculated by the equation considering the surface area of the body was 13.75, indicating insufficient reproducibility.

$$A = \frac{F \times D}{S}, \qquad \text{Eq. 2}$$

where A is 12-min arterial plasma radioactivity (cps/g), S is body surface area (m^2), D is total injection dose of FDG (cps), and F is a constant (m^2/g).

DISCUSSION

The 1-point blood sampling technique provides data comparable with more elaborate serial arterial sampling, and the results are applicable to the procedure for calculating CMR_{glc}. Glucose metabolism is determined using common convolution equations with the serial radioactivity that had been calculated using serial scaling factors (Table 1). The SD of the scaling factor consisting of 6 points between 5 s and 1 min is large (Fig. 2), but, because the period is only 1 min, it would affect the estimated IV less. These errors of the scaling factor with the initial 6 time points would strongly affect k1 in the 3-compartment model (*2,3*). However, this can be minimized by standardizing initial conditions such as the intravenous injection rate. Arterial data obtained in the order of second during this period are not usually used for convolution.

Twenty blood sampling points are required for obtaining the input function by the routine method. Phillips et al. (*6*) have discussed the minimum number of plasma samples required, and they proposed an improved method with several arterial samplings. As long as multiexponential

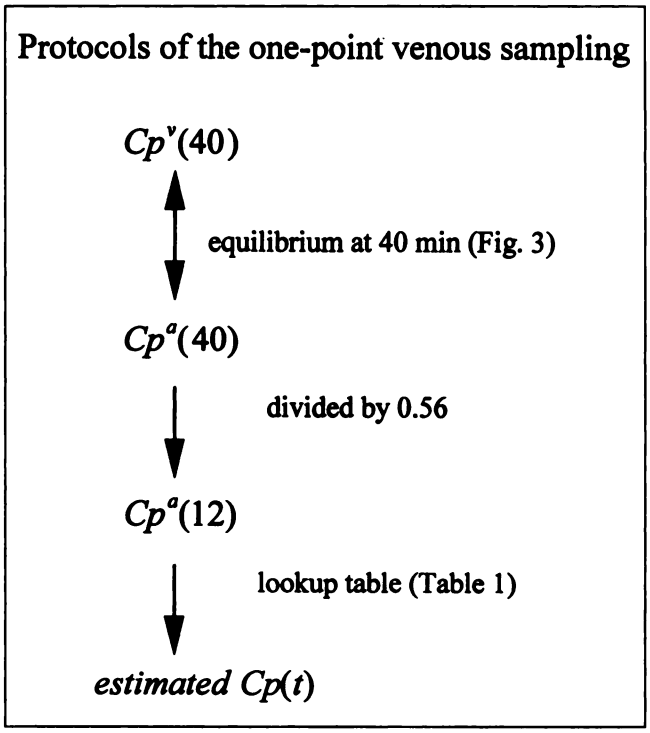

FIGURE 6. Protocols of 1-point venous sampling. Factor 0.56 means scaling factor at 40 min. $Cp^a(12)$ and $Cp^a(40)$ mean values of arterial plasma radioactivity at 12 and 40 min, respectively. $Cp^v(40)$ means value of venous plasma radioactivity at 40 min.

functions are based (*4,6*), the single sampling method is impossible. On the basis of inductive reasoning from our arterial sampling of 120 patients, the feature of the input function infused constantly for 40 s indicated that variation of the plasma radioactivity became stable 5 min after FDG injection and that there was almost no major variation of decease in the activity after 9 min. Thus, the use of a common shape of input function is 1 approach that not only simplifies the procedure but also minimizes potential error sources associated with multiple blood sampling and measurement. Using only a single blood sample, 2 major conditions may be cited. One may be the speed of intravenous FDG injection during the early period; the other may be affected by the systemic circulation. On the basis of our results, the susceptive period affected by these factors may go on by 12 min. Although individual variation of the systemic circulation may become predominant after 12 min, individual features of the decrease in activity are similar, and the radioactivity gradually becomes small. At this time point, a constant value for integration of the input function was obtained even when the sampling period was extended to >40 min. Therefore, the calibration curve remained stable after 40 min, permitting easy estimation of IVs of the input function.

The shape of the input function is potentially altered by physiologic conditions of organs that participate in the metabolism of glucose, and it is important for clinical applications to confirm the validity of the simplified methods in abnormal physiologic conditions such as prolonged hypo- or hyperglycemia. In fact, the scaling factors were the same for patients with blood glucose levels ranging from 60 to 367 mg/dL, indicating that the shape of the input function did not change with changes in the blood glucose levels of these patients. When the same amount of radioactivity of FDG was administered to patients with hypo- or hyperglycemia, the blood radioactivity tended to be low in the former and high in the latter patients. Therefore, on an individual basis, the nonblood sampling method would be potentially violated in these patients. However, this problem can be resolved by 1-point sampling.

To establish the optimal time point for 1-point arterial sampling, we initially planned to select the 1 of 20 time points at which the radioactivity count in the arterial plasma sample exhibited the highest correlation with the real IV obtained by multiple arterial samplings based on the equations representing correlation (Fig. 1). Good correlation was obtained 5 min after FDG injection and thereafter, at any sampling time point after 5 min. Variation associated with differences in the amount of administered FDG exhibited linearity on regression analysis (n = 120) and was not problematic. However, selection of the time point solely on the basis of the calculated value of the correlation coefficient was somewhat risky, because, even though the correlation was good, IVs of the estimated input function and those of the real input function were not necessarily consistent. Therefore, using values obtained by the current method of 20 consecutive blood samplings in 120 patients, the real IVs were divided by the measured value at each time point, and the time point at which the obtained value exhibited the least variation was selected. The CV tended to increase before and after 12 min. Thus, scaling factors were determined and the input function could be estimated using scaling factors.

In investigating the venous blood sampling method, which is less invasive than arterial blood sampling, arterial blood and venous blood were collected simultaneously at 7 time points after intravenous FDG injection (120, 300, 720, 900, 1800, 2100, and 2400 s), and differences in plasma levels over time were examined (Fig. 3). The difference between levels decreased gradually to almost zero ~40 min after intravenous FDG injection. Similar results have been reported by Ohtake et al. (*8*). The arterial plasma level at 12 min could be estimated by dividing the venous plasma value at 40 min by 0.56, which is the scaling factor for the 40-min arterial plasma value (Fig. 6). Therefore, estimation of IVs by the venous blood sampling method was also possible. IVs of the input function estimated by the 1-point venous blood sampling method were well correlated with those calculated by the multiple arterial blood sampling method, and the percentage error of IV estimation was 3.64% (Fig. 5). For the nonblood sampling methods that can be applied to PET examination without causing any pain to patients, we attempted to estimate IVs of the input function considering body surface area and other factors but did not obtain adequate results.

Many simple procedures for the image-derived input function obtained from the large vascular structures have been developed; however, care should be taken in using image-derived input functions without appropriate quality control, such as venous blood samples (*9*). Quantification based on the 1-point sample method can be applied to various fields using FDG PET. Although normalized CMR_{glc} or ratios may be a better diagnostic index, accurate quantification is very important for monitoring response to therapy in oncology patients and reproducing functional impairment of affected brain regions in focal or diffuse disorders in dementia (*10,11*). In combination with our simple method for calculating rate constants (*12*) based on Gjedde-Patlak plotting (*13,14*), rate constants (k1, k2, and k3) can be obtained easily, and our method may be applicable to multitask FDG PET studies (*15–17*).

CONCLUSION

The 1-point blood sampling method for FDG PET does not require measurement of the dynamics in Cp or fixing the FDG dose. We conclude that the 1-point sampling method works in a manner that is comparable with serial arterial sampling and should be useful for clinical PET.

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