Annals of Nuclear Medicine Vol. 15, No. 3, 203–207, 2001

Double-injection FDG method to measure cerebral glucose metabolism twice in a single procedure

Sadahiko NISHIZAWA,* Hiroto KUWABARA,** Makoto UENO,*
Taro SHIMONO,* Hiroshi TOYODA* and Junji KONISHI*

*Department of Nuclear Medicine and Diagnostic Imaging, Graduate School of Medicine, Kyoto University, Kyoto, Japan
**Health Science Center, West Virginia University, West Virginia, USA

[^{18}F]fluorodeoxyglucose (FDG) and positron emission tomography (PET) may be used to examine changes in cerebral glucose metabolism in two physiological conditions. We proposed and evaluated a double injection-single session FDG method with biological constraints for this purpose. ***Methods:*** Simulated brain time-radioactivity curves (TACs) generated by using a plasma TAC from an actual study and physiological combinations of input values in a kinetic model were analyzed to evaluate the accuracy of the proposed method. The reproducibility of the estimated values obtained by this method was tested in five normal volunteers who were studied with a dynamic PET scan and two injections of FDG in a single session while fasting. ***Results:*** The simulation study showed that the estimated values obtained by the proposed method agreed well with the input values. In the human study, plasma glucose levels were 5.3 ± 0.2 and 5.0 ± 0.2 mM in the first and second measurements, respectively. The difference between the plasma glucose measurements was small but statistically significant ($p < 0.05$). Although no systematic deviations were noted in K^*_1 or rCMRglc, there were small deviations in K* (less than 10%) and LC (less than 5%) with a statistical significance ($p < 0.01$). ***Conclusion:*** The deviation between the measurements in K* and LC seemed to relate to the difference in the plasma glucose level. The double-injection FDG method with biological constraints can be used to estimate rCMRglc and LC sequentially in a single PET scanning session.

Key words: positron emission tomography, constrained FDG method, double-injection, kinetic analysis

INTRODUCTION

[^{18}F]FLUORODEOXYGLUCOSE (FDG) and positron emission tomography (PET) may be used to examine changes in the regional cerebral glucose consumption rate (rCMRglc) in either two physiological or two cognitive conditions. The double injection-single session procedure is expected to yield more accurate estimates of changes than the single injection-two session procedure by reducing intrasubject errors between the measurements done on separate days.[1–3] Nevertheless, the double-injection procedure may suffer uncertainties due to the increased number of parameters to estimate in order to cope with the radioactivity in the brain remaining from the first injection. The constrained FDG method requires one less parameter to estimate and shorter scan duration.[4] It is hoped that the constrained method will help overcome the potential uncertainties, and this method can yield an independent estimate of the lumped constant (LC) which may change in diseased conditions[5,6] and in relation to the plasma glucose level.[7,8]

We devised a kinetic model of the double-injection FDG method in which the constrained method was used to estimate the remaining radioactivity in the brain from

Received November 30, 2000, revision accepted February 22, 2001.

For reprint contact: Sadahiko Nishizawa, M.D., Ph.D., Biomedical Imaging Research Center, Fukui Medical University, 23 Shimoaizuki, Matsuoka-cho, Yoshida-gun, Fukui 910–1193, JAPAN.

E-mail: sadahiko@fmsrsa.fukui-med.ac.jp

the first injection. The accuracy and reproducibility of the proposed method were evaluated by analyzing simulated noisy brain data and actual PET data in normal subjects who received two injections of FDG while fasting.

MATERIALS AND METHODS

Theory

According to a three-compartment model for the kinetics of FDG, the total radioactivity in the brain ($M_T(t)$) after the first injection of FDG (t = 0) is given by the following equation[4]:

$$M_T(T) = K^*_1\left[A_1 \int_0^T Ca(u)\, e^{-b_1 u} du + A_2 \int_0^T Ca(u)\, e^{-b_2 u} du\right] + V_0 Ca(T) \quad [1]$$

where Ca(t) is the radioactivity of FDG in plasma at time t, K^*_1 is the rate constant for unidirectional plasma clearance of FDG, V_0 is the correction term for the intravascular radioactivity, and

$$b_{1,2} = (k^*_2 + k^*_3 + k^*_4 \pm ((k^*_2 + k^*_3 + k^*_4)^2 - 4k^*_2 k^*_4)^{(1/2)})/2 \quad [2]$$

$$A_1 = (b_2 - k^*_2)/(b_2 - b_1), \text{ and } A_2 = (b_1 - k^*_2)/(b_1 - b_2) \quad [3]$$

where k^*_2 is the rate constant for fractional brain-blood clearance of FDG, k^*_3 is the phosphorylation coefficient of FDG, and k^*_4 is the dephosphorylation coefficient of FDG.

After the second injection at t_2, the total radioactivity in the brain is given as the sum of the radioactivity from the second injection (X(t)) and the radioactivity remaining from the first injection (Y(t)) as follows:

$$X(T) = K^*_1\left[A_1 \int_{t_2}^T Ca(u)\, e^{-b_1 u} du + A_2 \int_{t_2}^T Ca(u)\, e^{-b_2 u} du\right] + V_0 Ca(T) \quad [4]$$

$$Y(T) = M_e(t_2)\,[A_1 e^{-b_1 T} + A_2 e^{-b_2 T}] + M_m(t_2)\,[B_1 e^{-b_1 T} + B_2 e^{-b_2 T}] \quad [5]$$

$$M_T(T) = X(T) + Y(T) \quad [6]$$

where $Me(t_2)$ and $M_m(t_2)$ are the concentrations of FDG and FDG-6-phosphate in the brain at the time of the second injection, respectively, and

$$B_1 = A_1 (k^*_2 + k^*_3 - b_1)/k^*_3, \text{ and } B_2 = A_2 (k^*_2 + k^*_3 - b_2)/k^*_3 \quad [7]$$

In the constrained method,[4] the transport and phosphorylation ratios (τ and φ, respectively) of FDG to glucose are assumed to be real constants (we chose $\tau = 1.1$ and $\varphi = 0.3$ in this study). The half-saturation constant for glucose transport across the blood-brain barrier (K_t) and brain water volume (V_d) are also constant and were set at 4.8 mM and 0.78 m*l*/g, respectively. The LC, k^*_2 and k^*_3 were then replaced in terms of the net clearance rate, K*, and K^*_1 as follows:

$$LC = \varphi + (\tau - \varphi)\, K^*/K^*_1, \quad [8]$$

$$k^*_2 = (K^*_1 + \mu K^*)/V_d, \quad [9]$$

$$k^*_3 = K^* k^*_2/(K^*_1 - K^*) \quad [10]$$

where μ is given by $\tau C_p/(LC\ K_t)$ and C_p is the plasma glucose concentration.

Simulation study

Simulated time-radioactivity curves (TACs) of the brain for 120 minutes were generated by means of equations [1] through [10]. The time of the second injection (t_2) was set at 70 minutes. K* ranged between 0.01 and 0.05 m*l*/g/min and K^*_1 ranged between 0.03 and 0.16 m*l*/g/min, whereas k^*_4 was fixed to 0.0068/min and V_0 to 0.036 m*l*/g. Gaussian noise (mean ± SD: 0 ± 2% and 0 ± 4%) was added to a total of 100 noiseless TACs to generate noisy data sets. We used the actual TAC of plasma (Ca(t)) obtained from a subject who received two injections of FDG at 0 and 70 minutes. The feasibility of the proposed method was evaluated by comparing the estimated values for K*, K_1*, LC and rCMRglc with the input values, and the effects of scan duration on the estimated values were also examined. We fixed V_0 of the second measurement to the estimated V_0 value of the first measurement, and k_4* was also fixed to 0.0068/min both for the first and second measurements. Errors in K*, K^*_1, LC and rCMRglc caused by the errors in fixed V_0 and k_4* were also evaluated.

Human study

Five normal subjects (20–29 year-old males) underwent a dynamic PET scan for 120 minutes with two injections of FDG at 0 and 70 minutes while fasting (Fig. 1). The

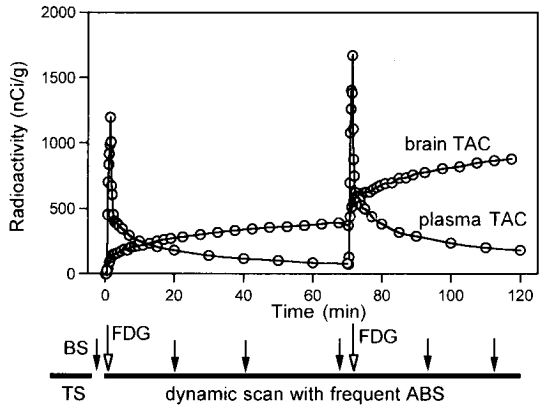

Fig. 1 Typical time-radioactivity curves (decay corrected) from brain and plasma are shown with a simplified schema of the procedure. A dynamic scan for 120 minutes was performed with two injections of FDG at 0 and 70 minutes. A transmission scan for attenuation correction was obtained just before the dynamic scan. Frequent arterial blood sampling was performed during the scan. Plasma glucose concentration was measured three times for each measurement. TS: transmission scan. BS: measurement of plasma glucose concentration. ABS: arterial blood sampling.

Table 1 The results of the simulation study (reliability of the method)

Noise	Analyzed data duration (min)	K*	K^*_1	LC	rCMRglc
		first measurement			
2%	0–30	0.1 ± 3.6	0.1 ± 1.8	0.0 ± 1.8	0.1 ± 2.2
	0–40	0.1 ± 1.9	0.1 ± 1.8	0.0 ± 1.3	0.1 ± 1.2
	0–50	0.0 ± 1.5	0.0 ± 1.7	0.0 ± 1.2	0.0 ± 1.0
4%	0–30	−0.4 ± 5.2	0.0 ± 3.3	−0.4 ± 3.0	−0.1 ± 3.0
	0–40	0.0 ± 3.8	−0.2 ± 3.5	0.0 ± 2.7	0.0 ± 2.3
	0–50	0.3 ± 2.7	−0.1 ± 3.4	0.2 ± 2.2	0.1 ± 2.0
		second measurement			
2%	65–100	−0.3 ± 6.7	−2.2 ± 6.6	0.8 ± 3.1	−1.0 ± 6.0
	65–110	−0.2 ± 4.2	−1.9 ± 6.7	0.7 ± 2.7	−0.9 ± 4.8
	65–120	0.1 ± 3.8	−1.9 ± 6.7	0.9 ± 2.5	−0.8 ± 4.8
	60–110	0.2 ± 3.9	−0.8 ± 5.5	0.4 ± 2.5	−0.2 ± 3.9
	70–110	−0.1 ± 6.8	−2.7 ± 11.6	1.2 ± 3.6	−1.3 ± 8.8
4%	65–100	0.9 ± 12.3	−1.1 ± 11.2	0.5 ± 5.8	0.5 ± 11.2
	65–110	−0.9 ± 8.3	−1.4 ± 11.4	−0.1 ± 4.6	−1.0 ± 8.8
	65–120	−0.7 ± 5.5	−1.2 ± 11.0	−0.1 ± 4.2	−0.8 ± 7.3
	60–110	−0.5 ± 6.0	−0.2 ± 7.8	−0.2 ± 4.1	−0.3 ± 5.5
	70–110	−1.0 ± 12.4	−2.1 ± 21.8	0.3 ± 7.1	−1.4 ± 16.5

Values are expressed as the mean ± SD of % differences between the estimated and input values.
% differences = 100 × (estimated − input)/input.

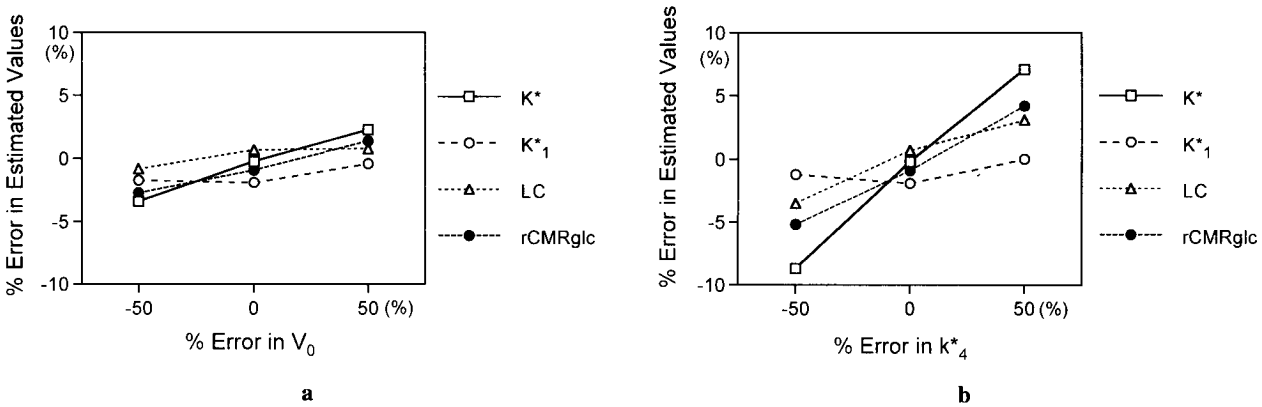

Fig. 2 Percentage errors in estimated K*, K^*_1, LC and rCMRglc of the second measurement caused by the errors in V_0 (a) and k^*_4 (b) were shown. All parameters were insensitive to errors in V_0 and k^*_4.

subject's head was lightly immobilized in a head holder with belts and sponges for fixation. A total of 260 MBq of FDG was divided into two doses and subjects received about 150 MBq for the first scan and about 110 MBq for the second scan. The dynamic PET scan was performed on an Advance scanner (GE Medical Systems, Milwaukee, WI) in a high sensitivity 2D mode and included six 30-sec, seven 1-min, five 2-min, ten 5-min, six 30-sec, seven 1-min, five 2-min and six 5-min scans. Images were reconstructed by a filtered back-projection method with a Hanning filter having a cutoff value of 0.5 cycles/pixel, resulting in reconstructed resolution of 6.0 mm full width at half maximum. Before the dynamic scan, a transmission scan was performed for 10 minutes with two standard rod sources of $^{68}Ge/^{68}Ga$ for attenuation correction. Fifty-two arterial blood samples were drawn through a small catheter inserted into the brachial artery every 10 seconds for the first 3 minutes after each injection, then at gradually increased intervals (20 seconds to 10 minutes) during the scan. Plasma glucose levels were measured just before and at 20 and 40 minutes after each injection. We checked the head position before and after the dynamic scan by means of fixed laser beams and confirmed that the movement of each subject was as small as about 3 mm.

Three pairs of regions of interest (ROIs), about 5 cm^2 each in size, were drawn manually on the bilateral frontal cortices in three slices of summed PET images and applied to dynamic PET images to obtain regional brain

Table 2 The results of the human study (bias and errors between the measurements)

Analyzed data duration (min)	K*	K^*_1	LC	rCMRglc
first/second				
0–30/65–100	11.2 ± 9.6	−0.2 ± 8.6	5.7 ± 4.1	0.3 ± 5.2
0–30/65–110	8.9 ± 9.4	−0.6 ± 8.7	4.7 ± 3.8	−1.0 ± 5.2
0–30/65–120	7.3 ± 9.2	−1.0 ± 8.9	4.1 ± 3.6	−2.0 ± 5.3
0–40/65–110	10.1 ± 9.3	−1.6 ± 8.9	5.7 ± 3.8	−0.9 ± 5.2
0–40/65–120	8.5 ± 9.0	−2.0 ± 9.1	5.1 ± 3.7	−1.9 ± 5.3

Values are expressed as the mean and SD of % differences between the first and second measurements.
% differences = 2 × 100 × (2nd − 1st)/(2nd + 1st).

Table 3 The results of the human study (estimated values)

	first (0–30 min)	second (65–110 min)	
BS (mM)	5.3 ± 0.2	5.0 ± 0.2	$p < 0.05$
K* (ml/g/min)	0.041 ± 0.004	0.044 ± 0.003	$p < 0.01$
K^*_1 (ml/g/min)	0.117 ± 0.011	0.116 ± 0.009	ns
LC	0.58 ± 0.02	0.61 ± 0.03	$p < 0.01$
rCMRglc (μmol/100 g/min)	37.1 ± 2.8	36.7 ± 1.9	ns

K*, K^*_1, LC and rCMRglc are average values from frontal cortices of 5 subjects.
BS: plasma glucose level, ns: not significant

TACs. The reproducibility of two measurements of cerebral glucose metabolism by this method was evaluated by the mean (bias) and SD (error) of percentage differences between estimated values of the first and second measurements.

The study was performed according to the guidelines of the ethical committee of Kyoto University Hospital for human studies, and all subjects gave written informed consent.

RESULTS

The results of the simulation study are summarized in Table 1. Errors in the estimates became larger when analyzing data for shorter scan duration and/or data with a higher noise level, but hardly any systematic bias was noted in any of the estimates both in the first and second measurements for any analyzed data duration or noise level. All estimates in the second measurement were insensitive to errors in V_0 and k^*_4 (Figs. 2a and 2b).

The results of the human study are summarized in Tables 2 and 3. Plasma glucose levels were 5.3 ± 0.2 and 5.0 ± 0.2 mM in the first and second measurements, respectively. The difference between the plasma glucose measurements was small but statistically significant ($p < 0.05$). No bias was noted in K^*_1 and rCMRglc between the first and second measurements, whereas a small bias was observed in K* (less than 10%) and LC (less than 5%). The differences in K and LC between the serial measurements were statistically significant ($p < 0.01$).

DISCUSSION

The simulation study showed that the proposed FDG method yielded accurate estimates of kinetic parameters for cerebral glucose metabolism from data with realistic noise levels and circulation times of 30 and 45 minutes for the first and second measurements, respectively. This means that two serial but independent measurements of cerebral glucose metabolism can be done in 90 to 120 minutes, including more than 15 minutes in which a steady state for the second condition is established. The validity of the method was also demonstrated in the actual PET studies, showing the error in repeated measurements of rCMRglc to be as small as 5%, as expressed by the SD of percentage differences between the first and second measurements.

The reproducibility of rCMRglc in a resting condition measured by [^{11}C]deoxyglucose and PET twice in two hours was reported to be 5.5% to 8.7% as expressed by the coefficient of variation of repeated measurements,[1] but intrasubject variation is greater for measurements performed on separate days (−25%).[2] Cerebral glucose metabolism may fluctuate to some extent even in a resting condition but seems to be rather stable within a few hours. Measurements should therefore be repeated within a few hours to relate a finite change in cerebral glucose consumption to any physiological and/or pharmacological effects. To perform two FDG studies in a few hours, a kinetic modeling is necessary to deal with radioactivity remaining in the brain from the first injection, although this may be another source of error.

Chang et al.[3] reported a double-injection FDG protocol to measure rCMRglc in two behavioral states. They performed two static PET scans each after an injection of FDG with arterialized venous blood sampling, and reported the SD of percentage differences between same behavioral states in rCMRglc to be about 5%, which was comparable to our results. In their kinetic model, however, they assumed an instantaneous change in the physiological state from the first to the second condition. In some circumstances, the change may be gradual and it takes time to establish a new steady state for the second condition. This may cause errors. On the other hand, our kinetic model utilizing the constrained method enabled independent estimation of kinetic parameters for the second condition. Moreover, in addition to measuring rCMRglc, it can measure other parameters describing cerebral glucose metabolism, K*, K^*_1 and LC, which may have important implications for the understanding of the physiological and pharmacological effects on cerebral glucose metabolism.

The proposed method with biological constraints based

on Michaelis-Menten kinetics reduced the number of parameters to be estimated. This enabled independent assessment of model parameters for the second condition by incorporating $M_e(t_2)$ and $M_m(t_2)$ in the model to be estimated. The biological constraints employed between FDG and native glucose, the transport ratio (τ) across blood-brain barrier and ratio of phosphorylation (φ) by hexokinase, are likely to remain constant over a wide range of physiological conditions with little regional or intersubject variation.[9] By applying biological constraints, the LC can also be calculated individually and independently from K^*, K^*_1, τ, and φ (equation [8]) for two measurements, which is another advantage of this method. Because the LC is known to change in diseased conditions and in relation to the plasma glucose level,[5–8] the proposed method seems to yield more accurate estimates of model parameters.

In the study of normal subjects who received two injections of FDG in a single dynamic PET scanning session, there was no significant difference between the first and second measurements in K^*_1 and rCMRglc. Nevertheless, slight but significant differences were observed in both K^* and LC. K^* and LC are known to change in relation to the plasma glucose level,[7,8] whereas rCMRglc remains relatively stable.[10] Therefore, these small differences in K^* and LC may be caused by the small change in the plasma glucose level because all the subjects, even after an overnight fast, had a slight but consistent decrease in the plasma glucose level during the scan. Physiological and mental stresses may cause a slight increase in the plasma glucose level at the beginning of the scan, followed by a gradual decrease to the baseline level. Kinetic parameters may be sensitive to changes in the plasma glucose level and our method may be useful for detecting such a small effect.

CONCLUSION

Kinetic parameters, including the LC, of cerebral glucose metabolism in two different conditions can be reliably and sequentially estimated by using the double-injection FDG method in a single PET scanning session. This method enables a better understanding of the changes in cerebral glucose metabolism caused by various physiological and pharmacological effects.

REFERENCES

1. Reivich M, Alavi A, Wolf A, Greenberg JH, Fowler J, Christman D, et al. Use of 2-deoxy-D[1-^{11}C]glucose for the determination of local cerebral glucose metabolism in humans: variation within and between subjects. *J Cereb Blood Flow Metab* 1982; 2: 307–319.
2. Duara R, Gross-Glenn K, Barker WW, Chang JY, Apicella A, Loewenstein D, et al. Behavioral activation and the variability of cerebral glucose metabolic measurements. *J Cereb Blood Flow Metab* 1987; 7: 266–271.
3. Chang JY, Duara R, Barker W, Apicella A, Yoshii F, Kelley RE, et al. Two behavioral states studied in a single PET/FDG procedure: error analysis. *J Nucl Med* 1989; 30: 93–105.
4. Kuwabara H, Evans AC, Gjedde A. Michaelis-Menten constraints improved cerebral glucose metabolism and regional lumped constant measurements with [^{18}F]fluorodeoxyglucose. *J Cereb Blood Flow Metab* 1990; 10: 180–189.
5. Gjedde A, Wienhard K, Heiss WD, Kloster G, Diemer NH, Herholz K, et al. Comparative regional analysis of 2-fluorodeoxyglucose and methylglucose uptake in brain of four stroke patients. With special reference to the regional estimation of the lumped constant. *J Cereb Blood Flow Metab* 1985; 5: 163–178.
6. Reutens DC, Gjedde AH, Meyer E. Regional lumped constant differences and asymmetry in fluorine-18-FDG uptake in temporal lobe epilepsy. *J Nucl Med* 1998; 39: 176–180.
7. Schuier F, Orzi F, Suda S, Lucignani G, Kennedy C, Sokoloff L. Influence of plasma glucose concentration on lumped constant of the deoxyglucose method; effects of hyperglycemia in the rat. *J Cereb Blood Flow Metab* 1990; 10: 765–773.
8. Suda S, Shinohara M, Miyaoka M, Lucignani G, Kennedy C, Sokoloff L. The lumped constant of the deoxyglucose method in hypoglycemia: effects of moderate hypoglycemia on local cerebral glucose utilization in the rat. *J Cereb Blood Flow Metab* 1990; 10: 499–509.
9. Dienel GA, Cruz NF, Mori K, Holden JE, Sokoloff L. Direct measurement of the lambda of the lumped constant of the deoxyglucose method in rat brain: determination of lambda and lumped constant from tissue glucose concentration or equilibrium brain/plasma distribution ratio for methylglucose. *J Cereb Blood Flow Metab* 1991; 11: 25–34.
10. Orzi F, Lucignani G, Dow-Edwards D, Namba H, Nehlig A, Patlak CS, et al. Local cerebral glucose utilization in controlled graded levels of hyperglycemia in the conscious rat. *J Cereb Blood Flow Metab* 1988; 8: 346–356.