Annals of Nuclear Medicine Vol. 10, No. 3, 323–328, 1996

Simple method to quantify myocardial glucose metabolism from MB ratio in myocardial FDG PET

Jun-ichi NISHIKAWA,* Tohru OHTAKE,* Ikuo YOKOYAMA,** Toshiaki WATANABE,* Toshimitsu MOMOSE* and Yasuhito SASAKI*

*Department of Radiology and **Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan

To provide a simple means of quantifying myocardial glucose metabolism, we tried to estimate the K complex (KC) from the myocardium to background ratio (MB ratio), which was obtained with a single static FDG scan and single venous sampling.

In 48 fasting subjects and 74 subjects under oral glucose loading or insulin clamp, the reference KC was obtained from Patlak analysis by using an input function. We compared the reference KC with the MB ratio at 35 min 45 sec, 45 min 45 sec, and 55 min 45 sec, and with the FDG uptake index (FUI) reported by Tamaki. The correlation between KC and each index was very close during fasting ($r = 0.97$, 0.98, 0.98 and 0.97, respectively $n = 48$), and clinically acceptable during oral glucose loading and insulin clamp ($r = 0.92$, 0.91, 0.90 and 0.93, respectively $n = 74$). The average differences between the reference KC and KC estimated from the simple method were 13%, 10%, 8%, and 13%, respectively, during fasting, and 15%, 14%, 14%, and 16%, respectively, during oral glucose loading and insulin clamp.

Both the MB ratio and FDG uptake index can be used for the simple estimation of myocardial glucose metabolism not only during fasting but also during oral glucose loading and insulin clamp, although the MB ratios at 45 min and at 55 min were slightly better than MB that at 35 min and the FDG uptake index during fasting.

Key words: fluorine-18 FDG, positron emission tomography (PET), heart, myocardial glucose metabolism, K complex, quantitative analysis (MB ratio)

INTRODUCTION

2-(^{18}F)fluoro-2-deoxy-D-glucose (FDG) was first used in positron emission tomography (PET) imaging of the myocardium by Phelps et al.[1] Many early myocardial PET studies were based on the qualitative evaluation of regional FDG uptake and its relation to flow,[2–5] but quantification of regional glucose utilization in the myocardium seemed to hold the potential for providing more reliable information about myocardial viability and cardiomyopathy.

A three-compartment FDG kinetic model for cerebral tissues was introduced by Sokoloff et al.[6] This model was used with PET to estimate local cerebral glucose metabolic rates in humans. Patlak graphic analysis[7,8] and standard nonlinear regression (curve fitting) methods were used to quantify cerebral glucose metabolic rates.[9] The latter two methods could be applied to the heart, but these methods require dynamic PET data and arterial blood sampling.

A simple noninvasive method has already been developed by Gambhir et al. (UCLA group), in which a time activity curve of the left ventricle blood pool is used as the input function.[10] We developed another simple noninvasive method, in which a corrected time activity curve of the descending aorta is used,[11] but these two methods require dynamic PET scaning and computer processing. Tamaki et al. developed a simpler method in which FDG uptake is estimated from % injected dose.[12] This method requires only a single static scan, but can be validated only during fasting, not during glucose loading or insulin clamp. We

Received March 13, 1996, revision accepted June 6, 1996.

For reprint contact: Jun-ichi Nishikawa, M.D., Department of Radiology, University of Tokyo, 3–28–6 Mejirodai, Bunkyo-ku, Tokyo 112, JAPAN.

report a very simple, acceptably accurate method that can be used under any conditions and requires only a single static scan and single venous sampling.

MATERIALS AND METHODS

Preparation of FDG

FDG was synthesized by the method described previously by Ehrenkaufer et al.[13] The radiochemical purity was greater than 95%.

Human subjects and blood sampling

Forty-four subjects (mean age ± s.d., 44.6 ± 17.3) who had less than a 1% likelihood of ischemic heart disease (IHD) based on clinical and laboratory studies (non-IHD)[14] and 78 subjects (61.9 ± 6.3) with IHD were examined. Eighty-two subjects had borderline or abnormal glucose tolerance or hyperinsulinemia (25 non-IHD subjects and 57 IHD subjects). Each patient was informed as to the investigative nature of the study and its potential risks and benefits before informed consent was obtained. The study protocol had been approved by the University of Tokyo's Human Subject Protection Committee.

Forty-eight subjects (9 non-IHD subjects and 39 IHD subjects) had a carbohydrate meal 4–7 hr before the study during the fasting state (FS). Fifty subjects (20 non-IHD subjects and 30 IHD subjects) had a half carbohydrate lunch 2–4 hr before the study and a bottle of 75 g glucose 1 hr before FDG injection during oral glucose loading (OG). Twenty-four subjects (15 non-IHD subjects and 9 IHD subjects) were studied during insulin clamp, in which plasma glucose was equilibrated between 80 and 120 mg/dl by the constant infusion of insulin (more than 1 mU/min/kg) and glucose (more than 6 mg/min/kg).[15] Then 185–370 MBq (5–10 mCi) of FDG was injected intravenously over a 30–60 sec period. Venous blood was sampled seven times, from 13 min to 56 min. To define the time course of equilibration of F-18 activity between red blood cells and plasma, all blood samples were divided into two aliquots. Fluorine-18 activity in whole blood and in plasma was measured in a well counter and corrected for radioactive decay. Plasma glucose concentrations were measured at the beginning, middle and end of the study by using standard enzymatic techniques.

Image acquisition

Subjects were studied with a HEADTOME IV PET scanner (Shimadzu Corp. Kyoto, Japan) with seven imaging planes. In-plane resolution was 4.5 mm at full width at half maximum (FWHM), axial resolution was 9.5 mm at FWHM and sensitivity was 14 and 24 kcps/(μCi/ml), respectively, for direct and cross planes.[16] In all studies, transmission images were acquired in order to correct photon attenuation prior to obtaining the PET emission images. Nineteen dynamic scans were obtained during a 60 min 45 sec period by using the following protocol: five 15 sec, three 30 sec, four 120 sec, four 300 sec and three 600 sec scans.

Calibration and image processing

To obtain a calibration factor relating tomographic measurement of myocardial activity to blood sample activity obtained from the well counter, a cylindrical phantom (20 cm diameter) containing Ga-68 was scanned within a few days of the study.[11] A known volume of activity from the cylinder was also counted in the well counter. All values obtained from PET were converted to cts/min/ml.

Cross-sectional images were reconstructed and corrected for the physical decay of F-18 to the FDG injection time.

The input function was obtained by correcting the time activity curves of the descending aorta for the partial volume effect and the difference between plasma and whole blood counts with the plasma and whole blood counts of a vein sampled seven times.[11]

Corrections

All data were corrected for the effects of the scanner's dead time so as to reduce the error to less than 1%.

Calculation of regional K complex

The three-compartment FDG tracer-kinetic model was used in the present study. The regional myocardial glucose utilization rate (rMGU) can be calculated as rMGU = (Cp/LC)k1k3/(k2 + k3). Cp is the plasma concentration of glucose; LC is the lumped constant that accounts for differences in the transport and phosphorylation of FDG and glucose.[6,9] 0.67 was used for LC.[17] To estimate rMGU, Patlak graphic analysis was employed.[7,8]

The dephosphorylation rate constant (k4) of FDG has been assumed to be zero. Am(t) is tissue activity at time t, Cp(t) is plasma activity at time t, and W is a function of the steady-state volume of the reversible compartments and effective plasma volume. A plot of Am(t)/Cp(t) vs. $\int$ Cp(s)ds/Cp(t) should give a linear relationship at late times with a slope equal to k1k3/(k2 + k3) and a y intercept equal to W. Thus this graphic approach enabled rMGU to be calculated by providing a direct estimate of k1k3/(k2 + k3) from the slope of the linear relationship on the spot.

Tissue activities at seven separate time points (from 13 min 15 sec to 55 min 45 sec) were used to estimate the slope in Patlak analysis in all pixels of seven image planes. We obtained functional transaxial images of the K complex (KC), and calculated the maximal myocardial KC value in each subject.

To estimate KC more simply, we compared it with the ratio of myocardium to background (MB ratio), which was obtained by dividing the maximal myocardial FDG count by the venous plasma FDG count at the same time (MB35 at 35 min 45 sec, MB45 at 45 min 45 sec and MB55 at 55 min 45 sec). This was the simple method used

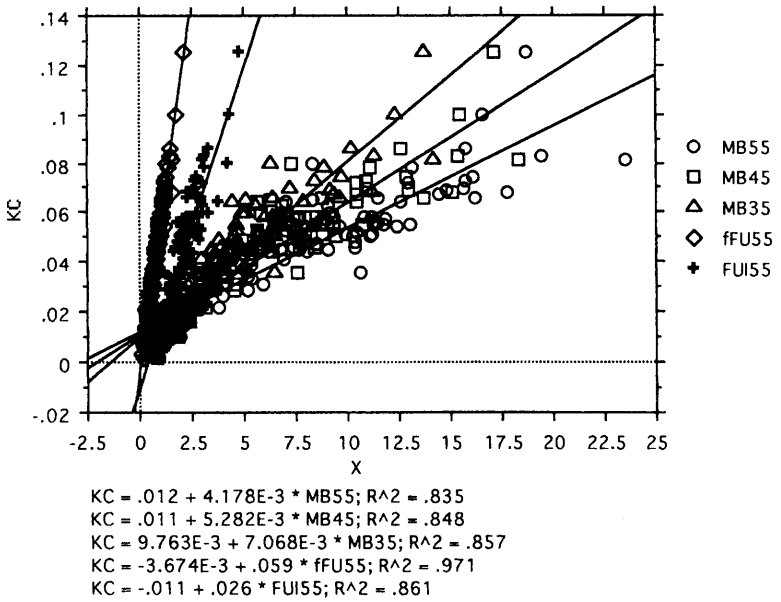

Fig. 1 Relation between K complex (y) and MB55 (x), MB45(x), MB35(x), fFU55 (x) and FUI55 (x) during insulin clamp, oral glucose loading and fasting (n = 122).
The relation between K complex (KC) and fFU55 is very close because the input function is used in fFU55. fFU55 is not really a simple method because arterial blood sampling or dynamic PET scan is needed.

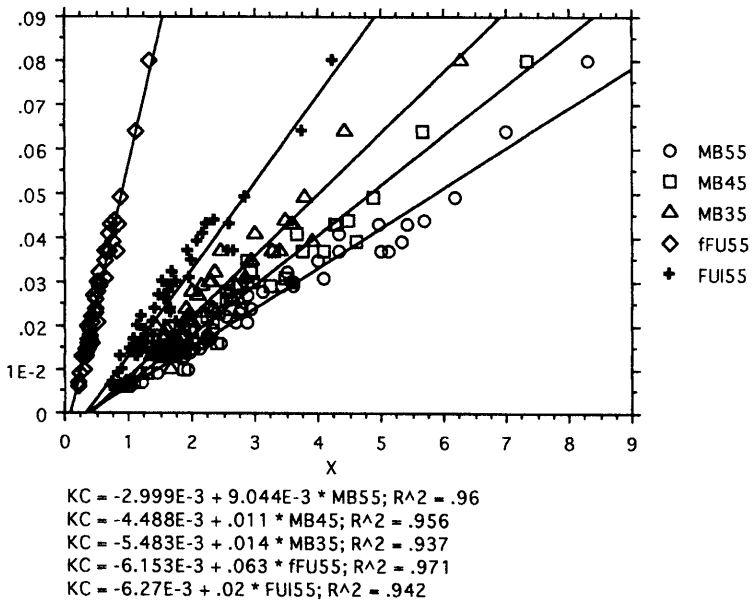

Fig. 2 Relation between K complex (y) and MB55 (x) , MB45 (x), MB35 (x), fFU55 (x), and FUI55 (x) during fasting (n = 48).
The correlation between KC and MB55 was as close as that between KC and fFU55. The correlation between KC and FUI55 was close but slightly less than that between KC and MB55.

for quantification.

To compare our method with the simple method reported by Tamaki, we calculated the FDG uptake index (% dose/100 m*l* of 60 kg of BW) (FUI) and fractional FDG uptake (fFU).[12] Neither method requires dynamic scanning, just a single static scan. Our method uses single venous blood sampling, FUI requires the count of the injected dose, and fFU requires input function. FUI55 (%) = C55 * 100 (m*l*) * BW * 100/dose of FDG (mCi) * CF1 * 60, where C55 is the maximal myocardial FDG count measured at 55 min 45 sec, BW is the patient's body weight and CF1 is the calibration factor between mCi on the Curie meter and cpm/m*l* on the PET images.[12]

fFU55(%) = C55/ $\int$ Cp(t)dt, where $\int$ Cpdt is the inte-

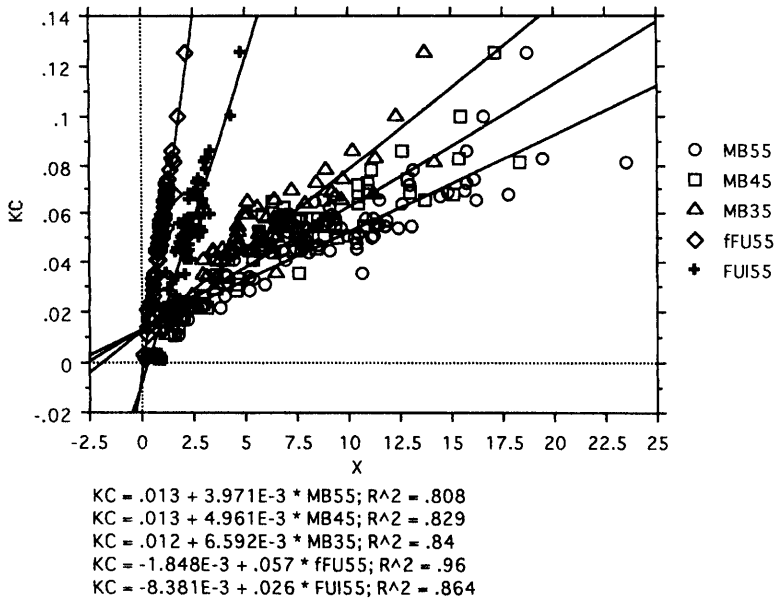

Fig. 3 Relation between K complex (y) and MB55 (x), MB45 (x), MB35 (x), fFU55 (x) and FUI55 (x) during fasting (n = 74).
The correlation between KC and MB55, and KC and FUI55 were close but slightly worse than that for fFU55 because plasma FDG clearance varied in subjects.

Table 1 Comparison of correlation coefficients between K complex and simple methods

total 122 cases	MB35	MB45	MB55	FUI55	fFU55
Pearson	0.926	0.921	0.914	0.928	0.985
Spearman	0.955	0.958	0.959	0.930	0.987
Kendall	0.829	0.835	0.840	0.778	0.918
fasting 48 cases	MB35	MB45	MB55	FUI55	fFU55
Pearson	0.968	0.978	0.980	0.971	0.986
Spearman	0.950	0.964	0.979	0.956	0.981
Kendall	0.838	0.865	0.905	0.835	0.903
oral glucose loading or insulin clamp 74 cases	MB35	MB45	MB55	FUI55	fFU55
Pearson	0.918	0.912	0.901	0.930	0.980
Spearman	0.908	0.912	0.911	0.894	0.974
Kendall	0.763	0.766	0.764	0.734	0.887

MB35: myocardium to background ratio (MB ratio) at 35 min 45 sec
MB45: MB ratio at 45 min 45 sec
MB55: MB ratio at 55 min 45 sec
FUI55: FDG uptake index at 55 min 45 sec
fFU55: fractional FDG uptake at 55 min 45 sec

gral of the FDG plasma values from the time of injection to the mid-scan time (55 min 45 sec).[12]

We compared FUI55 and fFU55 with KC.

We calculated the correlation coefficient by means of Pearson, Spearman and Kendall analyses for MB35, MB45, MB55, FUI55 and fFU55.

We estimated KC from the line obtained by simple linear regression and the MB35, MB45, MB55, fFU55 and FUI55 values in each subject, and calculated the difference value (%): 100 * | obtained KC – true KC | / true KC.

RESULTS

The correlations between KC and MB35, MB45, MB55, FUI55 and fFU55 were good (Table 1, Figs.1–3). The correlation between KC and fFU55 was especially good because the input function was used in fFU55. In all subjects during FS, OG and IC, the correlation coefficient (r) was between 0.91 and 0.93 in MB35, MB45, MB55 and FUI55 according to Pearson's analysis. While this was relatively good, it was not as good as that for fFU55. With Spearman and Kendall analyses, the correlation coefficients (r) for MB35, MB45 and MB55 were better than those for FUI55 but worse than those for fFU55. In subjects during OG or IC, the trend was almost the same. In subjects during FS the correlation coefficient for MB55 was almost the same as that for fFU55 in all analyses and better than those for MB35, MB45 and FUI55 in Spearman's analysis and Kendall's analysis. MB45 was better than MB35 or FUI55 in Spearman and Kendall analyses.

The difference value is shown in Table 2. It was about 15% during OG or IC in MB35, MB45, MB55 and FUI55, and it was about 7% in fFU55. The value was about 10% during FS in MB35, MB45, MB55, FUI55 and fFU55. It was smaller in MB55 than in MB35 ($p < 0.005$) and FUI55 ($p < 0.02$).

Table 2 Difference between estimated K complex and actual K complex

	fasting	oral glucose loading or insulin clamp
MB35	12.5 ± 12.5%	15.2 ± 14.6%
	$p < 0.025$	
MB45	9.8 ± 11.4%	14.0 ± 11.0%
	NS	
MB55	8.4 ± 8.5%	14.3 ± 13.4%
	$p < 0.025$	
FUI55	12.7 ± 9.7%	15.9 ± 12.1%
	$p < 0.001$	
fFU55	7.9 ± 7.0%	6.5 ± 7.2%

fFU55 vs. MB35 $p < 0.01$
MB55 vs. MB35 $p < 0.005$
others NS
paired t-test

fFU 55vs. MB35, MB45, MB55, FUI55
$p < 0.001$
others NS
paired t-test

MB35: myocardium to background ratio (MB ratio) at 35 min 45 sec
MB45: MB ratio at 45 min 45 sec
MB55: MB ratio at 55 min 45 sec
FUI55: FDG uptake index at 55 min 45 sec
fFU55: fractional FDG uptake at 55 min 45 sec

DISCUSSION

The data indicate that the MB ratio can be used as an indicator of FDG uptake and KC in Patlak analysis of myocardium. With this simple index, only a single static scan and single venous blood sampling are necessary.

Compared with conventional quantification methods that require frequent arterial or arterialized venous blood sampling and dynamic PET data, this method makes quantification extremely easy for patients and physicians.

Comparison with other simple methods

In the simple methods reported by Gambhir[10] and ourselves,[11] which require dynamic PET data, subjects need to remain motionless for more than one and a half hours, and some have complained about this. And if an FDG study is performed after an NH_3 study, subjects have to remain on the bed at least 30 minutes before N-13 decay. Further, to obtain the input function from dynamic data, more than 30 minutes of data processing is needed. This may be a burden if more than three FDG studies are performed in a day.

Compared with these methods, the new method allows subjects to relax on the bed between the FDG injection and the beginning of the static scan. FDG can be injected soon after the NH_3 study because N-13 may decay before the beginning of the FDG static scan. In addition, there is no need for data processing.

In terms of the accuracy of estimating KC, this method may be inferior to those mentioned above, especially during oral glucose loading or insulin clamp. The average error in estimating KC by our MB ratio method was about 15% during OG or IC and about 10% during FS. We consider this rough estimation of KC adequate for clinical use.

Comparison with fFU

With the fFU method, KC could be accurately estimated during FS, OG and IC, but this method requires an input function, which is obtained by frequent arterial blood sampling, frequent arterialized venous blood sampling or dynamic PET scan (noninvasive calculation of input function from dynamic data). The fFU method involves the same problem.

Comparison with Tamaki's FUI method

The FUI method is as easy as our MB ratio method. Both need only a single static scan and counting of injected dose, or single venous blood sampling.

Which is better? We think our MB ratio method is slightly better because the error in estimating KC was slightly smaller with our MB ratio method than with the FUI method ($p < 0.02$ during FS, NS during OG or IC) and the r values in Spearman and Kendall analyses were better. In the FUI method, the integral of plasma FDG counts is estimated from the injected dose corrected by body weight, but rapid clearance of blood FDG may result in overestimation of the integral of plasma FDG counts especially in OG or IC. Another consideration is that the clearance of blood FDG may change according to the difference in plasma-glucose and serum insulin levels during OG or IC. Thus during OG and IC, estimates of the integral of plasma counts derived from the injected dose varies. The variation in the middle value was especially large (Figs. 1, 3). Our MB ratio method is also influenced by plasma FDG clearance. During OG or IC the MB ratio value tended to be large because the plasma FDG value decreased. But the variation in the middle value was slightly less than with FUI method. Thus the error in estimating KC decreases slightly with the MB ratio method. Tamaki's method also may be useful during OG or IC if the linear regression line is calculated during OG or IC, although the error may be slightly larger.

And unlike the FUI method, the MB ratio method can be utilized in any facility in the same way.

If the plasma FDG value is estimated from the static image by using the left ventricle blood pool or another method, KC may be estimated for all FDG data without venous sampling by the MB ratio method.

Comparison of MB35, MB45 and MB55

During OG or IC, MB35 and MB45 were almost the same as MB55 in terms of r or the estimate of KC. But during FS, MB55 was slightly better than MB45 (not significant) and MB55 and MB45 was significantly better than MB35, probably because plasma FDG clearance was slow during

fasting. Static data should be collected at least 40 min after FDG injection, especially during fasting. MB45 and MB55 may be the same.

Several problems involved in calculating the true KC in this study were discussed in the previous report.[11] As the partial volume effect in myocardium was not corrected in calculating KC, KC was underestimated. The purpose of this study, however, was to evaluate our simple method (MB ratio) by comparing it with the fractional FDG uptake.

Recently, Nakagawa et al. reported a simple quantitative method for myocardial glucose utilization.[18] A simple and accurate quantitative method is mandatory when using cardiac PET for routine clinical study.

In conclusion, this study demonstrated that the MB ratio can be used to roughly estimate KC and rMGU both during FS and during OG or IC. We consider these rough estimates adequate for clinical use. This method may help to diagnose ischemic viable myocardium or diffuse myocardial disease, and this may contribute to clinical PET.

REFERENCES

1. Phelps ME, Hoffman EJ, Selin CE, Huang SC, Robinson G, MacDonald N, et al. Investigation of (F-18)2-fluoro-2-deoxyglucose for the measurement of myocardial glucose metabolism. *J Nucl Med* 19: 1311–1319, 1978.
2. Marshall RC, Tillish JH, Phelps ME, Huang SC, Carson R, Henze E, et al. Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, F-18-labeled fluorodeoxyglucose and N-13 ammonia. *Circulation* 67: 766–777, 1983.
3. Brunken R, Tillish J, Schwaiger M, Child JS, Marshall R, Mandelkern M, et al. Regional perfusion, glucose metabolism and wall motion in chronic electrocardiographic Q-wave infarctions. Evidence for persistence of viable tissue in some infarct regions by positron emission tomography. *Circulation* 73: 951–963, 1986.
4. Brunken R, Schwaiger M, Grover-Mckay M, Phelps ME, Tillisch J, Schelbert HR. Positron emission tomography detects tissue metabolic activity in myocardial segments with persistent thallium perfusion defects. *J Am Coll Cardiol* 10: 557–567, 1987.
5. Schwaiger M, Brunken R, Grover-Mckay M, Krivokapich J, Child J, Tillisch JH, et al. Regional myocardial metabolism in patients with acute myocardial infarction assessed by positron emission tomography. *J Am Coll Cardiol* 8: 800–808, 1986.
6. Sokoloff L, Reivich M, Keneddy C, Des Rosiers MH, Patlak CS, Pettigrew KD, et al. Tomographic measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 28: 897–916, 1977.
7. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 3: 1–7, 1983.
8. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *J Cereb Blood Flow Metab* 5: 584–590, 1985.
9. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (^{18}F)2-fluoro-2-deoxy-d-glucose: validation of method. *Ann Neurol* 6: 371–388, 1979.
10. Gambhir SS, Schwaiger M, Huang SC, Krivokapich J, Schelbert HR, Nienaber CA, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18 deoxyglucose. *J Nucl Med* 30: 359–366, 1989.
11. Ohtake T, Kosaka N, Watanabe T, Yokoyama I, Moritan T, Masuo M, et al. Noninvasive method to obtain input function for measuring tissue glucose utilization of thoracic and abdominal organs. *J Nucl Med* 32: 1432–1438, 1991.
12. Tamaki N, Yonekura Y, Kawamoto M, Magata Y, Sasayama S, Takahashi N, et al. Simple quantification of regional myocardial uptake of fluorine-18-deoxyglucose in the fasting condition. *J Nucl Med* 32: 2152–2157, 1991.
13. Ehrenkaufer RE, Potocki JF, Jewett DM. Simple synthesis of F-18 labeled 2-fluoro-2-deoxy-D-glucose. *J Nucl Med* 25: 333–337, 1984.
14. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 300: 1350–1358, 1979.
15. Knuuti MJ, Nuutila P, Ruotsalainen U, Saraste M, Harkonen R, Ahonen A, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 33: 1255–1262, 1992.
16. Kanno I, Iida H, Miura S, Yamamoto S, Amano M, Hirose Y, et al. Design concepts and preliminary performances of stationary-sampling whole-body high-resolution positron emission tomography: HEADTOME IV. *KAKU IGAKU (Jpn J Nucl Med)* 26: 477–485, 1989.
17. Ratib O, Phelps ME, Huang SC, Henze E, Selin CE, Schelbert HR. Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. *J Nucl Med* 23: 577–586, 1982.
18. Nakagawa K, Namba H, Iyo M, Fukushi K, Irie T, Yamanouchi M, et al. Simplified PET quantitation of myocardial glucose utilization. *J Nucl Med* 36: 2094–2102, 1995.