Simple Quantification of Regional Myocardial Uptake of Fluorine-18-Deoxyglucose in the Fasting Condition

Nagara Tamaki, Yoshiharu Yonekura, Masahide Kawamoto, Yasuhiro Magata, Satoshi Sasayama, Norio Takahashi, Ryuji Nohara, Hirofumi Kambara, Chuichi Kawai, and Junji Konishi

Department of Radiology and Nuclear Medicine, The Third Division, Department of Internal Medicine, Kyoto University Faculty of Medicine, Kyoto, Japan

Quantitative measurement of myocardial uptake of fluorine-18-deoxyglucose (FDG) is required for assessing tissue viability in the fasting state due to suppressed FDG uptake in the normal myocardium. A simple FDG uptake index (% dose per 100 ml tissue) has been introduced to compare with the fractional FDG uptake in 21 patients who underwent serial arterial blood sampling (14 under fasting and 7 under postprandial conditions) and to measure the normal range in each myocardial segment in the study of 10 normal subjects (all in the fasting condition). Since the integral of plasma FDG values correlated with the body-weight corrected injected FDG dose ($r = 0.82$), an excellent correlation was observed between the FDG uptake index and the fractional FDG uptake ($r = 0.98$) in the fasting condition. In addition, the FDG uptake index correlated well with the regional metabolic rate of glucose calculated with the Patlak graphic analysis ($r = 0.99$). But this correlation was different in the postprandial condition and in the fasting condition in diabetic patients. In the study of normal subjects, the FDG uptake index was slightly higher in the lateral and inferior segments, as compared to the septal and anterior segments ($p < 0.05$, each). We conclude that the FDG uptake index is considered as a simple and reliable parameter for quantitative assessment of myocardial FDG uptake in the nondiabetic patients in the fasting condition. Since its uptake was heterogeneous, FDG uptake should be carefully evaluated for assessing myocardial viability by comparing normal values in each segment.

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Recent developments in positron emission tomography (PET) permit quantitative assessment of regional myocardial blood flow and metabolism in vivo (*1–3*). A glucose analog, 2-^{18}F-fluoro-2-deoxyglucose (FDG), has been used most often to measure the rate of exogenous glucose utilization.

A combined study using FDG and ^{13}N-ammonia has been shown to be helpful for differentiating myocardial ischemia from myocardial scar in patients with coronary artery disease (*4–7*). Uptake of FDG has been assessed qualitatively in relation to perfusion in most of the studies (*4–8*). A quantitative measurement of its uptake may offer a more accurate assessment of tissue viability. Such quantification would be particularly helpful when patients are studied in the fasting condition, in which FDG uptake in the normal myocardium is suppressed and that in the ischemic myocardium is enhanced. However, a recent report showed heterogeneity of FDG uptake in the normal myocardium, particularly in the fasting condition (*9*), suggesting that a simple evaluation of relative uptake may be misleading.

A three-compartment model of FDG kinetics was introduced and validated (*10,11*). This model was subsequently extended to estimate the myocardial metabolic rate of glucose in vivo (*12,13*). Recently, two simplified PET approaches, one using dynamic PET scans and Patlak graphic analysis (*14*), were applied to measure myocardial glucose utilization (*15*); the second measures the fractional FDG uptake in relation to the delivered FDG dose (*16*). However, these techniques need dynamic PET acquisition and/or sequential arterial blood sampling which may not be suitable for clinical studies. We postulated that the body weight corrected injected dose may represent the integral of arterial FDG counts. Accordingly, we measured FDG uptake in the myocardium at 60 min after injection in relation to the total injected dose of FDG of a standard body weight (60 kg) as a percent dose per unit volume of myocardium (% dose/100 ml) on routine clinical PET studies. This simplified technique only requires one emission scan to measure myocardial PET counts, injected dose, body weight and an accurate calibration of PET counts versus curie meter (calibration factor), but does not require arterial blood sampling or dynamic PET scans. The purposes of this study were (1) to validate this FDG

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For reprints contact: Nagara Tamaki, MD, Department of Nuclear Medicine, Kyoto University Hospital, Shogoin, Sakyo-ku, Kyoto, 606 Japan.

uptake index by comparing it with the fractional FDG uptake by serial arterial blood sampling and regional metabolic rate of glucose by Patlak method and (2) to demonstrate the normal range of this index.

MATERIALS AND METHODS

FDG Preparation

FDG was prepared as described previously (*17,18*). Briefly, following production of ^{18}F, FDG was synthesized by the acetyl hydrofluorite method.

Subjects

This study includes 10 normal subjects who had less than 1% likelihood of coronary artery disease based on the clinical and laboratory studies (*19*) and 21 patients with documented coronary artery disease. Three patients had diabetes mellitus, based on an oral glucose tolerance test, but none were treated with insulin.

Ten normal subjects and 14 patients fasted at least 5 hr before the PET study. For comparison, seven patients were studied 1–2 hr after a carbohydrate meal and were given a 50–75 g oral glucose load 30–60 min before administration of FDG. To estimate substrate levels, plasma-glucose, serum-insulin and nonesterified fatty acid (NEFA) levels were measured at the time of FDG injection (*17*). Each subject gave written informed consent, based on the Human Clinical Research Comittee of Kyoto University Hospital.

Study Protocol

PET scanning was performed using a whole-body, multi-slice positron emission tomograph (Positologica III, Hitachi) (*20*). The spatial resolution was approximately 9 mm in the horizontal direction and 12 mm in the z-axis direction (full width at half maximum) after reconstruction. To obtain calibration factors before the curie meter, PET images, and well counter, a 20-cm diameter cylindrical phantom containing ^{18}F solution was scanned prior to the study. These provided the calibrations between: (1) cpm/ml millicuries on the curie meter and cpm/ml on the PET images and between (2) cpm/ml on the PET counts and cpm/ml on the well counter.

In each study, a transmission scan was performed for 15 min using a rotating germanium-68/gallium-68 standard plate source for measuring the attenuation factor. The position of the subject was aided by echocardiography and by marking the patient's chest wall with a felt pen to align the marks with the reference light beam of the tomograph.

Each subject was given 4.9–9.0 mCi (181–333 MBq) of FDG at rest. Approximately 60 min (50–74 min) after tracer injection, each subject was carefully realigned on the PET camera with the aid of the marks and two emission scans were carried out to obtain 14 contiguous transverse slices with 8-mm intervals (*21*). In seven patients, dynamic PET images were obtained every 4 min immediately after FDG injection for 60 min. Each PET image was reviewed after correction for deadtime and physical decay of the tracer. In 21 patients, serial arterial blood sampling was carried out from the time of tracer injection to the end of emission scan to measure plasma radioactivity.

Data Analysis

From 14 transverse slices, the middle and lower slices were selected for quantitative analysis. A 7 × 7 mm square region of interest was drawn in seven myocardial segments, including five segments from the mid-slice (posteroseptal, anteroseptal, anterior, anterolateral, and posterolateral regions) and two segments (apical and inferior regions) from the lower slice.

After calibration of the injected dose of FDG into PET cpm/ml, the injected dose of FDG was standardized as 60 kg of body weight. Then, the FDG uptake index in the myocardium (% dose/100 ml) was calculated as follows:

$$\text{FDG uptake index (\% dose/100 ml of 60 kg of BW)} = \frac{C_T \times 100\ (\text{ml})}{\text{dose of FDG (mCi)} \times CF_1 \times 60/BW} \times 100\ (\%)$$

where C_T is the myocardial tissue activity of FDG (cpm/ml) measured at time T ranging from 54 to 78 min, BW is the patient's body weight and CF_1 is the calibration factor between mCi on the curie meter and cpm/ml on the PET images.

In 21 patients who underwent sequential arterial blood sampling, the fractional FDG uptake was calculated, according to the following formula (*16*):

$$\text{fractional FDG uptake \%} = \frac{C_T \times CF_2}{\int_0^T Cp(t)dt},$$

where $\int_0^T Cpdt$ is the integral of the FDG plasma values from the time of injection to the mid-scan time (T) and CF_2 is the calibration factor between cpm/ml on the PET images and on well counter.

In seven patients who had dynamic PET imaging and serial arterial blood sampling, the Patlak graphic analysis was performed to calculate regional metabolic rate of glucose (*14,15*). The serial tissue counts were calculated after drawing regions of interest in seven myocardial segments, as described previously. The serial plasma counts also were calculated by the well counter after correction for physical decay. Assuming that the dephosphorylation rate constant (k4) of FDG was zero, a plot of $C(t)/Cp(t)$ versus $Cp(t)/\int_0^t Cp(s)ds$ have a linear relationship at a later time with a slope $[K = k1 \times k3/(k2 + k3)]$ (*14,15*), where k1-4 were the rate constants of FDG in a three-compartment model (*12–15*). The slopes (K) of these two parameters in seven segments were estimated by linear regression analysis. The regional metabolic rate of glucose (MRGlu) was calculated as follows (*14, 15*):

$$MRGlu = Cp^* \times K/LC,$$

where K is a rate constant of FDG calculated from the slope on the Patlak plot, LC is lumped constant (0.67) and Cp^* is plasma-glucose level (*12,13*).

Statistical Analysis

All values were expressed as mean ± s.d. Comparisons of the differences in plasma substrate levels within the patients were performed using a two-tailed Student's t-test for unpaired data. Analysis of variance was used to compare the differences in the FDG uptake index among the segments. Probability values of less than 0.05 were considered statistically significant.

RESULTS

Biochemical Data

Table 1 shows the biochemical data in the subjects in the fasting and postprandial conditions. Plasma-glucose and serum-insulin levels in the postprandial state were significantly higher than those in the fasting condition. In

TABLE 1
Plasma Glucose, Insulin, and Nonesterified Fatty Acid (NEFA) Values in Each Subject

Subject	Condition	n	Glucose (mg/dl)	Insulin (μU/ml)	NEFA (μEq/L)
Normals	Fasting	10	92.5 ± 9.5	5.75 ± 3.86	990 ± 321
Patients	Fasting	11	89.8 ± 6.4	3.82 ± 1.61	808 ± 574
Patients	Postprandial	7	147.4 ± 30.8*	15.80 ± 13.67†	559 ± 590
Patients (DM)	Fasting	3	102.7 ± 6.8	6.97 ± 3.56	1946 ± 1748

* $p < 0.001$ and † $p < 0.05$ versus fasting condition.
DM = diabetes mellitus.

addition, the relatively larger standard deviation was observed in the postprandial condition (21% of the mean value for glucose, 87% for insulin, and 116% for NEFA values) compared to the values in the fasting state (7%, 42%, and 71%, respectively).

Correlation of FDG Uptake Index

In the 21 patients who underwent serial arterial blood sampling, the integral of plasma FDG counts were correlated with the body weight corrected injected dose of FDG (Fig. 1). The correlation between these parameters in the fasting state was r = 0.82. The integral of plasma counts tended to be lower with respect to the injected dose in the postprandial state with relatively poor correlation (r = 0.54), compared to the fasting state, suggesting faster FDG clearance from the blood in the postprandial condition. Similar findings were observed in the diabetic patients under the fasting condition.

When the FDG uptake index correlated with the fractional FDG uptake (Fig. 2), an excellent correlation was obtained between these parameters with a correlation coefficient of 0.98 in the fasting state and 0.89 in the postprandial state. The FDG uptake index tended to be lower in relation to the fractional FDG uptake in the postprandial state, due to lower integral of plasma FDG counts with faster clearance of FDG from the plasma.

In the seven patients who underwent both dynamic PET and serial arterial blood sampling, the FDG uptake index was compared to the regional metabolic rate of glucose calculated from Patlak analysis (Fig. 3). An excellent correlation was observed with a correlation coefficient of 0.99 in the fasting state and 0.91 in the postprandial state. Again, the FDG uptake index tended to be lower in relation to the regional metabolic rate of glucose in the postprandial condition and in the diabetic patients under the fasting condition.

Normal Range of FDG Uptake Index

Table 2 shows the values of FDG uptake index in seven myocardial segments in the normal subjects in the fasting condition. The values in the posterolateral and inferior segments were significantly higher than those in the posteroseptal, anteroseptal, and anterior segments ($p < 0.05$ each). The upper limits of the normal range (mean ± 2

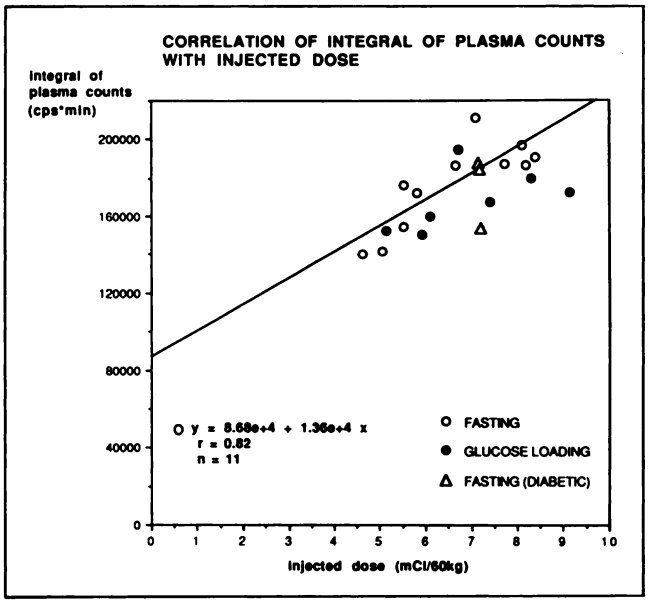

FIGURE 1. Correlation of the integral of plasma FDG counts with the body weight corrected injected dose of FDG.

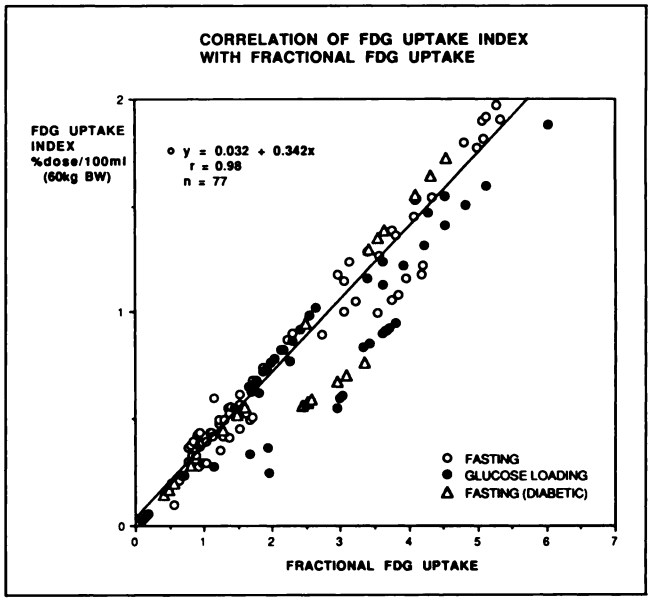

FIGURE 2. Correlation of the FDG uptake index with the fractional uptake of FDG.

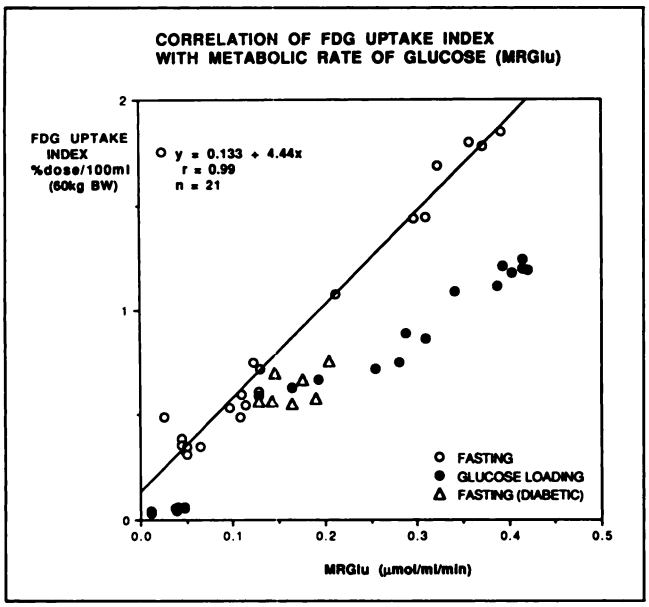

FIGURE 3. Correlation of the FDG uptake index with regional metabolic rate of glucose.

s.d.) were approximately 0.6% dose/100 ml in the anterior and septal regions and 0.7% dose/100 g in the lateral and inferior regions.

DISCUSSION

These data indicate that the FDG uptake index, expressed as %dose/100 ml tissue of myocardium normalized to a standard body weight, can be used as an indicator of FDG uptake in the myocardium in the fasting state. With this simple FDG uptake index, only a single emission scan is necessary. Thus, serial patient studies can be performed with clinical PET for the evaluation of coronary artery disease (*22*).

Correlation with Fractional FDG Uptake

Our data showed an excellent correlation of the integral of plasma FDG values from the time of injection to the mid-scan time with the body weight corrected injected dose of FDG. Therefore, the FDG uptake index correlated well with the fractional FDG uptake calculated from serial arterial blood sampling and the regional metabolic rate of glucose calculated from the Patlak graphic analysis. In the fasting state, where the plasma-insulin level is low and constant, the glucose disappearance from blood is slow. As a result, the integral of plasma FDG values over 60 min after FDG injection is relatively constant and related with the body weight corrected injected dose, as shown in our study (Fig. 1). Thus, to simplify the estimate of FDG uptake in the myocardium, the integral of plasma FDG values may be replaced with the injected dose of FDG measured by a curie meter in the fasting state.

In the postprandial state, on the other hand, where the plasma-insulin level is high, glucose rapidly disappears from the blood. Thus, the disappearance rate of FDG from blood depends on the plasma-insulin level, which may change from injection of the tracer to the emission scan and may be different in each patient, since a variety of patterns were seen in oral glucose tolerance tests. Therefore, the integral of plasma FDG values may change according to the difference in plasma-glucose and serum-insulin levels in the postprandial state. Since the regional metabolic rate of glucose was dependent on plasma-glucose levels, studying patients in the postprandial state increases the variation of its value and decreases the correlation with the FDG uptake index.

The correlation of the FDG uptake index with other parameters was rather poor in diabetic patients even under fasting conditions. This may be due to the fact that plasma-glucose and insulin levels in these patients were similar to those in the postprandial state. Although these diabetic patients have to be separately assessed in a FDG study, a correction of the differences in the substrate levels may potentially solve this problem in the future.

TABLE 2
The FDG Uptake Index in the Normal Subjects and the Upper Limits (Mean ± 2 s.d.) in Each Myocardial Segment

Segment	mean ± s.d.	Upper Limit
Posteroseptal	0.428 ± 0.074	0.576
Anteroseptal	0.443 ± 0.080	0.603
Anterior	0.426 ± 0.078	0.586
Anterolateral	0.485 ± 0.078	0.641
Posterolateral	0.474 ± 0.100*	0.674
Apical	0.456 ± 0.083	0.622
Inferior	0.483 ± 0.097†	0.677

% dose/100 ml in 60 kg of body weight.
* $p < 0.05$ versus anterior segment.
† $p < 0.05$ versus posteroseptal, anteroseptal, anterior, and apical segments.

Fasting Versus Postprandial Condition

Accumulation of FDG in the myocardium is influenced by nutritional state and serum insulin and NEFA levels. It is unclear whether an FDG study should be performed in the fasting or postprandial (glucose loading) condition (*5,9,23,24,25*). In the fasting state, FDG uptake in ischemic tissue should increase while that in the normal myocardium is suppressed. As a result, the ischemic myocardium is shown as a hot spot of FDG uptake. This technique may be suitable to delineate ischemic myocardium from normal or infarcted tissue. However, this may potentially overestimate the presence of ischemic myocardium (*5*). Particularly when FDG uptake is displayed as a relative value with the highest count in the myocardium as 100%, even minimal uptake of FDG in infarcted myocardium might be enhanced as a hot spot. Thus, a certain quantification of FDG uptake is needed for accurate evaluation of myocardial viability. In the glucose-loaded condition, on the other hand, FDG uptake in both the ischemic and normal myocardium is increased. Thus, FDG uptake in regions of interest may be easily assessed by

comparing its uptake with that of normal myocardium in controls. However, this display may underestimate tissue viability in severely ischemic but viable myocardium (*5*) because of relatively decreased uptake of FDG in such regions in comparison with that in normal regions (*25*).

In addition, FDG uptake in normal myocardium may vary depending on plasma-glucose and serum-insulin levels in the postprandial state. It may cause substantial errors in calculating the myocardial metabolic rate of glucose when plasma-glucose and serum-insulin levels change from the time of injection to the emission scan. For maintenance of these levels, a glucose clamp method, using a constant infusion of glucose and insulin, could be applied (*23*). In this respect, the fasting condition makes it easier to maintain the required steady-state conditions of the nutritional substrates and serum-insulin levels after FDG injection.

Heterogeneity of FDG uptake

In our quantitative measurement of FDG uptake in the normal myocardium, there is heterogeneity of FDG uptake with relatively increased uptake of FDG in the lateral and inferior regions compared to the septal and anterior regions. Gropler et al. (*9*) also demonstrated similar heterogeneity of FDG uptake in the fasting state. Moreover, a recent report (*23*) indicates heterogeneity of glucose utilization even in the glucose-loaded condition. Therefore, a relative display of FDG uptake images with peak counts as 100% may cause an error in interpretations (*24*). However, when FDG uptake is displayed as a quantitative value of FDG uptake and compared with the normal range in each segment (*25*), such misinterpretation could be minimized.

Potential Limitations

Since FDG uptake in the myocardium was lower and residual blood-pool activity slightly higher in the fasting state than in the postprandial state, the image quality seems relatively poor in the former. However, our quantitative measurement in the fasting state showed high FDG uptake indicative of increased glucose utilization in the ischemic myocardium and low FDG uptake in the normal and infarcted myocardium. As a result, a high correlation of the FDG uptake index was observed with the fractional FDG uptake and regional glucose utilization.

In the quantitative analysis of FDG uptake, the partial volume effect should be considered (*27*). Since the myocardium is much thinner than twice the spatial resolution of the PET camera [approximately 9 mm in FWHM after reconstruction (*20*)], the FDG concentration in the myocardium should be underestimated. This effect may cause a data fluctuation of FDG uptake index, and correction of this effect after measurement of wall thickness may be necessary in the future.

To maintain a steady state, overnight fasting might be better than a 5-hr fast to minimize variation of plasma-glucose and serum-insulin levels. On the other hand, there are a number of diabetic patients whose plasma-glucose and serum-insulin levels are high in 5–6 hr fasting condition. Augmented FDG uptake, which is occasionally seen in such diabetic patients, may cause difficulties in interpretation of tissue viability. To eliminate such misinterpretation, plasma-glucose, serum-insulin and NEFA levels should be measured at the time of FDG injection in each patient. In the study of diabetic patients, the insulin clamp may be better to maintain the steady state (*23*). Alternatively, the FDG uptake index might become a useful parameter in interpretation after correction of plasma-glucose and insulin levels.

Clinical Implications

The FDG uptake index requires only one emission scan approximately 60 min after FDG injection. This simplified protocol permits more patients to be studied each day.

We conclude that a simple quantification of FDG uptake in the myocardium is possible. Such quantification of FDG uptake seems to be valuable in the fasting state for assessing tissue viability as a clinical PET study. Since the FDG uptake in the normal myocardium is heterogeneous, its uptake should be carefully interpreted by comparing with the normal range in each myocardial segment.

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