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Glucose tolerance and myocardial F-18 fluorodeoxyglucose uptake in normal regions in coronary heart disease patients

Shinji HASEGAWA,* Hideo KUSUOKA,* Toshiisa UEHARA,* Hitoshi YAMAGUCHI,* Masatsugu HORI** and Tsunehiko NISHIMURA*

*Division of Tracer Kinetics, Biomedical Research Center and **First Department of Medicine, Osaka University Medical School

To elucidate the relation between glucose tolerance and myocardial uptake of F-18 fluorodeoxyglucose (FDG), FDG-PET with 75 g oral glucose loading was performed on 43 coronary artery disease patients (twice in 2 patients). The patients were divided into 4 groups based on the blood glucose level (BS) and the insulinogenic index (II): group 1, normal (n = 9); group 2, impaired glucose tolerance (IGT, n = 12); group 3, mild diabetes mellitus (DM) (II > 0.4, n = 12); and group 4, severe DM (II ≤ 0.4, n = 12). Percent (%) dose uptake of FDG in the normal regions of the myocardium was not significantly different in groups 1, 2, and 3, but it was much lower in group 4 than in groups 1 and 2. In groups 2, 3, and 4, % dose uptake showed a definite negative correlation with BS 60 min after glucose loading ($r = -0.450$, $p < 0.05$), and a close positive correlation with II ($r = 0.363$, $p < 0.05$). These findings indicate that myocardial FDG uptake in normal regions is not greatly impaired in patients with IGT or mild DM. Myocardial viability can be assessed by oral glucose loading in patients with IGT and mild DM as well as in patients with normal glucose tolerance.

Key words: glucose tolerance, FDG, % dose uptake, insulin secretion, insulin resistance

INTRODUCTION

MYOCARDIAL POSITRON EMISSION TOMOGRAPHY (PET) with F-18 fluorodeoxyglucose (FDG) has been considered a superior method of assessing myocardial viability,[1,2] but many factors, including ischemia,[3] hormones,[4] catecholamine,[5] metabolic variables[4] and diet, affect the myocardial uptake of glucose and FDG and make it difficult to quantify myocardial viability accurately by FDG-PET. Glucose tolerance, in particular, affects FDG uptake directly. Previous studies on the quantification of FDG uptake by dynamic PET scan and Patlak graphic analysis have suggested that the insulin clamp method might be much more useful in patients with diabetes mellitus (DM), than oral glucose loading,[6,7] but the insulin clamp method is complicated and not practicable in all patients in whom FDG-PET is performed. The aim of this study was to investigate the relationship between glucose tolerance and myocardial FDG uptake and to clarify the limits of the glucose loading method in terms of reliable assessment.

MATERIALS AND METHODS

Forty-three patients with coronary heart disease were enrolled in this study (males 36, females 7; age, 60.7 ± 9.2 years old, mean ± SD); 32 of them had experienced a myocardial infarction and the other 11 patients had ischemia alone. Percutaneous transluminal coronary angioplasty was performed before this study in 9 patients, and coronary artery bypass grafting was done in 9 patients. Patients with severe 3-vessel disease or severe heart failure were excluded. FDG-PET studies were performed twice, at different stages in 2 patients, so that the total number of studies was 45. The protocol was approved by the Ethics Committee of Osaka University Hospital, and all patients gave written informed consent.

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For reprint contact: Tsunehiko Nishimura, M.D., Ph.D., Division of Tracer Kinetics, Biomedical Research Center, Osaka University Medical School, 2–2 (D9) Yamada-oka, Suita, Osaka 565–0871, JAPAN.

E-mail: nisimura@tracer.med.osaka-u.ac.jp

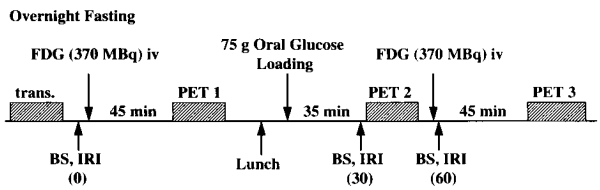

Fig. 1 One-day protocol for the FDG-PET study. The first emission scan (PET 1) was performed after the transmission scan. The second (PET 2) and the third emission scan (PET 3) were performed after 75 g oral glucose loading after lunch. Blood sugar (BS) level and immunoreactive insulin (IRI) level were measured before the 1st FDG injection, and 30 min and 60 min after the oral glucose loading.

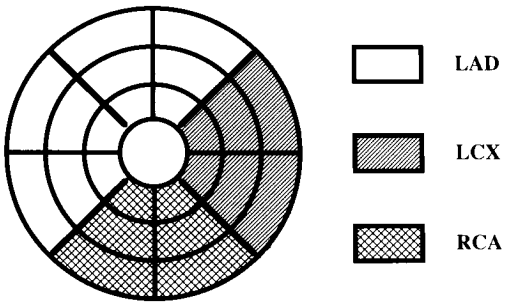

Fig. 2 Segments of the left ventricle on the bull's eye image map. The map is divided into 24 segments, 8 segments each for the basal, middle, and apical ventricle. The counts in the segments were added to obtain the count in each of the three regions, the region supplied by the left ascending artery (LAD), the circumflex artery (LCX), and the right coronary artery (RCA), respectively. The region to which each segment belonged was determined according to the coronary arteriography findings.

FDG-PET

The FDG-PET study was performed with a whole-body PET camera (SET-2400W [Headtome V], Shimadzu Medico Co., Kyoto, Japan) under both fasting conditions and oral glucose loading conditions on the same day (Fig. 1). The Headtome V has 32 rings that provide 63 tomographic slices at 3.125 mm intervals. The spatial resolution in the tomographic plane was 4 mm full-width half-maximum (FWHM) at the center, and the axial resolution was 5 mm FWHM.

Sterile F-18 FDG was produced at the radioisotope laboratory in Osaka University Hospital. The study was started after an overnight fast (for at least 12 hours). Transmission scanning with rotating Ge-68 line sources was first performed for attenuation correction. Then 370 MBq of FDG was injected via an antecubital vein under fasting conditions. Forty-five minutes later the first emission scan (PET 1) was performed for 10 min, and the patient was then allowed to have lunch. Within 30 min after lunch, 75 g of glucose was orally loaded, and 50 min later another 370 MBq of FDG was injected. The second emission scan (PET 2) was performed 15 min before the second FDG injection, and the third emission scan (PET 3) was performed 45 min after the second FDG injection. A series of transverse slices was reconstructed from the acquisition data, and oblique tomograms perpendicular to the long and short axes of the left ventricle were reconstructed.

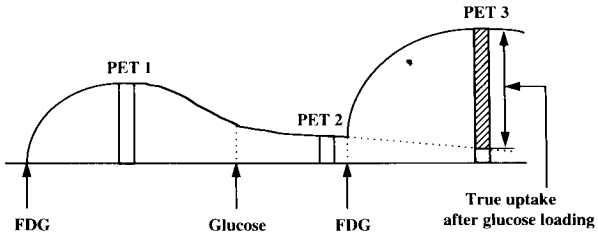

Fig. 3 Scheme of changes in myocardial FDG uptake in this protocol. True uptake after glucose loading was estimated by subtracting the PET 2 data from the PET 3 data, considering the time-dependent decrease of radioactivity.

Image analysis

A bull's eye image map of the left ventricle was made from the short-axis image data, and the map was divided into 24 segments (8 segments for each slice of the basal, middle, and apical ventricle; Fig. 2). The FDG uptake in each segment was quantitatively expressed as the body weight (BW)-corrected percent of the injected dose per 100 g of tissue (% dose uptake) according to the following equation:

$$\%\ \text{dose uptake of FDG (\% dose/100 mL of 60 kg of BW)} = \frac{Ct \times 100}{\text{Dose of FDG (MBq)} \times CF \times 60/BW} \times 100\ (\%)$$

where Ct is the myocardial tissue activity of FDG (cpm/mL), BW is the patient's body weight (kg), and CF is the calibration factor for MBq on the curie meter and counts per minute per milliliter on the PET images.[2,8] The segment counts were then added to yield in each of the three regions, i.e., the region supplied by the left ascending artery, the left circumflex artery, and the right coronary artery. Coronary angiography findings were referred to in order to determine which region the segment belonged to.

The additional myocardial uptake of FDG after glucose loading was estimated by subtracting % dose uptake obtained by the PET 2 image from that obtained by the PET 3 image, considering the time-dependent physical decrease in radioactivity (Fig. 3).

In this study we analyzed the increases in % dose uptake of FDG in the normal regions after glucose loading. We defined "normal regions" as regions supplied by coronary artery branches in which stenosis was less than 90% and that had not been affected by myocardial infarction. If two regions fit the definition, the region which had the larger % dose uptake was selected as the "normal region." By means of echocardiography, we confirmed

that all selected regions had no asynergy.

Glucose tolerance

Blood was sampled three times, i.e., before the first injection of FDG in the fasting state, and 30 min and 60 min after oral glucose loading (Fig. 1), and glucose concentrations were measured in whole blood (BS (0), BS (30), BS (60), mg/dL) and immunoreactive insulin concentrations in plasma (IRI (0), IRI (30), IRI (60), μU/mL). The insulinogenic index (II), the index of insulin secretion ability, was calculated by means of the following formula[9]:

$$II = [IRI\ (30) - IRI\ (0)] / [BS\ (30) - BS\ (0)].$$

We divided the patients into 4 groups based on glucose tolerance according to the Committee Report on the Diagnosis of Diabetes Mellitus by the Japanese Diabetes Association (10): group 1, normal glucose tolerance (GT) pattern (BS (60) < 160 mg/dL, n = 9); group 2, impaired glucose tolerance (IGT, BS (60) ≥ 160 mg/dL but < 200 mg/dL, n = 12); group 3, mild diabetes mellitus (mild DM, BS (60) ≥ 200 mg/dL and II > 0.4, n = 12); and group 4, severe diabetes mellitus (severe DM, BS (60) ≥ 200 mg/dL and II ≤ 0.4, n = 12). We also divided them into 4 groups based on insulin secreting ability: group A, normoinsulin (IRI (60) < 160 μU/mL and belongs to the normal GT or IGT group, n = 13); group B, hyperinsulin (IRI (60) ≥ 160 μU/mL, n = 12); group C, pseudonormoinsulin (IRI (60)

Table 1 Myocardial FDG uptake in normal regions of the myocardium after glucose loading according to glucose tolerance

	Group 1 (normal GT)	Group 2 (IGT)	Group 3 (mild DM)	Group 4 (severe DM)
n	9	12	12	12
% dose uptake	0.68 ± 0.24	0.69 ± 0.21	0.63 ± 0.26	0.47 ± 0.17*

(I)GT: (impaired) glucose tolerance, DM: diabetes mellitus, *: $p < 0.05$ vs. groups 1 and 2

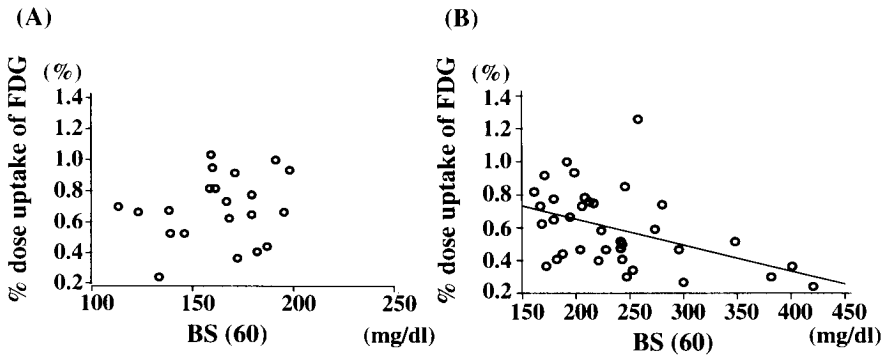

Fig. 4 Relationship between the % dose uptake of FDG and glucose concentration in whole blood 60 min after oral glucose loading (BS (60)). (A) Patients without DM, i.e., groups 1 and 2. (B) Patients with abnormal glucose tolerance, i.e., groups 2, 3, and 4. The line in panel B (y = − 1.59x + 974) is the linear regression line.

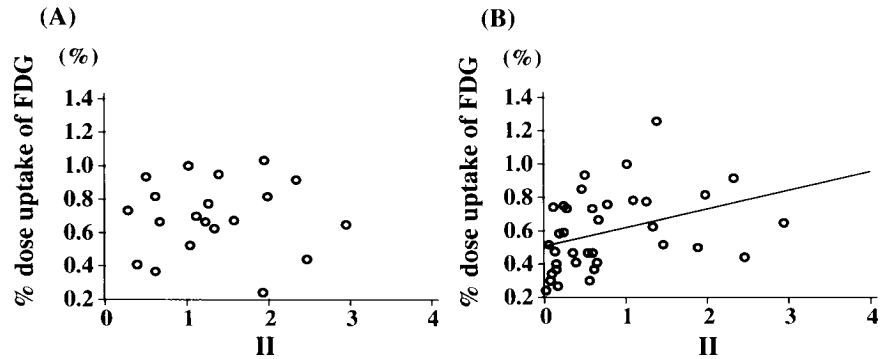

Fig. 5 Relationship between the % dose uptake of FDG and the insulinogenic index (II). (A) Patients without DM, i.e., groups 1 and 2. (B) Patients with abnormal glucose tolerance, i.e., groups 2, 3, and 4. The line in panel B (y = 112x + 509) is the linear regression line.

Table 2 Myocardial FDG uptake in normal regions of the myocardium after glucose loading according to insulin secretion ability

	% dose uptake	n
group A		
normoinsulin	0.65 ± 0.21	13
group B		
hyperinsulin	0.76 ± 0.25	12
normal	0.74 ± 0.27	3
IGT	0.77 ± 0.22	5
DM	0.77 ± 0.35	4
group C		
pseudonormoinsulin	0.54 ± 0.21*	9
group D		
hypoinsulin	0.47 ± 0.17*	11

IGT: impaired glucose tolerance, DM: diabetes mellitus, *: $p < 0.05$ vs. Group B

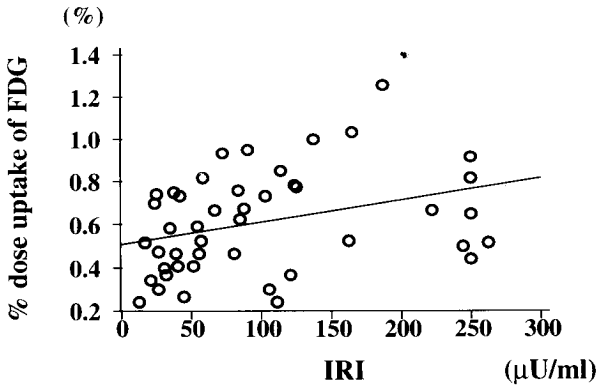

Fig. 6 Relationship between % dose uptake of FDG and the immunoreactive insulin (IRI) in plasma 60 min after oral glucose loading. The line in panel B ($y = 1.01x + 512$) is the linear regression line.

≥ 45 μU/mL but < 160 μU/mL and belongs to the mild DM or severe DM group, n = 9); and group D, hypoinsulin (IRI (60) < 45 μU/mL and belongs to the mild DM or severe DM group, n = 11). For the treatment of DM, insulin, sulfonylureas (SU), and α-glucosidase inhibitors (AGI) were used; 1, 4, 1 and 3 patients received insulin, SU, AGI, and SU + AGI, respectively. The use of these drugs was not inhibited on the day of the study, but only after the fasting study.

Statistical analysis

Values are expressed as means ± SD. Correlations were assessed by Pearson's correlation coefficient (r) and Fisher's method. Differences among the groups were assessed by one-way analysis of variance (ANOVA). A p value less than 0.05 was considered significant.

RESULTS

Relationship between Glucose Tolerance and Myocardial FDG Uptake

Myocardial FDG uptake in the normal region after glucose loading in each group classified by glucose tolerance is summarized in Table 1. Percent dose uptake of FDG was not significantly different among the normal GT, IGT and mild DM groups, but it was much lower in the severe DM group than in the normal GT and IGT groups.

In patients without DM (i.e., groups 1 and 2), % dose uptake of FDG was not correlated with either BS (60) (Fig. 4-A, r = 0.224, ns) or II (Fig. 5-A, r = −0.094, ns). In the patients with abnormal glucose tolerance (i.e., groups 2, 3, and 4), on the other hand, % dose uptake was definite negatively correlated with BS (60) (Fig. 4-B, r = −0.450, p = 0.005) and close positively correlated with II (Fig. 5-B, r = 0.363, p = 0.029). These findings indicate that BS (60) and II are factors for myocardial FDG uptake in patients with abnormal glucose tolerance.

Relationship between Insulin Secretion and Myocardial FDG Uptake

Myocardial FDG uptake in normal regions of the myocardium after glucose loading in each group classified by insulin secretion is summarized in Table 2. Percent dose uptake in the pseudonormoinsulin and hypoinsulin groups decreased definitely compared to the hyperinsulin group. There were no differences in FDG uptake among the normal GT, IGT and DM groups in the hyperinsulin group.

Percent dose uptake of FDG after glucose loading was closely positively correlated with IRI (60) in all patients (Fig. 6, r = 0.329, p = 0.027).

These findings suggest that myocardial FDG uptake is partially determined by IRI (60), and the hypersecretion of insulin compensates for mild impairment of glucose tolerance from the standpoint of FDG uptake.

Effect of Blood Sugar Control on Myocardial FDG Uptake

Figure 7 shows changes in the FDG-PET images of a DM patient in different stages of blood sugar control. This patient belonged to the severe DM group when FDG-PET was performed in both stages. In the poor control stage of DM (BS (0) = 186, BS (60) = 382, IRI (60) = 27, II = 0.059), FDG uptake was severely attenuated (Fig. 6-A, % dose uptake = 0.30%). By contrast, in the good control stage (BS (0) = 114, BS (60) = 349, IRI (60) = 17, II = 0.080), FDG uptake was improved (Fig. 6-B, % dose uptake = 0.52%). In this patient, IRI (60) and BS (0) in the poor control stage were higher than in the good control stage, indicating higher insulin resistance in the poor control stage. This suggests that myocardial FDG uptake can change according to the blood sugar control stage, even in individuals whose insulin secreting ability is decreased, and that insulin resistance also strongly affects myocardial FDG uptake in such patients.

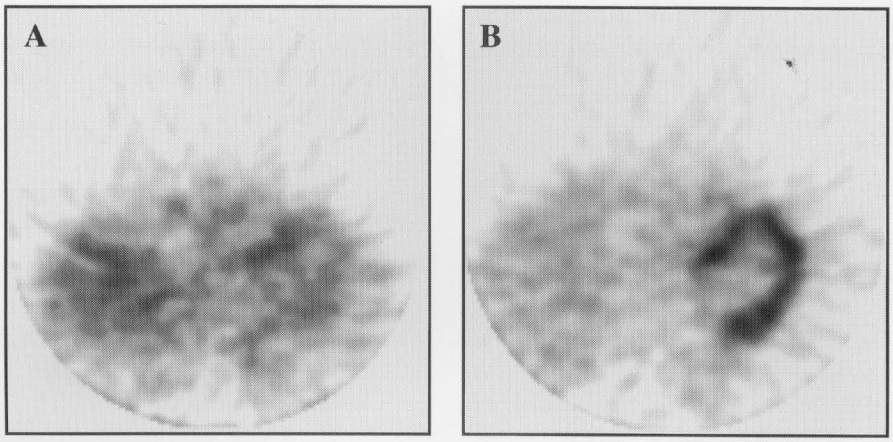

Fig. 7 FDG-PET images of a patient with severe DM. FDG uptake in the poor control stage (panel A, % dose uptake = 0.30%) was lower than in the good control stage (panel B, % dose uptake = 0.52%).

DISCUSSION

Our findings suggest that myocardial viability can be assessed by using oral glucose loading in DM patients whose insulin secreting ability is not decreased as well as in patients with normal glucose tolerance and patients with impaired glucose tolerance.

Relationship between Glucose Tolerance and Myocardial FDG Uptake

We examined myocardial FDG uptake in the normal regions of the myocardium in patients with coronary artery disease. Myocardial FDG uptake was not decreased in patients with IGT and mild DM, because increased secretion of insulin compensated for the attenuation in the insulin sensitivity. Myocardial viability can therefore be assessed by using oral glucose loading in such patients as well as in patients with normal glucose tolerance, but insulin secretion was markedly decreased in the patients with severe DM, and myocardial FDG uptake could not be compensated for, so that it may be difficult to assess myocardial viability by using oral glucose loading alone. The significant positive correlation between myocardial FDG uptake and IRI (60) indicates that the insulin level is an important factor affecting myocardial glucose uptake. In addition, as the example in Fig. 7 shows, changes in insulin resistance in response to therapy noticeably affected the myocardial FDG uptake in patients whose insulin secretion ability was severely attenuated.

It has been reported that myocardial glucose utilization rates (MRGlc) are significantly lower in oral glucose loading than in insulin clamp in patients with non-insulin-dependent DM,[7] but the investigators did not take into account the degree of glucose tolerance. It is speculated from our data that there may be no significant difference between oral glucose loading and insulin clamp in patients with mild DM or IGT whose insulin secreting ability is preserved.

It has also been reported that MRGlc following glucose loading was found to be positively correlated with plasma glucose and insulin levels in healthy male volunteers.[4] As the definition of MRGlc includes the glucose concentration in the equation,[11] no doubt there is a correlation between them. Our data showed that FDG uptake was not significantly correlated with the glucose concentration in the patients who did not have DM, but there was a weak positive correlation between them. If glucose tolerance is normal, FDG uptake might show a correlation with the glucose concentration.

The lumped constant (LC) represents the ratio of FDG uptake to glucose uptake, and was assumed to be constant.[11] Recently it was reported that the LC is not constant, and that it is affected by insulin and glucose concentrations.[12,13] If the glucose concentration is high, FDG uptake might lead to underestimation of the true glucose uptake, so that the glucose uptake of patients with DM may be better preserved than estimated on the basis of FDG data.

Limitations

In this study oral glucose loading was performed after the lunch. This may cause underestimation of glucose tolerance because we adopted the criterion of oral glucose tolerance test under the fasting condition. In addition, the administration of anti-DM drugs or insulin was not inhibited on the day of the study, which may affect the value of BS (60). These conditions may affect the classification of the DM state by glucose loading, but the relationship between BS (60)/II and FDG uptake was concomitant with glucose loading, and may be independent of the meals and/or the treatment.

The major factors in glucose tolerance are insulin secretion and insulin resistance. In this study, we used the II as an indicator of insulin secretion, but did not measure any indicators of insulin resistance itself, either by the

glucose clamp technique[14] or the minimal-model approach.[15] We judged insulin resistance indirectly on the basis of the BS, IRI and II values.

Percent dose uptake of FDG is a simple index of FDG uptake, but may be affected by many factors, such as distribution to other organs. This index has been reported to be reliable in non-diabetic patients under fasting conditions, but the correlation between % dose uptake and MRGlc was not good under postprandial conditions or in diabetic patients,[8] but it was suggested that MRGlc does not represent glucose uptake accurately, because the LC changes in diabetic patients.[12]

In this study we examined the relationship between glucose tolerance and the myocardial FDG uptake in normal regions alone. It has been reported that thallium-201 uptake in ischemic regions increases more than in normal regions after glucose loading.[16] This suggests that ischemic regions are more sensitive to insulin than normal regions, so that myocardial FDG uptake may also be more enhanced in ischemic regions than in normal region.

In conclusion, myocardial FDG uptake is not decreased significantly in patients with IGT and mild DM, and myocardial viability can be assessed by using oral glucose loading in such patients as well as in the patients with normal glucose tolerance. Nevertheless, in patients with severe DM, whose insulin secreting ability is decreased, it is necessary to use more accurate methods such as insulin clamp to assess myocardial FDG uptake.

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