Effect of the Duration of Fasting on Myocardial Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography Images in Normal Males

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To evaluate the effect of the duration of fasting on myocardial fluorine-18-fluorodeoxyglucose (FDG) uptake and distribution, 16 FDG-positron emission tomography (PET) studies were performed in 7 normal volunteers under three different conditions: glucose loading, 6 h fasting and overnight fasting. In the glucose-loaded condition, all subjects had good image quality, and myocardial metabolic rates of glucose (MRGlc) were significantly higher than those in the other two conditions. In the 6 h and overnight fasting conditions, image qualities varied according to MRGlc. Although there were visually distinct regional differences with MRGlc ranging from 0.05 to 0.15 $\mu\text{mol}/\text{min per g}$, these differences were not impressive by a quantitative analysis. The ranges of MRGlc in these two fasted conditions overlapped each other. There was a significant negative linear correlation between MRGlc and serum free fatty acid levels. Thus, MRGlc and image quality in fasted normal subjects varied with the extent of the fed-to-starved transition under clinical fasting conditions (6 h to overnight), and this transition does not depend solely on the duration of fasting. These findings may explain the heterogeneity in FDG studies under fasting conditions.

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THE clinical value of the measurement of F-18-labeled fluorodeoxyglucose (FDG) uptake by positron emission tomography (PET) for evaluating the myocardial uptake of exogenous glucose is well established. Particularly in the diagnosis of coronary artery disease, many studies have suggested that it is useful for the noninvasive assessment of myocardial viability^{1–3} and

recent studies have suggested that it may be useful for evaluating the prognosis of patients^{4–7}. However, the myocardial uptake of FDG depends on several metabolic variables^{8–10}. Moreover, the most suitable dietary state for FDG imaging is still controversial^{11,12}. The study of FDG uptake by PET under fasting conditions provides a sensitive method for detecting metabolically abnormal segments of the myocardium^{13,14} and attempts to enhance myocardial glucose uptake in the postischemic myocardium of patients with exercise-induced ischemia are usually performed under fasting conditions¹⁵.

Key words:

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TABLE I METABOLIC STATES AND THE RATE OF MYOCARDIAL GLUCOSE UPTAKE (MRGlc) IN EACH CASE

Condition	Case	Glucose (mg/dl)	Insulin (μ U/ml)	Free fatty acid (mmol/L)	MRGlc (μ mol/min per g)
Glucose Loaded	1	115	17.84	0.18	0.60
	2	113	45.43	0.05	0.59
	3	119	31.98	0.06	0.78
	4	89	27.44	0.17	0.63
	Mean $\pm$ SD	109.0 $\pm$ 11.7*	30.67 $\pm$ 9.93*	0.12 $\pm$ 0.06*	0.65 $\pm$ 0.07*
6 h fasted	1	80	6.23	0.50	0.24
	2	83	11.39	0.41	0.18
	3	88	8.49	0.40	0.14
	5	77	7.35	0.61	0.11
	7	91	10.42	0.85	0.02
	Mean $\pm$ SD	83.8 $\pm$ 5.1	8.78 $\pm$ 1.90	0.55 $\pm$ 0.17	0.14 $\pm$ 0.075
Overnight fasted	1	81	6.09	0.83	0.02
	2	94	9.58	0.68	0.01
	3-1	85	2.34	0.38	0.28
	3-2	91	6.18	0.58	0.15
	4	79	4.46	0.50	0.03
	6	88	9.58	0.67	0.04
	7	87	8.02	0.34	0.20
	Mean $\pm$ SD	86.4 $\pm$ 4.9	6.61 $\pm$ 2.48	0.57 $\pm$ 0.16	0.10 $\pm$ 0.097

*: $p < 0.01$ vs both 6 h and overnight fasting studies.

On the other hand, studies with glucose-loading generally have good image quality and the heterogeneity of FDG uptake is reduced⁸⁻¹¹

In 1990, Gropler et al and Berry et al reported marked case-by-case differences and regional disparities in the myocardial accumulation of FDG under fasting conditions with normal subjects. They also noted that this significant heterogeneity may limit the specificity of PET with FDG for detecting myocardial ischemia in fasting subjects^{8,9}. These studies suggest that the glucose-loaded condition may be preferable to the fasted condition. However, the cause of the case-by-case differences and regional disparities in the fasted condition has not been adequately evaluated. To the best of our knowledge, only one trial has compared the effects of different fasting times on myocardial FDG uptake¹⁶ and there has been no comparison of the results of repeated studies in the fasting condition in normal subjects.

To evaluate the effect of the duration of

fasting and metabolic conditions on myocardial FDG uptake and distribution, we performed FDG-PET in normal volunteers under three different conditions (overnight fasting, 6 h fasting, and glucose loading).

METHODS

Subjects

Sixteen PET studies were performed in 7 healthy male volunteers (age: 32.4 ± 3.7 , range 29-39 years). All subjects were asymptomatic and had no significant risk factors for cardiovascular disease. Written informed consent was obtained from each subject.

Four, 5 and 6 cases were studied under glucose loading, 6 h fasting, and overnight fasting conditions, respectively. Reproducibility of the overnight fasting condition was tested with case 3, who underwent the trial twice (Table).

Tracer Synthesis and Instrumentation

FDG was synthesized by the acetylhyposulfite method with a "CYPRIS" small cyclotron, and a "CUPID" automatic tracer synthesizer (Sumitomo Heavy Industries). The radiochemical purity of FDG was more than 95%. The preparation was tested in accordance with the standards of the cyclotron committee of Chiba University Hospital.

PET images were obtained with a Shimadzu-SET 130W PET scanner (HEAD-TOME III). This scanner can obtain three slices simultaneously with a slice thickness of 16.5 mm, and the spatial resolution was 10.5 mm FWHM.⁷ A Ramp filter and a Butterworth filter (cut-off frequency: 12 mm^{-1}) were used for image reconstruction, resulting in an in-plane spatial resolution of 12.8 mm (FWHM).

Study Protocol

The subjects studied under the glucose-loaded condition were told to have a usual breakfast and were given 50 g of oral glucose 60 min prior to PET scanning. Subjects in the "6 h fasted" group were allowed to have a light breakfast, and then were instructed to take nothing but water by mouth for at least 6 h. Subjects in the "overnight fasted" group had a light dinner and then fasted overnight for at least 15 h prior to PET scanning.

After transmission scans were obtained with a [⁶⁸Ge] ring, about 148 MBq of FDG was administered intravenously and serial scanning was started simultaneously (3 times for 1 min each, 5×for 2 min each 11×for 4 min each, and once for 6 min). The counts were corrected for radioactive decay and scanner deadtime. All reconstructions were performed without ECG gating. Venous blood was obtained immediately before FDG administration. Plasma glucose, free fatty acid (FFA) and insulin levels were analyzed for each blood sample.

Data Analysis

To determine the myocardial activity curves, regions of interest (ROIs) were drawn on a late myocardial image at the mid-ventricle level and projected to serial PET images. The ROIs were divided into five segments (posteroseptal, anteroseptal, anterior, anterolateral, posterolateral regions) according to the method described by

Czernin et al.¹⁸ The size of each ROI was 3×3 pixels, with each point representing 2 mm. In two of the fasting trials with uninterpretable images, [¹⁵O] CO inhalation was performed to delineate the anatomical relation between the myocardium and blood pool. Arterial input function was obtained from the ROI in the center of the left ventricular cavity. The size of this ROI was 5×5 pixels.

To correct the observed myocardial activity for the recovery coefficient of the myocardium and the fraction of blood activity into the myocardium, we used the constant values of 0.63 and 0.18, respectively, assuming that the left ventricular wall thickness was 1.0 cm.

Arterial and tissue time activity curves were analyzed graphically.^{19,20} The slope of the points of measurement by graphic analysis was equal to the utilization constant of [¹⁸F] FDG (K), which represents the fractional rate of tracer transport and phosphorylation. The mean value of K for each segment was used for further calculations. The rate of myocardial glucose uptake (MRGlc) in each segment is given by

$$\text{MRGlc} = K \times P_{\text{glc}} / \text{LC}$$

where P_{glc} is the plasma concentration of glucose and LC (=0.67) is used to correct for differences in the transport and metabolism of FDG and glucose.²¹

Statistical Analysis

Simple and multiple linear regression analyses were performed for the various metabolic parameters, and the standard errors of the estimates were calculated. Data were presented as the mean $\pm$ SD. Unpaired t-tests were used to evaluate the significance of the difference in glucose, insulin, free fatty acid and MRGlc between the respective conditions and the difference in MRGlc between any two regions.

RESULTS

Image Qualities

All 4 trials in the glucose-loaded condition had good image quality and no appreciable blood pool activity. Myocardial FDG activity was homogeneously distributed, as shown in Fig 1a.

Fig 1. Mid-left ventricular level of transaxial FDG images of all trials.

a: Studies in the glucose-loaded condition.

All trials had good image quality and myocardial FDG activity was homogeneously distributed

b: Studies in the 6 h fasted condition.

In cases 1 and 2, image quality was good. In cases 3 and 5, image quality was poor and regional disparities were visually clear. In case 7, no appreciable myocardial FDG uptake above the blood pool activity was observed.

c: Studies in the overnight fasted condition.

In cases 3-1 and 7, image quality was good. In case 3-2, image quality was poor. In the other 4 cases (1,2,4,6), PET images showed no appreciable myocardial FDG uptake above the blood pool activity.

Fig 2. Regional MRGlc in the three conditions.

a: Studies in the glucose-loaded condition.

b: Studies in the 6 h fasted condition.

c: Studies in the overnight fasted condition.

MRGlc: Rate of myocardial glucose uptake

PS: Posteroseptal region, AS: Anteroseptal region, A: Anterior region, AL: Anterolateral region, PL: Posterolateral region, N.S.: not significant

□: Case 1, ◇: Case 2, ○: Case 3, ▤: Case 3 (second trial of overnight fasting),

△: Case 4, ▨: Case 5, ⋄: Case 6, ⊕: Case 7

Although there were statistically significant regional disparities in the fasting conditions, they were less impressive than by visual interpretation. Irregular regional MRGlc was also seen in the glucose loading condition.

Two of the 5 trials in the 6 h fasted condition had good image quality and minimal blood pool activity. Two other trials had poor image quality and regional disparities were visually evident in these cases. The PET image of the remaining case showed no appreciable myocardial FDG uptake above blood pool activity (Fig 1b).

Two of the 7 trials in the overnight fasted condition still had good image quality and minimal blood pool activity. One had poor image quality. In the other 4 trials, PET images showed no appreciable myocardial FDG uptake above the blood pool activity, as shown in Fig 1c.

Quantitative Analysis

In the glucose-loaded condition, MRGlc in all 5 regions ranged from 0.50 to 0.81 $\mu\text{mol}/\text{min per g}$ (Fig 2a). In the 6 h and overnight fasted conditions, MRGlc in all of the regions ranged from 0.00 to 0.29 $\mu\text{mol}/\text{min per g}$. In the 6 h fasted condition, MRGlc in the posterolateral region was slightly higher than those in the posteroseptal, anteroseptal and anterolateral regions, as shown in Fig 2b. MRGlc in the 4 cases with overnight fasting with no appreciable myocardial FDG uptake

was near 0 $\mu\text{mol}/\text{min per g}$.

Trials with MRGlc lower than 0.05 $\mu\text{mol}/\text{min per g}$ were associated with negligible myocardial FDG uptake. On the other hand, those with MRGlc higher than 0.15 $\mu\text{mol}/\text{min per g}$ were associated with distinct visual recognition of the myocardium. Trials with MRGlc between these two values had partial myocardial recognition and poor image quality.

In each subject, MRGlc values increased after glucose loading. Mean values averaged 0.10 $\mu\text{mol}/\text{min per g}$ during overnight fasting, 0.14 $\mu\text{mol}/\text{min per g}$ during 6 h fasting, and then rose significantly to 0.65 $\mu\text{mol}/\text{min per g}$ after glucose loading ($p < 0.0001$, Table). The ranges of the mean MRGlc for the overnight and 6 h fasting conditions overlapped from 0.01 to 0.28, and the range of the mean MRGlc for the glucose-loaded cases was 0.59 to 0.78.

Regional Disparities

By visual interpretation, there was greater FDG accumulation in the posterolateral regions than in other myocardial regions under the 6 h fasted conditions. However, by quantitative analysis, although the differ-

Fig 3. Relationships between parameters of metabolic states and the rate of myocardial glucose uptake (MRGlc).

+: glucose-loaded condition.

●: 6 h fasted condition.

□: overnight fasted condition.

a: Relationship between the serum free fatty acid level (FFA) and MRGlc

b: Relationship between the serum glucose level (Glu) and MRGlc

c: Relationship between the serum insulin level (IRI) and MRGlc

In Fig 3a, MRGlc was inversely correlated with FFA. This correlation was also significant without the glucose-loaded cases ($r=0.78$, $p=0.0028$). In Fig 3b and 3c, the dots were clearly separated to two groups (glucose-loaded cases and fasted cases). If the glucose-loaded cases were excluded, correlations were not observed. Although Glu and IRI were considered to be major factors in determining MRGlc in the glucose-loaded condition, they could not explain the differences in the degree of myocardial FDG accumulation in the fasted condition.

ences in MRGlc between the posterolateral and other regions were statistically significant, they were only slightly so.

Reproducibility in the Fasting Condition

As mentioned above, the ranges of the mean MRGlc for the overnight and 6 h fasting conditions overlapped each other. We investigated the reproducibility of FDG uptake by PET in both the overnight and 6 h fasting conditions. As shown in the Table, there was greater intra-subject variation in MRGlc than inter-subject variation.

In case 3, the overnight fasting trial was performed twice. In the first trial, the image quality was good and MRGlc was $0.28 \mu\text{mol}/\text{min}$ per g. However, the second trial showed poor image quality and MRGlc was $0.15 \mu\text{mol}/\text{min}$ per g. In the 6 h fasting trial, the same subject had poorer image quality and MRGlc was $0.14 \mu\text{mol}/\text{min}$ per g. In case 7, the overnight fasting trial showed good image quality and MRGlc was $0.20 \mu\text{mol}/\text{min}$ per g. The 6 h fasting trial in the same subject showed no appreciable

myocardial FDG uptake and MRGlc was $0.02 \mu\text{mol}/\text{min}$ per g. In these 2 cases, myocardial glucose uptake was greater after the longer fasting time. Therefore, it appears clear that image quality and MRGlc do not depend solely on the duration of fasting.

Metabolic Conditions

Serum glucose and insulin levels were significantly higher and free fatty acid levels were significantly lower in the glucose loading condition than in the other two conditions. No such differences were found between the 6 h and overnight fasting conditions.

Overall, the mean MRGlc was inversely correlated with the serum free fatty acid concentration (Fig. 3a, $r=0.90$, $p<0.0001$). This correlation was still significant even without the glucose-loaded cases ($r=0.78$, $p=0.0028$). The mean MRGlc correlated with both serum glucose and insulin levels (Fig. 3b, $r=0.76$, $p=0.0006$, Fig. 3c, $r=0.80$, $p=0.0002$). However, these correla-

tions were not observed if the glucose-loaded cases were excluded. Therefore, serum glucose and insulin levels are not important factors in the variation in MRGlc under fasting conditions.

DISCUSSION

There are two main problems with FDG studies in normal fasting subjects; first, regional disparities exist, and second; there is marked variation in the degree of myocardial FDG accumulation and image quality.

Regional Disparities in FDG Accumulation in Normal Volunteers

Gropler et al reported that myocardial FDG accumulation in the lateral wall of the left ventricle was greater than that in the ventricular septum under fasting conditions.⁸ Berry et al reported that the differences between the myocardial/blood-pool FDG activity ratios of the lateral wall and septum were not significant under both glucose-loading and fasting conditions.⁹ Hicks et al reported that regional myocardial glucose metabolism in the lateral wall determined by Patlak analysis (=MRGlc) is significantly higher than that in other regions, even under tightly controlled metabolic conditions of hyperinsulinemic-euglycemic clamping.¹⁰ Choi et al reported that MRGlc in the posterolateral region is significantly high despite the absence of a partial-volume effect under both glucose-loaded and fasting conditions.¹⁶ According to previous reports, when quantitation is performed accurately, although the MRGlc in the posterolateral region is only slightly higher than that in other regions, even under glucose-loaded or hyperinsulinemic-euglycemic clamping conditions, this difference is statistically significant.

The results of our quantitative analysis are consistent with these observations. The regional disparities in MRGlc in the glucose-loaded condition were not statistically significant in our study, perhaps due to the small number of samples. However, MRGlc of the posterolateral region were significantly higher (although still within 20%) than those of other regions in the fasting state. By visual evaluation, the regional disparities were pronounced in studies in which the value of MRGlc was in the transitional zone.

With regard to Gropler's report, it is conceivable that many subjects showed rather marked regional disparities in the transitional zone because scans were taken after relatively short periods of fasting (5 to 8 h), and regional variations in FDG accumulation could have been overestimated, since they were evaluated using automatic edge-detection, including partial-volume effects which gives the relative counts of regions of interest. In Berry's series, studies were carried out with relatively long periods of fasting (more than 12 h). This could have resulted in high blood-pool activities of FDG, which might have affected the semi-quantitative analysis and resulted in the loss of statistical significance.

Thus, visual evaluation is more likely to emphasize regional disparities. Therefore, an accurate quantitative analysis should be undertaken to evaluate glucose uptake by myocardium. Currently, to detect viable but ischemic myocardium, additional information, such as myocardial perfusion, coronary artery anatomy and wall thickness, are taken into account when interpreting PET studies. Further studies are necessary to elucidate the exact mechanism of the regional disparities in normal myocardium. However, it should be fair to say that an apparently distinct difference the FDG uptake can be regarded as evidence of the existence of an abnormal glucose metabolism in the myocardium.

Deviations in Myocardial Glucose Uptake and Metabolic Conditions

In contrast to the brain, the heart uses multiple substrates for energy metabolism. Substrate utilization by the heart involves a complex interplay between myocardial perfusion, energy demand, hormonal control and the availability of substrates.²²⁻²⁶

Patterns of substrate uptake by human myocardium show marked differences between the fasting state, which shows low rates of uptake of carbohydrates and high rates of uptake of lipids such as free fatty acid and sometimes triglyceride, and the fed state, which shows high rates of uptake of glucose and lactate, and accounts for virtually all of the concurrent oxygen uptake. This change from predominantly carbohydrate to predominantly lipid usage is explained by the glucose-free fatty acid cycle

reported by Randle et al²⁶

In 1971, Lassers et al demonstrated a significant negative linear relationship between the myocardial extraction of glucose and the arterial free fatty acid concentration in healthy fasting men using arterial and coronary sinus catheterization.²⁷ Wisneski et al used coronary sinus catheterization and radioisotopic methods to demonstrate that the circulating level of free fatty acids played a major role in determining the amount of glucose extracted and oxidized by normal human myocardium.²⁸ They also demonstrated that a high percentage of arterial free fatty acids was extracted by the myocardium to undergo rapid oxidation.²⁹

Our study using non-invasive methods demonstrated a negative linear relationship between arterial free fatty acid levels and myocardial glucose uptake, as has been demonstrated invasively by most previous studies. Recently, using rats and a radioisotopic method, Holness et al studied the continuous change in glucose utilization and metabolic conditions during the fed-to-starved transition.³⁰ They found a rapid decline in cardiac glucose utilization during 9–24 h of starvation, and a concomitant elevation of arterial free fatty acid concentrations over the same period. The period of starvation in which cardiac glucose utilization declines during the fed-to-starved transition in humans has yet to be determined. Our results suggest that the decline in cardiac glucose utilization occurs during the period of clinical fasting in which FDG-PET studies are performed. Serum free fatty acid levels may increase during this same period in the fed-to-starved transition. Insulin and glucose levels do not reflect myocardial FDG uptake in the fasted states (Fig 3b, c) perhaps because they may change to a starved level earlier during starvation than the decline in cardiac glucose utilization, due to the effect of the glucose-free fatty acid cycle reported by Randle et al. Choi et al described a similar relation between myocardial FDG uptake and metabolic conditions.¹⁶ Since they performed one glucose-loaded study and one fasted study in each subject, they did not investigate the reproducibility of their results under fasting conditions. Our results that MRGlc under fasted conditions showed wide intra-subject variability and

that a good correlation exists between MRGlc and free fatty acid levels strongly suggest that the variation in MRGlc is primarily due to the difference in the extent of the fed-to-starved transition. Our results also suggest that the fed-to-starved transition in humans is not controlled solely by the duration of fasting, but also by other factors such as the previous meal, skeletal muscle activity, and the mental or hormonal state. If such factors are controlled and the free fatty acid level is maintained at a certain level, the variation in MRGlc may be reduced. In this study, the subjects were healthy volunteers and younger than the patients who are usually studied. However, factors other than the duration of fasting were quite different. Therefore, we should expect a wide variety in the metabolic conditions of the myocardium. This could have resulted in a more pronounced intra-subject difference in the degree of myocardial FDG accumulation or image quality than if we had examined actual patients. Inpatients, in particular, should have very uniform food intake and activity levels. Further studies will be needed to investigate these factors.

Conclusion

Myocardial glucose uptake in normal humans is considered to be suppressed in the fasting state with a continuous fed-to-starved transition. In addition, free fatty acid levels are thought to reflect the transition of myocardial glucose uptake. However, this transition is not controlled solely by the duration of fasting. Prominent regional disparities can be observed visually in subjects with an MRGlc in the transitional range. These facts must be considered when evaluating the results of FDG-PET studies under fasting conditions. Moreover, FDG-PET studies under fasting conditions have the potential to evaluate the ability of myocardium to use substrates efficiently. Additional studies will be required to confirm this conclusion and to establish a more reliable strategy for assessing myocardial glucose metabolism under fasting conditions using FDG and PET.

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