Characteristics of myocardial $^{18}$F-fluorodeoxyglucose positron emission computed tomography in dilated cardiomyopathy and ischemic cardiomyopathy

Hitoshi Yamaguchi, Shinji Hasegawa, Jun Yoshikawa, Toshiisa Uehara, Katsuji Hashimoto, Hideo Kusuioka, Tsunehiko Kuzuya, Masatsugu Hori and Tsunehiko Nishimura

*Division of Tracer Kinetics, Biomedical Research Center, Osaka University Graduate School of Medicine
**Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine
***Cardiovascular Division, Osaka National Hospital
****Institute for Clinical Research, Osaka National Hospital

Myocardial $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used to assess myocardial ischemia and viability, but few studies have conducted on FDG-PET for dilated cardiomyopathy (DCM). We investigated myocardial FDG uptake in patients with DCM in comparison with ischemic cardiomyopathy (ICM). Twenty-four patients with heart failure were included in this study. Fourteen of them were diagnosed as DCM and the other 10 were ICM. All of them underwent myocardial FDG-PET at fasting and after glucose loading the same day. FDG uptake was quantified by the ratio of the counts at the heart to those at the liver (H/L ratio). Left ventricular (LV) function was measured by echocardiography. We classified FDG distribution patterns in the myocardium in the fasting state into 3 types (faint uptake, regional uptake and diffuse uptake). In DCM patients, 5 had faint uptake, 7 had regional uptake, and the other 2 had diffuse uptake. On the other hand, all ICM patient had regional uptake ($p < 0.05$). In DCM, there were no significant relationships between the patterns and LV functions. On the other hand, there were close correlation between the H/L ratio after glucose loading and the left ventricular ejection fraction ($r = 0.680$, $p < 0.01$). The changes in PET images caused by glucose loading were classified into 2 types (non-reversing and reversing patterns). DCM significantly showed a non-reversing pattern (86%, 12 of 14 patients) whereas ICM showed mainly a reversing pattern (70%, 7 of 10 patients; $p < 0.05$). In conclusion, myocardial FDG uptake after glucose loading may indicate a myocardial viable mass although FDG uptake at fasting was not evidently related to LV function. The change in the pattern of the FDG image from fasting to glucose loading may be useful in differentiating DCM from ICM.

Key words: positron emission tomography, $^{18}$F-fluorodeoxyglucose, heart failure, dilated cardiomyopathy, ischemic cardiomyopathy

INTRODUCTION

$^{18}$F-fluorodeoxyglucose (FDG) was developed as an analog of glucose to assess myocardial glucose utilization.

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For reprint contact: Tsunehiko Nishimura, M.D., Ph.D., Division of Tracer Kinetics (D9), Biomedical Research Center, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, JAPAN.
E-mail: nishimura@tracer.med.osaka-u.ac.jp

FDG positron emission tomography (PET) has been mainly applied to ischemic heart disease, and is helpful in evaluating the severity of ischemic injury or residual viability of myocardial infarction, but there are few reports on heart failure patients such as those with dilated cardiomyopathy (DCM) because of the complexity of the pathology in DCM.

In this study, myocardial FDG accumulation was investigated in those patients who had heart failure due to DCM and ischemic cardiomyopathy (ICM). The relationship between myocardial FDG accumulation and severity
of heart failure was examined, and the difference in the characteristics of FDG images for DCM and ICM was elucidated.

**MATERIALS AND METHODS**

Twenty-four patients were involved in this study. Fourteen had DCM and 10 had ICM. All the patients had the study procedure explained to them, and gave their informed consent.

*Dilated cardiomyopathy*

Fourteen patients admitted to our hospital due to heart failure NYHA class III or IV were included. The LV ejection fraction (EF) was less than 40% at the time of admission. Eleven patients were men and three were women. Their mean age was 43 ± 15 years old. All underwent coronary angiography (CAG) and endomyocardial biopsy, which revealed that they did not have significant coronary artery stenosis, and were compatible with DCM. Patients with severe glucose intolerance (blood glucose > 200 mg/dl at glucose loading), a history of hypertension, vasospastic angina or valvular heart disease were not included.

*Ischemic cardiomyopathy*

All patients in the ICM group were diagnosed with coronary artery disease (CAD) by CAG or myocardial perfusion SPECT, and showed such signs of heart failure as LVEF less than 40% and NYHA class III or IV at the time of admission. Eight were men and two were women. Their mean age was 64 ± 7 years. Patients with valvular heart disease were not included.

As routine examinations, all patients underwent 2 dimensional echocardiography, stress/rest or delayed myocardial perfusion SPECT with ²⁰¹TI or ⁹⁹mTc-tetrofosmin, and cardiac catheterization within 2 weeks of the FDG-PET study.

With the B mode image of echocardiography in the parasternal long axis view, left ventricular dimensions were measured and the left ventricular ejection fraction was calculated by the Teichholz method.⁶

**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 and oral glucose loading conditions on the same day. The Headtome V had 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.

The FDG-PET study was performed from the morning after overnight fasting for at least 12 hours. Transmission scanning with rotating ⁶⁸Ge line sources was done for attenuation correction. Three hundred and seventy MBq of sterile FDG produced at the radioisotope laboratory in Osaka University Hospital was then injected via an antecubital vein under fasting condition. After a 45 minute distribution phase, the first FDG emission scan (PET1) was performed for 10 minutes, and the patients were then allowed to have lunch. Within 30 minutes after lunch, 75 g of glucose was orally loaded, and 50 minutes later another 370 MBq of FDG was injected. Fifteen minutes before the second injection, the second emission scan (PET2) was performed for subtraction images. The third emission scan (PET3) was performed 45 minutes after the second FDG injection. We used the PET1 image to show myocardial FDG uptake in the fasting condition, and the PET3 minus PET2 image to show myocardial FDG uptake under glucose loading. A series of transverse slices were reconstructed from the acquired data, and oblique tomograms perpendicular to the long and short axes of the left ventricle were reconstructed.

We obtained data on the metabolic substrate from samples of blood taken from patients when injecting FDG. We measured the levels of blood glucose, serum immunoreactive insulin and free fatty acid at fasting 10 minutes before injecting FDG, and blood glucose and immunoreactive insulin after glucose loading 10 minutes after injecting FDG.

**Image analysis**

Myocardial FDG uptake was evaluated visually and quantitatively.

Appropriate slices of the same thickness located in the mid position of the left ventricle or the liver were selected from transaxial view images of. Regions of interest were set on the heart and the liver to quantify the H/L ratio (Fig. 1). The H/L ratio was defined as Eq. 1, taking the physical half-life into account (32% of FDG decay in 60 min). The normal H/L value obtained from 3 normal male volunteers (age: 30 ± 1 years old) was 4.7 ± 1.0.

\[
H/L = \frac{HMC3 - 0.68 \times HMC2}{LMC3 - 0.68 \times LMC2}
\]  
(Eq. 1)

where HMC3 is Heart mean count in PET3, HMC2 is

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Fig. 2 Three types of myocardial FDG uptake pattern: (A) faint uptake pattern, (B) regional uptake pattern (in this case, FDG accumulation in anteroseptal and inferior walls was noted), and (C) diffuse uptake pattern.

A: Non-reversing  B: Reversing

Fasting

Glucose loading

Fig. 3 Two types of the change in myocardial FDG uptake induced by glucose loading. A: Non-reversing pattern: FDG accumulation is enhanced after glucose loading without any changes in distribution. In this case, anteroseptal and inferior walls show higher uptake both at fasting and after glucose loading. B: Reversing pattern: Glucose loading augmented FDG accumulation more strongly at the myocardium with low FDG uptake during fasting. In this case, anterior wall shows higher uptake than the other regions at fasting. On the contrary, after glucose loading, infero-septal wall shows higher uptake than anterior wall.

Heart mean count in PET2, LMC3 is Liver mean count in PET3 and LMC2 is Liver mean count in PET2.

The distribution of FDG patterns under fasting were visually classified into 3 groups: (1) faint uptake group, i.e., myocardial FDG uptake was almost equivalent to that of the ventricular cavity, and the myocardium was not identified (Fig. 2A), (2) regional uptake group, i.e., there were both high and low uptake regions in the myocardium (Fig. 2B), (3) diffuse uptake group, i.e., the FDG uptake was relatively high and almost evenly distributed in the left ventricle (Fig. 2C). At fasting, the count of 7000 per second per g organ weight (cps/g) was used as 100% of the scale because almost all DCM patients (12/14) had less than 7000 cps/g in the field of view. When the maximum counts of the myocardium were normalized in DCM patients (2/14) with more than 7000 cps/g (2 patients had a diffuse uptake pattern) at fasting. After glucose loading, almost all DCM patients had a diffuse uptake pattern and the maximum counts in the myocardium were $10529 \pm 4013$ cps/g, so that after glucose loading the maximum counts of the myocardium used to normalize in all DCM patients.

The changing types of the FDG uptake induced by glucose loading were classified visually into the following two patterns, i.e., non-reversing pattern and reversing pattern (Fig. 3). In the non-reversing pattern, the images at fasting had variable uptake pattern, but after glucose loading, all regions depicted high uptake. In this pattern, FDG accumulation in low uptake regions during fasting never exceeded that in the high uptake regions during fasting even after glucose loading. In the reversing pattern, the images at fasting had a regional uptake pattern, but after glucose loading, the regions showing low uptake at fasting revealed higher uptake than those showing high uptake at fasting.

Statistical analysis
Data are expressed as the mean ± 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). Independence was assessed by Chi-square test ($\chi^2$). A p value less than 0.05 was considered significant.

RESULTS

Blood data of subjects
Blood glucose levels at fasting were $87.5 \pm 10.1$ mg/dl in DCM patients and $98.4 \pm 8.8$ mg/dl in ICM patients (n.s.), respectively, but after glucose loading DCM patients (167 ± 41 mg/dl) had an appreciably lower blood glucose level than ICM patients (220 ± 43 mg/dl, p < 0.01). Serum immunoreactive insulin levels at fasting were 2.77 ± 4.13 μU/ml in DCM patients and 5.13 ± 3.83 μU/ml in ICM patients (n.s.). Those at 60 min after glucose loading in DCM patients (85.2 ± 64.8 μU/ml) and ICM patients (141.2 ± 97.4 μU/ml, n.s.) were not significantly different. Serum free fatty acid levels at fasting were 322 ± 185 mg/dl in DCM patients and 400 ± 231 mg/dl in ICM patients (n.s.). After glucose administration all patients had a high level of serum insulin and some patients had hyperglycemia, especially ICM patients. We considered that the fasting time was enough to lower the serum insulin level, and the amount of glucose administered to patients was enough to raise the insulin levels.

There was no significant correlation between blood data and the H/L ratio at fasting or after glucose loading. So the effect of fasting on FDG uptake might be little.

Relationship between FDG uptake pattern and left ventricular function
In the fasting condition, 5 of 14 DCM patients had a faint
Table 1  Left ventricular dimensions and ejection fraction in patients with dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) classified by myocardial FDG uptake patterns during fasting

<table>
<thead>
<tr>
<th></th>
<th>DCM</th>
<th>ICM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Faint uptake</td>
<td>Regional uptake</td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Dd (mm)</td>
<td>67 ± 7</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>Ds (mm)</td>
<td>51 ± 14</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>27 ± 15</td>
<td>36 ± 17</td>
</tr>
</tbody>
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Dd: enddiastolic dimension, Ds: endsystolic dimension, EF: ejection fraction.

2) This finding suggests that DCM and ICM have different changes in the patterns caused by glucose loading.

**DISCUSSION**

This study revealed that myocardial FDG uptake patterns at fasting in patients with DCM were of 3 types. Nevertheless, no relationship could yet be identified between these patterns and left ventricular function. On the other hand, all patients with ICM had a regional uptake pattern. The incidence of the regional pattern was significantly higher in ICM than in DCM. Secondly, the amount of myocardial FDG uptake after glucose loading in DCM significantly correlated with LVEF. Finally, the changes in the FDG uptake patterns induced by glucose loading were of two types: DCM patients had a non-reversing pattern, whereas ICM patients had a reversing pattern.

**Fasting image of myocardial FDG uptake**

In the fasting condition, normal myocardium uses fatty acid as an energy substrate rather than glucose so that FDG does not accumulate very much in normal myocardium. In this study, some patients both with DCM and ICM had a myocardial FDG uptake when fasting. In ICM, ischemia impairs the metabolism of free fatty acid and promotes glucose utilization instead of fatty acid, resulting in increasing FDG uptake when fasting. It is reported that glucose utilization in a failing heart also increases even during fasting as in infant's heart, and that several steps in energy metabolism in a failing heart were also altered to those in infants, but this metabolic change cannot explain the regional difference in FDG uptake observed in some DCM patients. The regional change may therefore be caused by different progress in atrophic change in a longitudinal time course.

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For quantification of myocardial FDG uptake, we measured the % dose uptake in the myocardium at fasting or after glucose loading, and the variation was very great. We therefore used the count of the myocardium normalized by that in liver.

**Glucose loading image of myocardial FDG uptake**

After glucose loading, myocardial FDG uptake evaluated by the H/L ratio significantly correlated with LVEF in DCM patients. This suggests that myocardial FDG uptake after glucose loading may reflect a viable and contractile myocardium. If so, myocardial FDG uptake under glucose loading may be a prognostic index in DCM. It was reported that the coefficient of variance of the regional FDG utilization rate could indicate the prognosis in patients with DCM. Further study should follow up the changes in myocardial FDG uptake under glucose loading and LV function in DCM to clarify the usefulness of this index in predicting clinical prognosis.

We did not analyze the H/L ratio in ICM patients, because almost all ICM patients had a regional uptake pattern whereas almost all DCM patients had a diffuse uptake pattern.

**Changes in myocardial FDG uptake pattern**

Changes in the pattern of FDG uptake induced by glucose loading were related to the presence of CAD. Patients with a reversing pattern had CAD more frequently than those who had a non-reversing pattern. It was speculated that with regard to the reversing pattern, FDG positive regions at fasting were due to myocardium impairment induced by ischemia, and had a smaller viable mass than a normal region. On the other hand, a non-reversing pattern suggests that the FDG pattern at fasting faithfully represents the distribution of mildly damaged myocardium and scar, but two DCM patients had a reversing pattern even though they had no CAD. It could be speculated that some severe impairment such as hypoxia due to microcirculation disorder or other pathological injury may be an underlying factor in the myocardium of these patients. On the other hand, three ICM patients had a non-reversing pattern. Two of them had completed myocardial infarction without residual ischemia, so FDG uptake was poor both at fasting and after glucose loading in these regions. That may result in a non-reversing pattern. The remaining one had ischemic myocardium with normal viability, so that FDG uptake was high in this region both at fasting and after glucose loading.

**Study limitations**

In the fasting condition, myocardial FDG uptake may be influenced by a difference in the fasting state, or the physical or mental, so that the reproducibility of the FDG image may come into question. It is difficult to check reproducibility because of the cost and exposure of FDG, so we did not check this point. FDG-PET study was therefore performed after sufficient fasting time, and the patients were asked to rest as much as possible.

After glucose loading myocardial FDG uptake may be influenced by glucose tolerance and the serum insulin level, and liver FDG uptake may change according to blood glucose level or liver blood pool making it difficult to assess myocardial viability only by the FDG count in the myocardium or liver after oral glucose loading. The insulin clamp technique may be the best, but not practical, and there was sufficient glucose loading in this study. Because patients with diabetes mellitus were excluded, image quality in this study is considered to be scarcely inferior to those obtained with insulin clamping.

In our method, the myocardium/liver FDG count ratio was measured simply by using one of the slices in the PET image. This method could be useful for DCM patients after glucose loading because almost all patients had a diffuse FDG uptake pattern in the left ventricle, but in most ICM patients, FDG uptake patterns were heterogeneous, so we did not analyze them in this method.

In conclusion, myocardial FDG uptake at fasting in DCM took on various patterns, but the relationship between the pattern and LV function was not observed. On the other hand, the fasting pattern in ICM showed only regional uptake. Myocardial FDG uptake after glucose loading correlates with left ventricular function. This finding suggests that a higher FDG uptake level after glucose loading is a sign of presence of a larger viable mass of myocardium. The presence of coronary artery disease may be indicated by the way in which the pattern of FDG uptake changes from fasting to glucose loading.

**REFERENCES**


