Quantitative analysis of myocardial glucose utilization in patients with left ventricular dysfunction by means of ^{18}F-FDG dynamic positron tomography and three-compartment analysis

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Abstract. *Purpose:* Myocardial glucose utilization (MGU) is altered in various heart diseases. The aim of this study was to quantitatively assess regional myocardial glucose utilization in patients with left ventricular (LV) dysfunction by dynamic ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET).
Methods: A total of 18 subjects were studied, including ten with LV dysfunction (seven with idiopathic dilated cardiomyopathy and three with aortic regurgitation; NYHA II in 8 and III in 2) and eight healthy normal volunteers. Patients with diabetes mellitus were excluded. A dynamic PET study was performed for 40 min following the injection of 370 MBq of FDG after 50-g glucose loading. On the basis of a three-compartment model, MGU, K_1, k_2, and k_3 were computed on a pixel by pixel basis to generate LV myocardial parametric maps. FDG standardized uptake value (SUV) was also calculated using static images obtained 40 min after FDG injection. These metabolic values were compared with myocardial flow distribution (%Flow), LVEF, LV volumes, and LV wall thickening (WT) determined by gated myocardial single-photon emission computed tomography using QGS software in eight myocardial segments.
Results: MGU correlated positively with LV volumes and negatively with LVEF. K_1 was significantly higher in the segments of the patients than in those of the normal volunteers (0.082±0.055 vs 0.041±0.017 ml min^{-1} g^{-1}, p<0.05), although there was no difference in MGU between the groups. On the other hand, SUV, k_2, and k_3 did not differ significantly between the groups. Among the patients, the K_1 values were significantly higher in the areas with impaired WT (%WT<17%) (0.109±0.063 vs 0.069±0.062 ml min^{-1} g^{-1}, p<0.05) and in the areas with flow reduction (%Flow<71%) (0.112±0.076 vs 0.071±0.046 ml min^{-1} g^{-1}, p<0.05).
Conclusion: These results indicate that glucose utilization was preserved in the patients with LV dysfunction, mainly due to an increase in glucose transport, particularly in the regions with severely impaired LV function. Thus, the quantitative assessment of myocardial glucose utilization by FDG dynamic PET may provide useful information for assessing the regional myocardial metabolic status in patients with LV dysfunction.

Keywords: Positron emission tomography – Heart failure – Glucose metabolism – Glucose transporter – ^{18}F-FDG

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Introduction

^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) imaging has been used to assess myocardial viability in clinical settings [1–10]. Myocardial glucose utilization (MGU) is preserved in viable myocardium and it may be modulated by myocardial energetic status or ischemia [10–14]. It has been reported that MGU is enhanced by increased energetic stress, pressure overload, and myocardial ischemia [12, 13]. Cellular and molecular mechanisms have been proposed to explain the enhancement of glucose

utilization. It is presumed that glucose transport into myocardial cells regulates the rate of glucose metabolism in the myocardium [10, 12, 13, 15–20]. The sarcolemmal expressions of glucose transporters (GLUTs), such as GLUT1 and GLUT4, have an important role in increasing glucose transport into myocardial cells [10, 13, 21].

MGU is assessed quantitatively using dynamic FDG PET [22–26]. The graphical plot method is widely used [27]. However, glucose metabolic rate derived from this method is calculated using the k complex regardless of the values of K_1, k_2, and k_3. Quantitative measurement of the myocardial glucose metabolic rate using a three-compartment model has been proposed [23], but its clinical implications have not been completely evaluated. The entry of glucose and its analogue is mainly regulated by glucose transporters [10]. In three-compartment analysis, K_1 may indicate a rate constant of glucose transport from blood to myocardial cells. Therefore, the K_1 value may reflect GLUT expression, which mainly depends on the process of glucose transport into myocardial cells. Myocardium with left ventricular (LV) dysfunction may show increased GLUT expression due to increased myocardial energetic stress; therefore, the individual assessment of each k value may provide new information regarding myocardial pathological conditions in a clinical setting. The aim of this study was to evaluate whether K_1, k_2, and k_3 values are affected in myocardium with LV dysfunction.

Materials and methods

Study population

Ten patients with LV dysfunction (eight males and two females, mean age 62±8 years) were enrolled in this study. The clinical characteristics are shown in Table 1. The ten patients comprised seven with idiopathic dilated cardiomyopathy (DCM) and three with aortic regurgitation (AR). The LV diastolic dimension and the percent fractional shortening were 64.1±8.0 mm and 17.8%±8.5%, respectively, on echocardiography. Patients with diabetes mellitus were excluded from this study. Plasma glucose concentration under the fasting condition was 92.6±5.0 mg/dl, and the percentage of hemoglobin A1c (HbA1c) was 5.3%±0.2% (normal upper limit <5.6%). Seven patients underwent myocardial perfusion single-photon emission computed tomography (SPECT). All medical treatments were continued before the scan. Two out of seven patients did not undergo ECG-gated SPECT owing to atrial fibrillation. All patients were proved to have no significant coronary arterial stenosis by coronary angiography. As the control group, eight normal volunteers (all males, mean age 33±5 years) without any abnormal ECG findings at rest were enrolled in this study. They had no history of cardiac disease, hypertension, hyperlipidemia, or diabetes mellitus. Their fasting glucose and HbA1c levels were 90.4±5.0 mg/dl and 5.1%±0.2%, respectively. Six of the normal volunteers underwent ECG-gated myocardial perfusion SPECT. The study was approved by the Ethics Committee of Hokkaido University Hospital. Written informed consent was obtained from all the patients and normal volunteers.

^{18}F-FDG PET and data processing

PET imaging was performed using a whole-body scanner (EXACT HR+; CTI/Siemens, Knoxville, TN, USA). After a minimum of 6 h fasting, a 50-g glucose solution was administered orally 30 min before FDG injection. A 2D data acquisition was used in this study. A transmission scan was performed using an external source of ^{68}Ga. Using an infusion pump, 370 MBq of FDG in 6 ml solution was injected intravenously over 3 min. After starting the injection, a dynamic PET data acquisition was performed for 40 min: 20 s×4, 40 s×4, 60 s×4, 180 s×4 and 300 s×4. A static image was also obtained from 40 to 50 min after FDG injection. The intrinsic resolution of the system was 4.5 mm full-width at half-maximum.

Input function was assessed from the time–activity curve drawn in the left atrium on dynamic PET images. Based on a three-compartment model, parametric maps were computed using a non-linear least squares fitting method pixel by pixel, with the correction of spillover from cardiac chambers to the myocardium [23] (Fig 1). The value of k_4 was assumed to be zero. The LV myocardium was divided into eight segments. The eight regions of interest (ROIs) for each case were drawn manually on the basal anterior, apical anterior, basal septum, apical septum, basal inferior, apical inferior, basal lateral, and apical lateral wall. The values of K_1, k_2, and k_3 were calculated for each ROI. MGU was calculated using the formula shown below. A blood sample was collected at the time of FDG injection to measure plasma glucose level, which was used for MGU calculation.

$$\mathrm{MGU}(\mu\mathrm{mol/g\ per\ min}) = 1/\mathrm{LC} \times (K_1 \times k_3)/(k_2 + k_3) \times \mathrm{Cp}$$

where LC is lumped constant (=0.67) and Cp is the plasma glucose level (mmol/l). The standardized uptake value (SUV) of the

Table 1. Clinical characteristics of the ten patients

Patient no.	Age (years)	Sex	Diagnosis	NYHA	%FS	LVDd (mm)	LAD (mm)	SPECT	QGS
1	45	F	DCM	II	9	64	52		
2	57	M	DCM	II	13	78	53		
3	56	M	AR	II	24	59	48		N.D.
4	69	M	DCM	III	23	60	41		
5	64	F	DCM	II	16	61	40		
6	65	M	DCM	II	7	54	35		
7	69	M	DCM	III	20	62	75		N.D.
8	57	M	DCM	II	8	78	51	N.D.	N.D.
9	71	M	AR	II	27	66	43	N.D.	N.D.
10	53	M	AR	II	31	59	49	N.D.	N.D.

%FS percent fractional shortening, *LVDd* left ventricular dimension in the diastolic phase, *LAD* left atrial dimension, *N.D.* not done

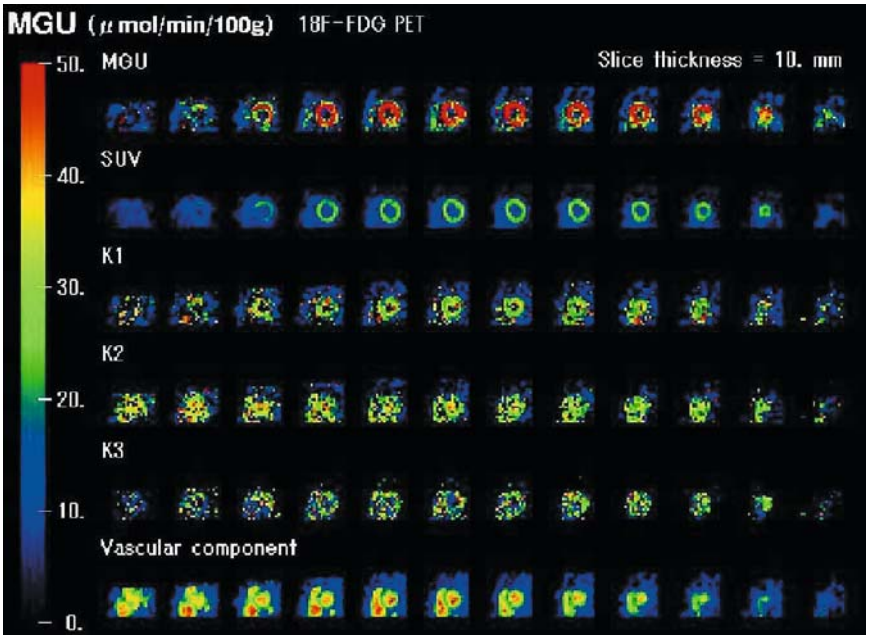

Fig. 1. Typical parametric images of glucose metabolic parameters in a patient with DCM (case 1). Parametric maps of MGU, SUV, K_1, k_2, k_3, and vascular compartment are shown from the *top row* to the *bottom row*

myocardium was also calculated using a static image obtained 40–50 min after FDG injection and employing the formula: SUV = myocardial uptake (Bq/g) × body weight (g)/injected dose (Bq).

Myocardial perfusion SPECT

Myocardial perfusion SPECT was performed using a rotating dual-detector gamma camera with the detectors mounted at right angles and fitted with high-resolution collimators (Vertex; ADAC Laboratories, Milpitas, CA, USA). Data acquisition was started 30 min after the injection of 740 MBq ^{99m}Tc-tetrofosmin at rest. The image acquisition variables included the following: a 140-keV photopeak with a 20% window, 64 projections at 40 s/projection over a 180° (90°/detector) elliptical orbit, a 38-cm roving detector mask, and a matrix size of 64×64. Acquisitions were gated for eight frames in a cardiac cycle.

The eight-interval projection data sets were prefiltered with a 2D Butterworth filter (order 2.5, critical frequency 0.22 cycles/pixel, pixel size 0.64 cm) and reconstructed with filtered backprojection using a ramp filter; no attenuation correction was performed. The resliced transaxial image sets were reoriented into short-axis sets that were then processed in the batch mode using a stand-alone workstation running automatic LVEF quantification software. The projection data sets were also summed and prefiltered with a 2D Butterworth filter (order 2.5, critical frequency 0.33 cycles/pixel, pixel size 0.64 cm), producing high-count short, vertical, and horizontal long-axis images for qualitative interpretation and for polar plot and circumferential count displays.

The LV myocardium was automatically divided into 20 segments according to quantitative perfusion SPECT (QPS) software (AutoQUANT; ADAC Lab., CA, USA). The most basal six segments and two apical regions were excluded from analysis. The average values of two regions in the septal and lateral segments corresponding to the segments on the FDG scan were calculated. A total of eight segments, comprising four basal and four apical segments, were used for analysis. The percentages of myocardial flow (%Flow) of these eight segments were calculated using the values of QPS software.

Regional LV function was assessed on the basis of the wall thickening (WT), derived from QGS software [28], of the eight segments. LV global functional parameters, such as LVEF, end-diastolic volume (EDV) and end-systolic volume (ESV), were also calculated using QGS software. Additionally, the average value of eight segmental regional WT was used as an index of LV global function.

Data analysis

The values of the parameters were compared between the patients with LV dysfunction and the normal volunteers. In addition, among the patients, the values of glucose metabolic parameters were compared between the groups with and without perfusion or wall thickening abnormality. Perfusion and wall motion abnormalities were defined as less than 71% for %Flow, and less than 17% for WT, respectively. These cut-off values were obtained from the average values in patients, because values of normal volunteers were not obtained in this study.

Statistical analyses

The values are expressed as mean ± SD. The differences in values were evaluated using a two-tailed unpaired *t* test. Regression analysis was performed using a linear regression method. A p value less than 0.05 was considered statistically significant.

Results

The blood glucose level at the time of ^{18}F-FDG injection was 160±21 mg/dl in the normal volunteers and 131±29 mg/dl in the patients (p=0.063). There was no significant

Table 2. Comparison of parameters between normal volunteers and patients with LV dysfunction

	Normal volunteers	Patients	*p* value
MGU (μmol/100 g per min)	27.6±12.7	35.8±17.6	0.3290
SUV	4.07±1.15	5.09±1.75	0.1931
K_1 (ml min^{-1} g^{-1})	0.041±0.017	0.082±0.055	0.0170*
k_2 (/min)	0.071±0.027	0.140±0.122	0.1585
k_3 (/min)	0.100±0.055	0.123±0.088	0.7449
WT (%)	44.7±6.1	17.0±6.8	0.0058*
%Flow (%)	76.6±4.5	71.7±11.2	0.7182
EDV (ml)	93.6±10.5	179.4±5.0	0.0034*
ESV (ml)	40.6±8.5	137.3±54.0	0.0045*
EF (%)	56.8±6.1	25.8±5.0	<0.0001*

*$p<0.05$

difference in rate–pressure products between the patients and normal volunteers.

MGU did not differ between the two groups, but K_1 in the patients with LV dysfunction was significantly higher than that in the normal volunteers (0.082±0.055 vs 0.041±0.017 ml min^{-1} g^{-1}, $p<0.05$) (Table 2). There was no significant difference in k_2, k_3 or SUV between the two groups.

Correlations between LV functional parameters and myocardial glucose metabolic parameters in patients are shown in Table 3. There were trends towards positive correlations between MGU and LV volumes, and an inverse correlation between MGU and EF. Moreover, MGU was inversely correlated with WT ($r=-0.908$, $p<0.05$).

In segment-based analysis, MGU, K_1, and SUV in the patients were significantly higher than those in normal volunteers (Table 2). However, there were no significant differences in k_2 or k_3 between the groups.

A comparison between patients with and patients without myocardial flow reduction is shown in Table 4. The K_1 value in the segments with a flow reduction was significantly higher than the value in those without a flow reduction despite the absence of a difference in MGU (0.112±0.076 vs 0.071±0.046 μmol/100 g per min, $p<0.05$).

Table 3. Correlation coefficient values between metabolic parameters and LV function

	EDV (ml)	ESV (ml)	EF (%)	WT (%)
MGU (μmol/100 g per min)	0.478	0.513	–0.551	–0.908*
SUV	0.264	0.216	0.290	0.333
K_1 (ml min^{-1} g^{-1})	0.031	0.056	–0.345	–0.864
k_2 (/min)	0.538	0.486	0.073	–0.352
k_3 (/min)	0.701	0.612	0.385	0.423

*$p<0.05$

Table 4. Comparison of parameters in segments with or without a flow reduction

	Segments with %Flow>71% (n=26)	Segments with %Flow<71% (n=14)	*p* value
MGU (μmol/100 g per min)	30.6±16.7	36.3±18.5	0.2470
SUV	4.63±1.53	4.83±1.62	0.5129
K_1 (ml min^{-1} g^{-1})	0.071±0.046	0.112±0.076	0.0407*
k_2 (/min)	0.134±0.164	0.232±0.244	0.0682
k_3 (/min)	0.156±0.158	0.118±0.099	0.7120
WT (%)	18.2±5.1	12.3±7.1	0.0034*
%Flow	79.1±5.7	59.4±9.2	<0.0001*

*$p<0.05$

Table 5. Comparison of parameters in segments with or without impaired WT

	Segments with WT>17% (n=30)	Segments with WT<17% (n=10)	*p* value
MGU (μmol/100 g per min)	34.0±18.2	42.9±19.0	0.1403
SUV	5.18±1.76	4.68±1.35	0.6197
K_1 (ml min^{-1} g^{-1})	0.069±0.062	0.109±0.063	0.0193*
k_2 (/min)	0.105±0.112	0.197±0.220	0.0208*
k_3 (/min)	0.203±0.168	0.110±0.098	0.1328
WT (%)	19.5±3.7	8.2±4.4	<0.0001*
%Flow (%)	75.7±9.8	66.1±12.1	0.0047*

*$p<0.05$

Furthermore, the segments with impaired WT had a higher K_1 value than those without impaired WT (Table 5, 0.109±0.063 vs 0.069±0.062, $p<0.05$).

Discussion

The major finding of this study is preserved MGU in patients with LV dysfunction, mainly due to an increased K_1 value. The increase in K_1 was most significant in the myocardial segments with perfusion and wall thickening abnormalities despite the absence of a difference in MGU. This analysis method provides values of each of the glucose metabolic parameters, including K_1, k_2, and k_3. These parameters seem to be useful in understanding the pathophysiological status of patients with LV dysfunction. Altered glucose transporters and glucose metabolism may be associated with the severity of the disease.

Comparison of glucose metabolism and GLUT expression

In experimental model studies, myocardial GLUT distribution and expression are affected by various stresses, such as ischemia, hypoxia, or left ventricular volume overload [10, 12, 15, 20, 29, 30]. On the other hand, Paternostro et al. reported that explanted failing human heart showed an increased GLUT-1 expression level and a decreased GLUT-4/GLUT-1 ratio [17]. Therefore, enhanced glucose utilization in patients with LV dysfunction may be due to an increased GLUT expression or translocation of GLUT in the myocardial cells. In this study, enhanced MGU in patients with LV dysfunction may be induced by increased myocardial wall stress or ischemia via enhanced GLUT expression or GLUT translocation. A significant increase in the K_1 value in patients may indicate increased GLUT distribution on the surface of myocardial cells. Enhanced or preserved myocardial glucose utilization is presumed to be beneficial for a heart which is under ischemia, or under increased pressure or volume overload [19, 31–33]. Metabolic switching from fatty acid to glucose metabolism via a molecular mechanism may be an adaptive response against ischemia or energetic stress [19]. On the other hand, recent data suggest that there is no difference in GLUT-1 and GLUT-4 expression in patients with non-ischemic heart failure in comparison with patients who have a non-failing heart. Thus, the biological relevance of an increased K_1 value is controversial [34]. Rate constant values derived using the three-compartment model may provide additional information regarding the myocardial glucose metabolic status and also GLUT activity in the myocardium, which may be useful to understand cardiac pathophysiology in a clinical setting. Moreover, it may be useful to provide new approaches to treat patients with coronary artery disease or a failing heart [10, 12, 19].

Comparison with ventricular dysfunction

An increase in MGU with an enhanced K_1 in patients with LV dysfunction may indicate that the myocardium with abnormal function preserves glucose utilization by enhancing K_1, which would seem to be a compensational effect. This finding is compatible with enhanced glucose utilization for hearts under increased stress or ischemia [12]. Furthermore, an increased K_1 value may reflect an increased GLUT expression level on the myocardial cell surface [29–31]. This may be a cardiac protective function [10, 13]. In the present study, MGU positively correlated with LV volume and negatively correlated with WT, indicating the relationship between myocardial glucose utilization and global LV function. Severe LV functional abnormality may induce enhanced glucose utilization. On the other hand, preserved glucose utilization in these segments may indicate the absence of significant fibrotic changes in our limited number of patients. A further study of a large number of patients is required to confirm our preliminary findings.

There was no significant difference in k_2 and k_3 values between the patients and the normal volunteers. There was also wide variability in the values of k_2 and k_3, particularly in the patients. This wide variability may reflect some aspects of glucose metabolic abnormality. However, the variability did not differ between the causes of LV dysfunction in this study.

Comparison with perfusion and wall thickening abnormalities

In this comparative study of patients with and patients without myocardial flow reduction and WT abnormality, there was a significant increase in K_1 values in the segments with flow reduction and WT reduction compared with the segments without such findings. However, MGU was not significantly different between the two groups. These findings may indicate that K_1 is a more sensitive index than MGU for the assessment of regional abnormality or disease severity. Although the precise mechanism underlying these findings is uncertain, an increased k_2 value may indicate increased efflux of glucose from myocardium to blood or impaired phosphorylation activity, which may be represented as the value of k_3. In this study, the k_3 value in segments with a severe WT abnormality tended to be lower than in those without such an abnormality. Myocardial WT may be closely associated with the metabolic status of the myocardium rather than with myocardial perfusion. In the quantitative analysis of glucose metabolism and the turnover rate of the tracer, partial volume effect should be considered. MGU may be greatly influenced by the partial volume effect, whereas the turnover rate of the tracer may be less affected. Therefore, K_1 may be more sensitive in assessing the alteration in glucose metabolism than MGU, particularly in the dysfunctional segments. An increased K_1 value may also be due to technical failure when fitting the time–activity curves of the blood pool and myocardium in the thinned myocardium for the appropriate mathematical model. In this respect, a basic study may be warranted to determine the technical reliability of each value under various conditions.

Advantages of compartment analysis in comparison with SUV measurements

SUV is considered a simple index for quantification of FDG uptake in the ROIs, and this technique has been used for the quantitative analysis of myocardial glucose utilization [35]. However, SUV may have a limitation in assessing the precise myocardial glucose metabolic status. In the assessment of cerebral glucose utilization, SUV exhibited limited accuracy in quantifying cerebral glucose metabolic status when compared with that derived using compartment analysis [36]. In myocardial analysis, too, myocardial metabolic conditions vary due to metabolic or myocardial pathological conditions. In particular, three-compartment analysis permits independent quantitative estimates of the rate constants K_1, k_2, and k_3 as well as the glucose metabolic rate. Considering these observations, compartment analysis may

provide insights into the precise myocardial pathophysiological status.

Study limitations

One of the major limitations of this study is the limited number of patients investigated. There seems to have been relatively large fluctuation in the estimated values due to pixel by pixel calculation. A further study with more patients might minimize such variation and yield more confident findings.

In this study, ^{18}F-FDG PET was performed after oral glucose loading, which may not maximize glucose utilization compared with hyperinsulinemic euglycemic clamp. In addition, the oral glucose loading technique may not ensure maintenance of the steady state condition for measurement of the kinetic constants or MGU. It has been reported that there is no difference in assessment of MGU between insulin clamp and oral glucose loading. However, the *k* complex value was lower in glucose loading than that in insulin clamp [37]. An increased K_1 value in patients with LV dysfunction was shown in this study after oral glucose loading. Moreover, the plasma glucose level of normal volunteers at the time of ^{18}F-FDG injection tended to be higher than that of patients with LV dysfunction, which likely explains that absence of a difference in MGU between the groups. Therefore, this increased K_1 value in patients seems to be a significant finding. However, measurement of glucose metabolic parameters under the steady state during hyperinsulinemic euglycemic clamp is needed to assess precise glucose metabolic parameters.

Patients with diabetes mellitus were excluded from this study, but there is a possibility of glucose tolerance abnormality in the participating patients. Consequently, the insulin level after glucose loading may be lower than that in patients without glucose tolerance abnormality. Initial glucose transport via GLUT-4 depends on the insulin level [10, 13, 16]. In addition, an insulin-induced GLUT-1 translocation pathway has been shown in a rat heart model [38]. Therefore, the K_1 value is assumed to be low in patients with glucose intolerance. In this study, the K_1 value was increased in patients, particularly in segments with impaired wall thickening. These findings indicate that increased MGU and K_1 values may be true in patients with LV dysfunction, even though the patients may have glucose intolerance. Substrates such as fatty acid and lactate may alter myocardial glucose transport, but they were not measured in this study.

Myocardial perfusion was assessed using SPECT without using PET. Percent flow (%Flow) represents relative flow distribution. Absolute myocardial blood flow measurement makes it possible to evaluate the precise relationship between myocardial blood flow and glucose metabolic status. However, the patients in this study did not have ischemic heart disease. Myocardial perfusion abnormality was mainly used to assess myocardial damage such as fibrotic changes. Additionally, K_1 may be dependent upon the level of myocardial perfusion, but it was not quantified in this study. A precise comparative study between glucose metabolic parameters and myocardial blood flow is needed.

In computing the parametric map of glucose metabolic parameters, spillover from blood activity into myocardial tissue was corrected [23]. However, accurate correction seems to be difficult. An insufficient spillover correction may cause overestimation of the K_1 value. This problem may be solved by means of phantom or blood pool imaging using ^{11}C-labeled carbon monoxide. Additionally, partial volume effect was not corrected in this study, because there was no significant difference in LV wall thickness between patients and normal volunteers.

Lumped constant (LC) was used as a constant with a value of 0.67. It has been reported that LC is not a constant and that the value for deoxyglucose decreases when myocardial glucose uptake is enhanced [39]. In this study, the myocardium in the patients may have had a low LC, so there is a possibility that the calculated MGU may have been underestimated.

Conclusion

Preserved glucose utilization mainly due to an increase in the K_1 value was demonstrated in patients with LV dysfunction. This finding was significant in the myocardial segments with severely impaired LV function. Therefore, quantitative assessment of myocardial glucose utilization by FDG dynamic PET and three-compartment analysis may provide useful information on the regional myocardial metabolic status in patients with LV dysfunction.

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