The Impact of Energy Substrates, Hormone Level and Subject-Related Factors on Physiologic Myocardial ^{18}F -FDG Uptake in Normal Humans

Juhye Jeong · Eunjung Kong · Kyungah Chun ·
Ihnho Cho

Received: 8 March 2013 / Revised: 12 August 2013 / Accepted: 16 August 2013 / Published online: 6 September 2013
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Abstract

Purpose In a whole-body ^{18}F -FDG PET/CT, non-specific ^{18}F -FDG uptake of the myocardium is a common finding and can be very variable, ranging from background activity to intense accumulation and inhomogeneity. We investigated the effect of energy substrates and plasma/serum hormones that may have an influence on myocardial ^{18}F -FDG uptake.

Methods F-FDG PET/CT was performed on 100 normal volunteers from November 2007 to August 2008. Blood samples were taken just before ^{18}F -FDG injection from all subjects. Myocardial ^{18}F -FDG uptake was measured as the mean (SUVmean) and maximal (SUVmax) standardized uptake value. The myocardium was delineated on the PET/CT image by a manual volume of interest (VOI). We analyzed the influence of age, sex, presence of diabetes, fasting duration, insulin, glucagon, fasting glucose, lactate, free fatty acid (FFA), epinephrine (Epi), norepinephrine (NEp), free triiodothyronine (T3), free thyroxine (T4), thyroid-stimulating hormone (TSH) and body mass index (BMI).

Results Overall, 92 subjects (mean age 50.28 ± 8.30 , male 57) were enrolled. The average of myocardial SUVmean was 2.08 and of myocardial SUVmax was 4.57, respectively and there was a strong linear correlation between SUVmean and SUVmax ($r=0.98$). FFA and fasting duration showed significant negative correlation with myocardial ^{18}F -FDG uptake, respectively ($r=-0.40$ in FFA; $r=-0.41$ in fasting duration). No significant relationships were observed between myocardial uptake and age, sex, presence of diabetics, insulin, glucagon, fasting glucose, lactate, Epi, NEp, free T3, free T4, TSH and BMI.

Conclusion Myocardial ^{18}F -FDG uptake decreases with longer fasting duration and higher FFA level in normal humans. Modulating myocardial uptake could improve ^{18}F -FDG PET/CT imaging for specific oncologic and cardiovascular indications.

Keywords ^{18}F -FDG PET/CT · Physiologic uptake · Myocardium · Free fatty acid · Fasting duration · Quantification

Introduction

Positron emission tomography (PET)/CT with ^{18}F -fluorodeoxyglucose (FDG) is a method used widely for the evaluation of cancer and also has an important role in the evaluation of ischemic heart disease. In a whole-body ^{18}F -FDG PET/CT, non-specific uptake of the myocardium is a common finding and can be very variable, ranging from background activity to intense accumulation and inhomogeneity. This phenomenon is mostly reported as a physiological pitfall. Although it is considered as physiological uptake, control of this unwanted uptake can potentially improve the use of ^{18}F -FDG PET/CT for patients with thoracic tumors, such as cardiac tumor neighboring or infiltrating the cardiac chambers, or any malignant mediastinal node [1, 2].

In the normal myocardium, metabolism is primarily oxidative by using various admixtures of substrates, such as free fatty acids (FFA), glucose and lactate. Glucose metabolism in the myocardium is influenced by the availability of substrate, myocardial workload and adequacy of myocardial perfusion [3]. Under fasting conditions, insulin levels fall, resulting in reduced transport of glucose into the myocytes and substrate shifts from glucose to FFA [4]. Previous reports have suggested that the degree of myocardial ^{18}F -FDG uptake is related to FFA and glucose levels [5–8], and insulin and glucagon

J. Jeong · E. Kong · K. Chun · I. Cho (✉)
Department of Nuclear Medicine, Yeung-Nam University Hospital,
#317-1 Daemyung 5-dong, Nam-gu, Daegu 705-717,
Republic of Korea
e-mail: nuclear126@ynu.ac.kr

are also related to myocardial glucose utilization [5]. Other reports showed that the patient's age, sex, fasting duration, enzymes or hormones might have an association with myocardial glucose uptake [9, 10]. Recently, dietary modification has appeared to affect myocardial ^{18}F -FDG uptake [11, 12].

The variability of myocardial ^{18}F -FDG uptake on whole-body PET/CT has been the subject of many discussions and some publications. The purpose of this study was to confirm the relationship between the intensity of myocardial ^{18}F -FDG uptake in fasting normal humans and the subject-related factors, including energy substrates and hormones, that have been suggested to have a possible influence in previous reports. Thus, this could improve ^{18}F -FDG PET/CT imaging for specific oncologic and cardiovascular indications.

Materials and Methods

Subjects and Subject-Related Biomarkers

From November 2007 to August 2008, 100 healthy volunteers were consecutively enrolled in this study. Consenting subjects completed a clinical questionnaire including questions about cardiovascular-related symptoms and associated medical conditions such as diabetes and coronary artery disease. Age, blood glucose level and fasting duration were recorded, and body mass index (BMI) was also calculated. In addition, blood samples were taken just before ^{18}F -FDG injection from all subjects to measure the serum levels of insulin, FFA, free triiodothyronine (T3), free thyroxine (T4), thyroid-stimulating hormone (TSH) and plasma levels of the glucagon, glucose, lactate, epinephrine (Epi) and norepinephrine (NEP). Serum insulin levels were measured with the insulin-specific immunoradiometric assay (IRMA) using the Dia-source kit (Diasource ImmunoAssays S.A, Louvain-La-Neuve, Belgium). Plasma glucagon levels were measured with radioimmunoassay (RIA) using Siemens kit (Siemens, LA, USA). Lactic acid, FFA and glucose levels were measured with the enzyme-linked immunosorbent assay (ELISA) using the LACT kit (Roche Diagnostics, Indianapolis, IN, USA), NEFA kit (Shinyang Diagnostics, Siheung-si, Korea) and GLUH kit (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), respectively. Electrochemiluminescence immunoassay (ECLIA) was also performed using FT3, FT4 and TSH kits (Roche Diagnostics, Naka-gun, Japan) for the measurement of the free T3, free T4 and TSH levels. Additionally, Epi and NEP levels were measured with the high-performance liquid chromatography-electrochemical detection (HPLC-ECD).

Exclusion criteria were (1) the impossibility of blood tests due to hemolysis, (2) patients showing cardiovascular-related symptom or diagnosed ischemic heart disease, (3) patients diagnosed with malignancy on the study, (4) systemic muscle uptake and (5) incomplete laboratory or personal data. The

parameters were assessed in the questionnaire, and the patients' characteristics are summarized in Table 1. This study was approved by the Institutional Review Board of Yeungnam Medical Center.

Imaging Technique

Subjects fasted for at least 6 h before the administration of ^{18}F -FDG, and the blood glucose concentration was confirmed to be less than 200 mg/dl. Insulin was not used to control blood glucose prior to ^{18}F -FDG injection. Patients received an intravenous injection of 296–444 MBq of ^{18}F -FDG in the arm and rested quietly for 60–90 min. A PET/CT image was acquired from the head to the upper thighs in the supine position using VCT or DVCT PET/CT scanners (GE Medical Systems, Milwaukee, WI, USA). First, a CT scan without intravenous contrast enhancement was obtained for attenuation correction, and all images were reconstructed with a 3.75-mm slice thickness at 2.4-mm increments. A three-dimensional mode PET scan was followed at 3 min per bed position, and iterative algorithms with two iterations and eight subsets were used for image reconstruction. Data were filtered (FWHM 5.0 mm) and corrected for scatter.

Quantitative Measurement of ^{18}F -FDG Uptake in Myocardium

One experienced nuclear medicine physician estimated SUVmean and SUVmax in the volume of interest (VOI)

Table 1 Characteristics of subjects ($n=92$)

Variable	No. of patients (% total study population)
Demographic data	
Sex	
Male	57 (61.96)
Female	35 (38.04)
Age (years old)	
Mean $\pm$ SD	50.28 $\pm$ 8.30
Range	23–74
Body mass index	
Mean $\pm$ SD	24.47 $\pm$ 3.37
Range	16.14–34.26
Diabetes	10 (10.87)
Duration of fast (h)	
Mean $\pm$ SD	15.72 $\pm$ 2.83
Range	6–24
Glucose level (mg/dl)	
Mean $\pm$ SD	103.42 $\pm$ 19.81
Range	75–195

defined on the left ventricular myocardium using TrueD[®] software on a Leonardo[®] workstation (Siemens Medical Solutions, Hoffman Estates, Knoxville, TN, USA). All regions of interest (ROIs) were drawn manually tracing around the ¹⁸F-FDG accumulation of the left ventricular myocardium on the transaxial fusion PET/CT images (Fig. 1). When the subject had low myocardial uptake as a blood pool, an ROI consisting of double U-shaped lines with about 1 cm distance [13] was drawn along the border of the left ventricle on the mid slice of the transaxial PET/CT images (Fig. 2). The ROI was copied to the next slice, and the outline of the ROI was adapted to the border of the left ventricle. Then, all ROIs were summed automatically. The SUVs of the ¹⁸F-FDG in the myocardial VOI were measured using commercial calculation methods and adjusted for body weight.

Statistical Analysis

All statistical analyses were performed with SPSS 19.0 software (SPSS, Chicago, IL, USA). The *t*-test for nominal scale and regression analysis with Pearson correlation for continuous parameters were used to assess differences in myocardial ¹⁸F-FDG uptake in relation to the patient-related factors. Multivariate analysis with the stepwise method was used to consider the effects of the investigated factors simultaneously. We also ascertained whether the factor had multicollinearity. All measurements and statistical analyses were performed using the index of SUVmean and SUVmax. A *p* value <0.05 was considered statistically significant.

Results

Patient Characteristics

Ninety-two studies were evaluated (mean age 50.28 ± 8.30 , male 57). The mean blood glucose level prior to the examination was 103.42 ± 19.81 mg/dl (range 75–195 mg/dl), and the mean duration of fasting was 15.72 ± 2.83 h (range 6–24 h). The demographic and clinical characteristics of the patients are summarized in Table 1. Two subjects with hemolysis, one subject with systemic muscle uptake, one subject who could not receive the injection dose, one subject who was diagnosed with malignancy and three subjects with cardiac-related symptoms were excluded.

Quantitative Myocardial ¹⁸F-FDG Uptake

The range of SUVmean of the myocardium was 0.69–10.47 g/ml (mean $\pm$ SD, 2.08 ± 1.72). SUVmax of the myocardium ranged between 1.17 and 27.49 g/ml (mean $\pm$ SD, 4.57 ± 4.12), with a very good linear correlation between SUVmean and SUVmax ($r=0.98$). The range of myocardial volume was 89.08–308.07 cm³ (mean $\pm$ SD, 173.28 ± 45.31).

Univariate analysis demonstrated a significant correlation between myocardial ¹⁸F-FDG uptake and FFA ($p<0.001$). The longer fasting duration was also associated with lower myocardial uptake ($p<0.001$). FFA and fasting duration showed a negative correlation with myocardial ¹⁸F-FDG uptake, respectively ($r=-0.40$ in FFA; $r=-0.41$ in fasting

Fig. 1 Quantification of myocardial ¹⁸F-FDG uptake in a 54-year-old woman with high uptake. Myocardial ¹⁸F-FDG uptake is measured in a volume of interest defined on the left ventricular myocardium. All regions of interest (ROIs) are drawn manually tracing around the ¹⁸F-FDG accumulation of the left ventricular myocardium on the transaxial fusion PET/CT images; then, all ROIs are summed using software on a workstation. PET/CT data present an SUVmean of 2.77, SUVmax of 5.46 and myocardial volume of 129.74 cm³

Fig. 2 Quantification of myocardial ^{18}F -FDG uptake in a 50-year-old man with low uptake. An ROI consisting of double U-shaped lines with about 1-cm distance is drawn along the border of the left ventricle on the mid slice of the transaxial PET/CT images. The ROI is copied to the next

slice, and the outline of the ROI is adapted to the border of the left ventricle. Then, all ROIs are summed automatically. PET/CT data present an SUVmean of 1.46, SUVmax of 2.61 and myocardial volume of 153.45 cm³

duration). No significant correlation was observed between myocardial uptake and age, sex, presence of diabetics, insulin, glucagon, fasting glucose, lactate, Epi, NEp, free T3, free T4, TSH and BMI (Table 2). Multivariate analysis also demonstrated that a significantly lower SUVmean of the myocardium was related to higher FFA ($p=0.016$) and longer fasting duration ($p=0.015$). Additionally, these variables were independent on the multicollinearity test. The same statistical analysis was performed for SUVmax as well, showing the same trend, with consistent results compared with those obtained for SUVmean (data not shown).

The fasting duration was correlated with FFA ($r=0.32$, $p=0.002$) but not correlated with glucose, glucagon, insulin and lactate. The FFA did not demonstrate any correlation with glucose, glucagon, insulin and lactate. Lactate was correlated with glucose ($r=0.27$, $p=0.010$), and glucose was correlated with the glucagon concentration ($r=0.28$; $p=0.007$) and lactate. Insulin did not show any correlation with glucose, glucagon, FFA and lactate. The patients with higher BMIs seemed likely to higher lactate ($r=0.26$, $p=0.011$) and fasting glucose concentrations ($r=0.36$, $p<0.001$). Variables associated with

myocardial ^{18}F -FDG uptake are presented in Table 2, Figs. 3 and 4.

Discussion

Non-specific uptake in the myocardium is a common finding in whole-body ^{18}F -FDG PET/CT for cancer staging or cancer screening [14]. The alteration from the intense ^{18}F -FDG uptake of a dominantly glycolytic myocardial metabolism to the scant uptake of a dominantly fatty acid metabolism is not entirely uniform either temporally or regionally. FFAs and glucose are the major substrates for myocardial metabolism [15]. Under fasting conditions, when the insulin level is low and glucagon level is high, the glucose concentration decreases and FFA concentration increases because of high lipolytic activity. In addition, FFA inhibits pyruvate dehydrogenase and phosphofructokinase activity in the glycolytic pathway, further reducing myocardial glucose utilization in the fasting state. As a result, FFA is the major energy source for the myocardium during fasting. Conversely, after feeding,

Table 2 Subject-related variables associated with myocardial ^{18}F -FDG uptake (n=92)

	Datum*	Pearson's correlation coefficient	p-value
Age	50.28±8.30 (23–74)	$r=0.16$	ns
Body mass index	24.47±3.37 (16.14–34.26)	$r=-0.19$	ns
Fasting duration	15.72±2.83 (6–24)	$r=-0.41$	$p<0.001$
Glucose level	103.42±19.81 (75–195)	$r=-0.15$	ns
Insulin (2–25 uIU/ml)	8.52±3.68 (1.6–20.4)	$r=-0.09$	ns
Glucagon (59–177 pg/ml)	51.91±19.29 (26–205)	$r=-0.06$	ns
Free fatty acid (100–900 uEq/l)	792.91±256.27 (162–1,716)	$r=-0.40$	$p<0.001$
Lactate (0.5–2.2 mmol/l)	1.02±0.41 (0.37–2.64)	$r=-0.09$	ns
Epinephrine (<0.3 ng/ml)	0.06±0.03 (0.01–0.17)	$r=-0.13$	ns
Norepinephrine (<0.8 ng/ml)	0.29±0.13 (0.10–0.65)	$r=0.01$	ns
Free T3 (1.5–5 pg/ml)	3.41±0.76 (2.07–6.88)	$r=0.02$	ns
Free T4 (0.9–1.9 pg/ml)	1.48±0.32 (0.98–3.69)	$r=-0.10$	ns
TSH (0.23–3.8 uU/ml)	2.33±1.90 (0.01–8.84)	$r=0.14$	ns

*Mean±SD (range), ns non-specific; T3 triiodothyronine; T4 thyroxine, TSH thyroid-stimulating hormone

Fig. 3 A scattergram showing the relationship between the myocardial ^{18}F -FDG uptake (SUVmean) and FFA ($n=92$). Linear regression analysis shows significant negative correlation between SUVmean and FFA ($p < 0.001$, $r = -0.40$). FFA=free fatty acid

the insulin level rises; the FFA concentration is lowered through anabolic and lipogenic processes incorporating FFA into triglyceride in adipose tissue. Consequently, glucose becomes an increasingly important substrate to meet the energy demands of the myocardium. This change from predominantly carbohydrate to predominantly lipid usage is explained by the glucose-free fatty acid cycle reported by Randle et al. [16].

Fig. 4 A scattergram showing the relationship between the myocardial ^{18}F -FDG uptake (SUVmean) and fasting duration ($n=92$). There is a negative correlation between SUVmean and fasting duration ($p < 0.001$, $r = -0.41$)

The shift in the fuel preference has been suggested to be caused by the changes in substrates and blood insulin concentration.

Previous studies have demonstrated the relationships between myocardial glucose uptake and glucose, FFA and insulin concentrations [5, 6, 8, 17, 18]. Furthermore, suppression of ^{18}F -FDG uptake in the myocardium resulting from the addition of lactate (second substrate of glucose) was reported [9]. According to our results in normal subjects, FFA had a significant negative relationship with myocardial uptake ($p < 0.001$, $r = -0.40$). This result is reasonable and in good agreement with previous reports and predictions, because the myocardium prefers to use FFA for energy production at the fasting state. However, no significant correlation was observed between myocardial uptake and insulin, glucagon, fasting glucose and lactate in our study. Moreover, FFA did not demonstrate any correlation with insulin, glucose, glucagon and lactate. The relationship between myocardial glucose uptake and FFA did not depend on the insulin concentration as in the study of Knuuti et al. [18]. Our data suggest that the decline in cardiac glucose utilization occurs during the period of fasting in which ^{18}F -FDG PET/CT study is performed. The serum FFA level may increase during this same period in the fed-to-starved transition. Insulin and other substrate levels do not reflect myocardial ^{18}F -FDG uptake in the fasting state probably because they may change to a starved level earlier during starvation than the decline in cardiac glucose utilization because of the effect of the glucose-free fatty acid cycle. Holness et al. studied the continuous change in glucose utilization and metabolic conditions during the fed-to-starved transition using rats. They found a rapid decline in cardiac glucose utilization during 9–24 h of starvation and a concomitant elevation of arterial FFA concentrations over the same period [19]. Similarly, the present study indicated that fasting duration was correlated with FFA, and myocardial ^{18}F -FDG uptake was suppressed with a longer fasting duration. It is assumed that the mean fasting duration in our study subjects was 15.72 ± 2.83 h (range: 6–24 h), which might have been sufficient to induce optimal circulating fatty acid levels. The result that a significantly lower SUVmean of the myocardium was related to higher FFA and longer fasting duration in multivariate analysis also supported these hypotheses.

No significant correlations between myocardial ^{18}F -FDG and concentrations of catecholamine were observed in our study, although catecholamine might be expected to decrease myocardial glucose uptake primarily by stimulating lipolysis and by elevating FFA concentrations [20, 21]. Additionally, free T3, free T4 and TSH did not have significant influence in our data, although it was assumed that hyperthyroidism enhances myocardial glucose utilization in starvation by a mechanism that may be secondary to changes in glucose-lipid interactions at the tissue level [22]. However, the results do not completely rule out possible effects of catecholamine and

thyroid hormone, because the concentrations of these hormones were within normal range in our normal subjects.

The report by Israel et al. showed myocardial ^{18}F -FDG uptake was significantly lower in diabetics [10]. Our study also demonstrated that the average of SUVmean in the myocardium was lower in diabetics than in non-diabetics, but the difference between diabetics and non-diabetics was not statistically significant. Because the number of diabetics was too small—10 diabetics and 82 non-diabetics—our result had a limitation concerning reaching a clear conclusion. Moreover, the severity and medications also could make a difference in the results.

It is well known that insulin resistance in obese subjects could cause an abnormal regulation of FFA metabolism. A previous study reported that myocardial glucose uptake was reciprocally related to BMI [10]. However, our result did not show statistical significance, despite a negative relationship between BMI and SUVmean of the myocardium.

The present study has some limitations. First, individual medications, subjects' eating habits and the cardiac work load, which are related to myocardial glucose consumption, were not checked. Second, PET/CT scans were obtained between 60 and 90 min after ^{18}F -FDG injection, not at the same time. Third, the software for quantitative analysis and PET/CT scanners we used were each from different vendors. Finally, this study evaluated only quantitative values with SUV for assessment of myocardial ^{18}F -FDG uptake. It was difficult to apply a scoring scale or criteria for the patterns of myocardial ^{18}F -FDG accumulation (including heterogeneity) because of diversity. However, in this study quantitative analysis was performed using SUVmean as well as SUVmax, because SUVmean was considered a more representative value, especially in case of uneven myocardial ^{18}F -FDG uptake.

The strength of this study was the healthy subjects who were not cancer or ischemic heart disease patients. Moreover, the subjects' energy substrates and hormone concentrations were measured at the time of ^{18}F -FDG injection. Additionally, quantitative analysis with SUVmean, using a manual VOI with exclusion of blood pool activity, was performed by comparison with previous studies using a VOI without exclusion of blood pool activity [10, 17].

Conclusion

This study evaluated the impact of 15 factors on myocardial ^{18}F -FDG uptake in normal subjects. Our data demonstrated that myocardial ^{18}F -FDG uptake had a significant relationship with FFA and fasting duration in normal humans. However, there was no significant correlation between myocardial ^{18}F -FDG uptake and subjects' age, sex, presence of diabetics, insulin, glucagon, fasting glucose, lactate, EPI, NEp, free T3, free T4, TSH and BMI.

Because energy metabolism in the myocardium is regulated by multiple factors, it is different in normal humans, diabetic, patients with insulin resistance, and those with ischemic heart disease or heart failure. Although our results from normal humans could not represent all clinical scenarios, our results would be useful for manipulating myocardial ^{18}F -FDG uptake on ^{18}F -FDG PET/CT study.

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