Annals of Nuclear Medicine Vol. 20, No. 3, 203–208, 2006

Evaluation of the relationship between physiological FDG uptake in the heart and age, blood glucose level, fasting period, and hospitalization

Tomohiro KANETA,* Takashi HAKAMATSUKA,* Kentaro TAKANAMI,* Takayuki YAMADA,* Kei TAKASE,* Akihiro SATO,* Shuichi HIGANO,* Shigeo KINOMURA,** Hiroshi FUKUDA,** Shoki TAKAHASHI* and Shogo YAMADA*

*Department of Radiology, Graduate School of Medicine, Tohoku University
**Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University

Objective: Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is widely used for evaluation of cancer and ischemic heart disease. Recently, increased myocardial FDG uptake has been reported to be related to some types of heart disease, such as sarcoidosis. However, the physiological increased FDG uptake in the heart often mimics the abnormal high uptake in these cases. In this study, we investigated the relationships between myocardial uptake and age, blood glucose level, fasting period, and hospitalization status (inpatient vs. outpatient). ***Methods:*** A total of 159 non-diabetic patients were enrolled in the present study. Patients were imaged on a PET/CT scanner, and a three-dimensional region of interest (ROI) was drawn on the fused PET/CT image to measure the maximum standardized uptake value (SUV_{max}) of the whole left ventricle. ***Results:*** No significant relationships were observed between myocardial uptake and age or fasting period. Blood glucose level showed a significant relationship ($p = 0.025$) with myocardial uptake, but the R-square was extremely small ($r^2 = 0.03$). With an SUV_{max} threshold of 3.0, there was no significant difference between inpatients and outpatients. However, outpatients showed a significantly higher frequency of myocardial uptake over SUV_{max} of 5.0 (χ^2 test: $p = 0.046$). ***Conclusion:*** It is difficult to predict the degree of physiological uptake in the heart from data regarding age, fasting period, or blood glucose level. Outpatients tend to show higher myocardial uptake than inpatients, which may make it difficult to detect abnormally increased uptake in the heart. A long fasting period, such as overnight fasting, is an inadequate means to reduce the physiological uptake of FDG in the heart.

Key words: FDG, heart, myocardium, fasting

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with fluorodeoxyglucose (FDG) is a method used widely for the evaluation of cancer and which also has an important role in the evaluation of ischemic heart disease.[1–3] Recently, increased myocardial FDG uptake has been reported to be related to some types of heart disease, such as sarcoidosis,[4–6] endocarditis,[7] and radiation-induced myocarditis.[8] In such cases, increased physiological uptake in the normal myocardium mimics abnormal findings and it is necessary to reduce FDG uptake in the normal myocardium. Recently, we encountered a case of cardiac sarcoidosis in which pre-therapy PET demonstrated focal high uptake in the myocardium and the mediastinal and axillary lymph nodes, suggesting sarcoidosis. Steroid therapy was performed, and post-therapy PET demonstrated decreased uptake in the mediastinal and axillary lymph nodes but a marked increase in uptake in the whole heart. Clinically, the increased uptake in heart was thought to be due to physiological uptake and not disease progression.

In the normal myocardium, metabolism is primarily oxidative and utilizes various admixtures of substrates,

Received September 21, 2005, revision accepted January 5, 2006.

For reprint contact: Tomohiro Kaneta, M.D., Ph.D., Department of Radiology, Tohoku University, 1–1 Seiryomachi, Aoba-ku, Sendai 980–8574, JAPAN.

E-mail: kaneta@rad.med.tohoku.ac.jp

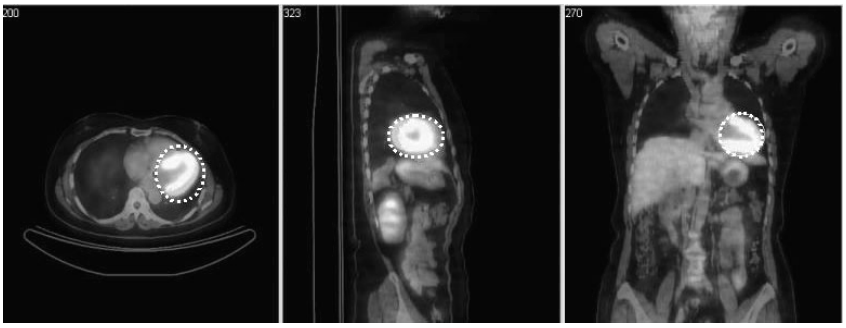


Fig. 1 Example of a three-dimensional ROI (*dotted ellipse*) on the fused PET/CT image to measure the SUV of the whole left ventricle.

such as free fatty acids (FFA), glucose, and lactate. On the other hand, under fasting conditions, plasma insulin levels fall, resulting in reduced transport of glucose into myocytes. Therefore, the fasting period seems to affect plasma insulin and glucose levels, and a long fasting period may reduce myocardial FDG uptake. Okumura et al. performed fasting FDG-PET to detect cardiac sarcoidosis with a fasting period of at least 12 hours,[5] which is much longer than that in conventional FDG-PET for cancer patients. In the present study, we analyzed myocardial uptake in FDG-PET with fasting periods of various lengths and investigated the relationships between myocardial uptake and age, blood glucose level, fasting period, and hospitalization status (i.e., inpatient vs. outpatient).

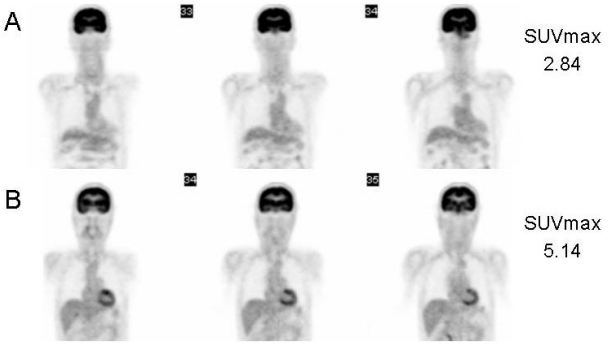


Fig. 2 Examples of FDG-PET images of the heart with SUV_{max} of about 3.0 and 5.0, respectively. (A) There is almost no visualization of the heart. (B) There is a distinct visualization of the whole heart. All images are expressed using the same scale of SUV of 0.0 to 5.0.

MATERIALS AND METHODS

Patients

One hundred and fifty-nine non-diabetic patients (105 men, 54 women) with a mean age of 61.1 ± 15.8 years (range 11–85 years) were enrolled in this study. Patients were referred to our department for whole-body FDG-PET to detect or evaluate malignant tumors. Patients' age, blood glucose level, fasting period, and hospitalization status (inpatient or outpatient) were recorded. No insulin or free fatty acid data were available prior to injection.

PET imaging protocol

Imaging studies were performed on a Biograph PET/CT scanner (Siemens, Hoffman Estates, IL), which produces transaxial, coronal, and sagittal reconstructions of CT, PET, and fusion PET/CT data for interpretation. The Biograph scanner combines a dual-detector spiral CT scanner (Somatom Emotion; Siemens, Erlangen, Germany) and a high-resolution PET scanner with spatial resolution of 4.5 mm and 3-dimensional image acquisition. A multimodality computer platform (Syngo; Siemens) was used for image review and manipulation.

After a fast of at least 4 h, patients received approximately 185 MBq (5 mCi) of ^{18}F-FDG by intravenous injection, which was followed by a rest period of about 60 min in a comfortable chair.

At the time of imaging, patients were placed in the supine position on the imaging table. Spiral CT was performed from the level of the middle of the skull to the level of the pelvic floor. A scout view was recorded with 30 mA and 130 kV(p), followed by a spiral CT scan at 50 mA, 130 kV(p), 5-mm section width, 4-mm collimation, and 12-mm table feed per rotation. This was followed by acquisition of PET emission images. Each image was acquired for 2 min per bed position (increments of 11.2 cm [3-dimensional mode]).

Analysis of myocardial uptake

All PET/CT images were read directly from the screen of the computer workstation. A three-dimensional region of interest (ROI) was drawn on the fused PET/CT image to measure the SUV of the whole left ventricle (Fig. 1): SUV = (peak kBq/m*l* in ROI)/(injected activity/g body weight). Myocardial FDG uptake was expressed as the maximum SUV (SUV_{max}).

The relationships between myocardial uptake and age, blood glucose level, fasting period, and hospitalization

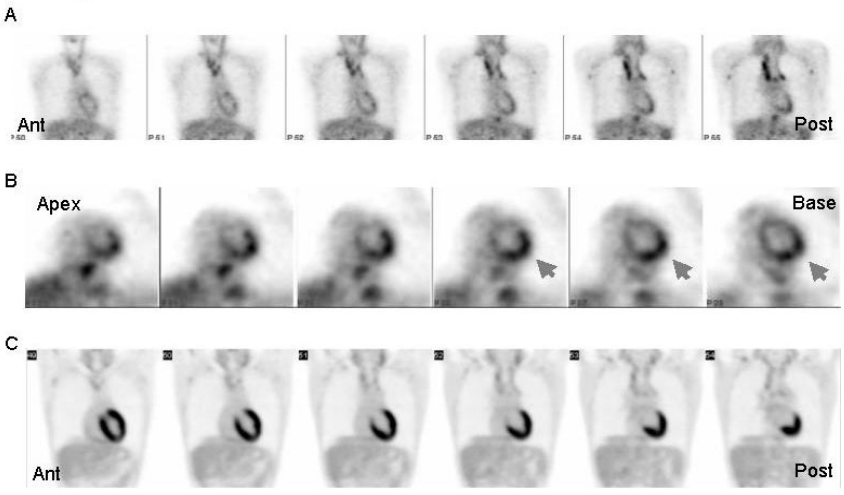


Fig. 3 Coronal FDG-PET images (A) obtained before steroid therapy showed increased uptake in the mediastinal and bilateral axillary lymph nodes. Short-axis slices of the heart (B) indicated increased uptake in the lateral to inferior wall (*arrow*). Follow-up FDG-PET performed one year later (C) showed decreased uptake in the mediastinal and bilateral axillary lymph nodes, and a marked increase in uptake in the whole heart. All images are expressed using the same scale of SUV of 0.0 to 5.0.

status (inpatient vs. outpatient) were analyzed. In addition, we evaluated the relationship between blood glucose level and fasting period. Patients were divided into two main groups according to fasting period: those fasted for over 13 hours, and those fasted for less than 8 hours. The former were examined before noon, and therefore fasted overnight and did not eat breakfast. The latter were examined in the afternoon, and they ate breakfast but did not eat lunch. We compared myocardial uptake between groups with and without overnight fasting. The results are expressed as means ± SEM. Statistical evaluation was performed using the Mann-Whitney test, and $p < 0.05$ was considered statistically significant.

The patients were also divided according to hospitalization status into outpatients and inpatients. The numbers and percentages of cases with SUV_{max} thresholds of 3.0 and 5.0 were examined. Figure 2A and 2B shows examples of images of the heart with SUV_{max} of about 3.0 and 5.0, respectively. Figure 2A shows almost no visualization of the heart, and is thought to be ideal for detecting abnormal high uptake in the heart. On the other hand, Figure 2B shows a distinct visualization of the whole heart, making it difficult to distinguish between abnormal high uptake and physiological uptake in the heart. The χ^2 test for trends in binominal proportions was used to determine the significance of differences in myocardial uptake between inpatients and outpatients, and $p < 0.05$ was considered statistically significant.

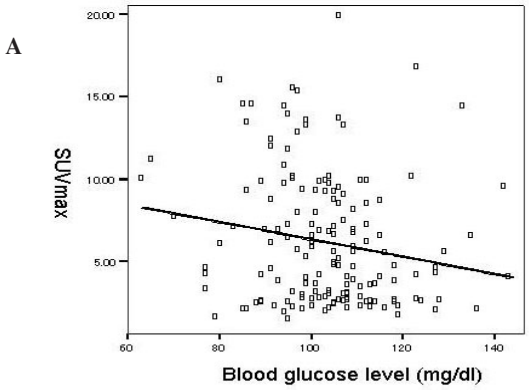
Case presentation

A 29-year-old man diagnosed with sarcoidosis by caneal bone biopsy was examined by FDG-PET. Increased uptake was observed in the mediastinal and bilateral axillary lymph nodes suggesting the presence of sarcoid lesions (Fig. 3A). Moreover, short-axis slices of the heart indicated increased uptake in the lateral to inferior wall (Fig. 3B). Uptake in other regions of the heart was almost the same as that in the mediastinum. No cardiac symptoms were evident in this patient, but cardiac sarcoidosis was strongly suspected. The patient received steroid therapy. Follow-up FDG-PET performed one year later showed decreased uptake in the mediastinal and bilateral axillary lymph nodes. However, a marked increase in uptake in the whole heart was observed (Fig. 3C). Clinically, progression of cardiac sarcoidosis seemed unlikely. The patient's blood glucose level was not high (100 mg/d*l*), but the cardiac findings were thought to be physiological. In this case, it was difficult to evaluate the cardiac involvement.

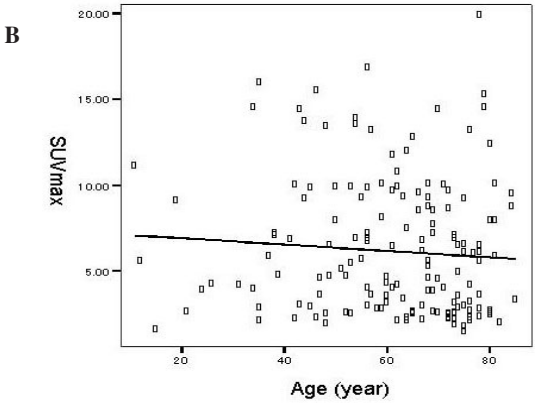
RESULTS

The mean blood glucose level prior to the examination was 103.2 ± 13.6 mg/d*l* (range 63–143 mg/d*l*) and the mean duration of fasting was 10.3 ± 4.7 h (range 4.5–16.0 h).

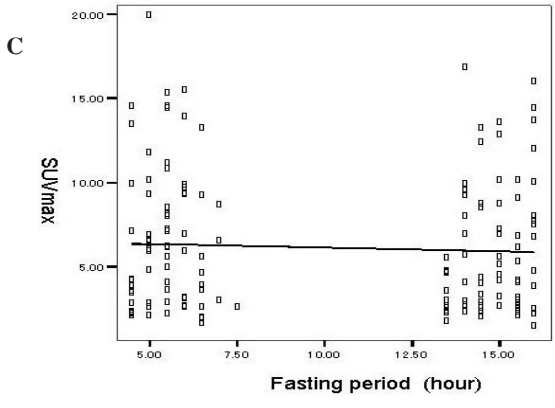
As shown in Figure 4A, there was a significant relationship between myocardial uptake and blood glucose level ($p = 0.025$). They showed a slight negative correlation, but the R-square was extremely small ($r^2 = 0.03$). On the other hand, as shown in Figure 4B and 4C, no significant relationships were observed between myocardial uptake and age or fasting period. Figure 5 also shows that there was no significant difference in myocardial uptake between the two groups with and without overnight fasting. Figure 6 shows a comparison of the results between outpatients and inpatients. With a SUV_{max} threshold of



$y = -0.05x + 11.55$ $r^2 = 0.03$, $p = 0.025$



$y = -0.02x + 7.29$ $r^2 = 0.01$, $p = 0.35$



$y = -0.05x + 6.66$ $r^2 = 0.00$, $p = 0.46$

Fig. 4 Relationships between SUV_{max} and blood glucose level (A), age (B), and fasting period (C).

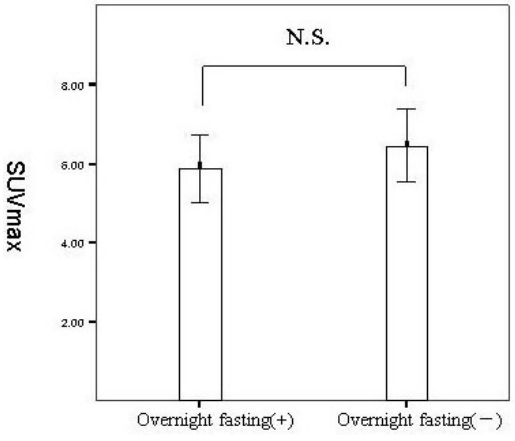
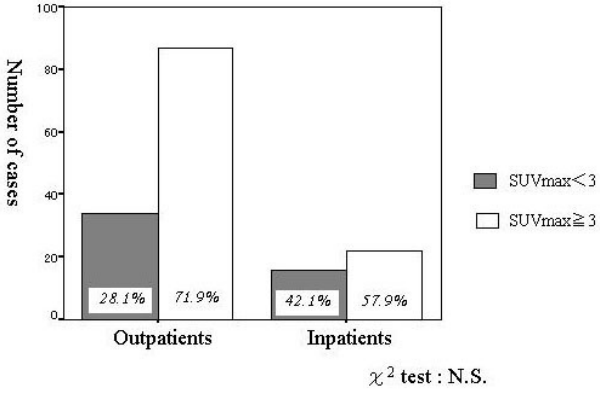


Fig. 5 Differences in SUV_{max} with or without overnight fasting. No significant differences were observed.



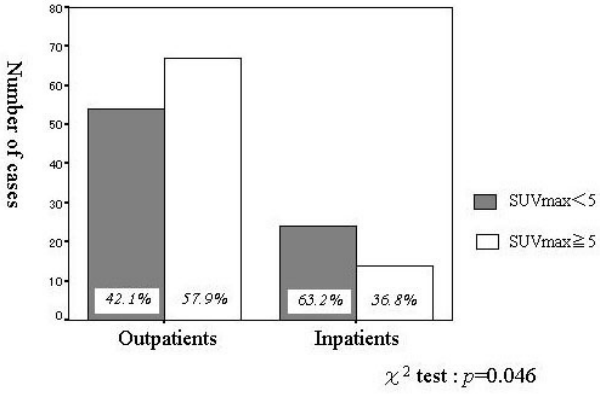


Fig. 6 Distribution of cases divided into outpatients and inpatients with SUV_{max} thresholds of 3.0 (A) and 5.0 (B). The χ^2 test showed a significant difference between outpatients and inpatients with an SUV_{max} threshold of 5.0.

3.0, χ^2 test showed no significant difference between the two groups, while the difference between the two groups was significant at a threshold of 5.0 ($p = 0.046$). There was no significant relationship between blood glucose level and fasting period ($r^2 = 0.01$, $p = 0.72$).

DISCUSSION

Previous studies reported that no significant correlations were observed between FDG uptake in the myocardium and age, blood glucose level, or fasting period.[9,10] In agreement with them, no significant correlations were observed between FDG uptake in the myocardium and age, or fasting period in the present study. However, there was a significant relationship between myocardial uptake and blood glucose level ($p = 0.025$). But the R-square was extremely small ($r^2 = 0.03$), and the regression line did not fit well, and its clinical significance is thought to be small. Thus, before the scan, it is difficult to predict myocardial uptake based on age, blood glucose level, or fasting period. Yamanouchi et al. reported that normal myocardial glucose uptake in humans is suppressed in the fasting state but is not controlled solely by the duration of fasting.[11] Our results showed no significant relationship either between blood glucose level and fasting period. Overnight fasting is often performed for evaluation of cardiac sarcoidosis, but our results suggested that there were no significant differences in myocardial FDG uptake in patients with or without overnight fasting. Therefore, overnight fasting does not seem to be an effective option for reducing normal myocardial uptake.

Our results indicated that outpatients showed significantly a higher frequency of myocardial uptake above SUV_{max} of 5.0. Background activity in the mediastinum is usually below SUV_{max} of 3.0. This degree of myocardial uptake is significantly higher than that in the mediastinum, and it makes it difficult to detect abnormally high uptake in the heart in pathological conditions such as cardiac sarcoidosis. Moreover, the frequency of cases with SUV_{max} exceeding 3.0 in the outpatients was over 70%. Therefore, there is a high likelihood that it will be difficult to detect abnormal myocardial uptake in outpatients. The reason why outpatients showed higher myocardial uptake than inpatients is not yet known and further investigations into this issue are warranted. The difference may have been due to diet—in our hospital, almost all inpatients take a rice-based diet with a total energy content of 1,900 kcal—or differences in exercise, medication, severity of disease, etc.

These results suggest that pharmacological intervention may be necessary to reduce FDG uptake in the normal heart. Heparin is known to release endothelial lipoprotein lipase, thereby promoting lipolysis of plasma triacylglycerols to FFA *in vivo*.[12] Therefore, heparin loading is thought to decrease FDG uptake in the heart. However, we must consider the risk of bleeding, especially in the brain. In addition, infusion of lipids is also thought to decrease glucose uptake in the heart. Randle et al. demonstrated an inhibitory effect of FFA on glucose uptake in the perfused rat heart.[13] Nuutila et al. performed FDG-PET studies with elevation of FFA by combined infusion of lipids and heparin, and demonstrated lower myocardial FDG uptake than in the control group.[14] Such methods may be necessary to reduce FDG uptake in the normal myocardium and to emphasize distinct visualization in inflammatory lesions.

This study has some limitations. First, the evaluation of myocardial uptake using SUV_{max} has possibilities to include extra-myocardial regions, such as blood pool or arteriosclerotic plaque. However, it seems hard to exclude them in our method. Second, almost all patients in this study were suspected of having or diagnosed with cancer. The risk of ischemic heart disease in cancer patients is not negligible, but we did not assess the possibilities of patients affected by myocardial disease precisely. Third, in the present study, we did not assess serum insulin or FFA levels. Insulin enhances the uptake of FDG by myocardial and skeletal muscle, which appears to be mediated via translocation of glucose transporters (GLUT4) from an intracellular pool to the plasma membrane.[15–17] In addition to these direct effects on glucose uptake and metabolism in cardiac myocytes, insulin effectively inhibits whole-body lipolysis.[13,16,18,19] Nicotinic acid derivatives such as Acipimox are also known to reduce FFA[20] and may increase myocardial FDG uptake under fasting. On the other hand, it has been reported that FFA inhibits glucose utilization *in vivo* in both human heart and skeletal muscle.[14] Moreover, many other factors can influence myocardial FDG uptake, including serum levels of thyroxine,[21] epinephrine,[22] glucagon, dehydroascorbic acid,[23] and insulin resistance.[24] These factors seem to be related to FDG uptake in the normal heart or the difference between inpatients and outpatients. The degree of disease aggressiveness may also be related to FDG uptake because many subjects in the present study had either confirmed or suspected cancer. Further detailed studies are required to clarify these issues.

CONCLUSIONS

FDG uptake in the myocardium showed a significant relationship with blood glucose level, but not with age or fasting period. Outpatients tended to show higher myocardial uptake than inpatients, and the frequency of exceeding SUV_{max} of 3.0 in outpatients was over 70%. A long fasting period, such as overnight fasting, is an inadequate means to reduce the physiological uptake of FDG in the heart.

REFERENCES

1. Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986; 314: 884–888.
2. Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, et al. Preoperative positron emission tomographic viability assessment and perioperative and postop-

erative risk in patients with advanced ischemic heart disease. *J Am Coll Cardiol* 1997; 30: 1693–1700.
3. Landoni C, Lucignani G, Paolini G, Zuccari M, Galli L, Di Credico G, et al. Assessment of CABG-related risk in patients with CAD and LVD. Contribution of PET with [^{18}F]FDG to the assessment of myocardial viability. *J Cardiovasc Surg (Torino)* 1999; 40: 363–372.
4. Yamagishi H, Shirai N, Takagi M, Yoshiyama M, Akioka K, Takeuchi K, et al. Identification of cardiac sarcoidosis with ^{13}N-NH$_3$/^{18}F-FDG PET. *J Nucl Med* 2003; 44 (7): 1030–1036.
5. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, et al. Usefulness of fasting ^{18}F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med* 2004; 45 (12): 1989–1998.
6. Takeda N, Yokoyama I, Hiroi Y, Sakata M, Harada T, Nakamura F, et al. Positron emission tomography predicted recovery of complete A-V nodal dysfunction in a patient with cardiac sarcoidosis. *Circulation* 2002; 105: 1144–1145.
7. Yen RF, Chen YC, Wu YW, Pan MH, Chang SC. Using 18-fluoro-2-deoxyglucose positron emission tomography in detecting infectious endocarditis/endoarteritis: a preliminary report. *Acad Radiol* 2004; 11: 316–321.
8. Jingu K, Nemoto K, Kaneta T, Takai Y, Ichinose A, Ogawa Y, et al. A case of high FDG-uptake into the myocardium after radiationtherapy for esophageal cancer. *Nippon Acta Radiol* 2005; 65: 266–269. (in Japanese)
9. Steinmetz AP, Cronin B, Wierzbicki AS, Lumb PJ, Maisey MN. Relationship of myocardial 18-FDG uptake in oncologic PET imaging to plasma lipid and glucose metabolism [abstract]. *Eur J Nucl Med* 2000; 27: 902.
10. de Groot M, Meeuwis AP, Kok PJ, Corstens FH, Oyen WJ. Influence of blood glucose level, age and fasting period on non-pathological FDG uptake in heart and gut. *Eur J Nucl Med Mol Imaging* 2005; 32: 98–101.
11. Yamanouchi M, Yoshida K, Niwayama H, Nakagawa K, Aioi S, Shikama N, et al. Effect of the duration of fasting on myocardial fluorine-18-fluorodeoxyglucose positron emission tomography images in normal males. *Jpn Circ J* 1996; 60: 319–327.
12. Grossman MI, Moeller HC, Palm L. Effect of lipemia and heparin on free fatty acid concentration of serum in humans. *Proc Soc Exp Biol Med* 1955; 90: 106–109.
13. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963; 1: 785–789.
14. Nuutila P, Koivisto VA, Knuuti J, Ruotsalainen U, Teras M, Haaparanta M, et al. Glucose-free fatty acid cycle operates in human heart and skeletal muscle *in vivo*. *J Clin Invest* 1992; 89: 1767–1774.
15. Cheung JY, Conover C, Regen DM, Whitfield CF, Morgan ME. Effect of insulin on kinetics of glucose transport in heart muscle. *Am J Physiol* 1978; 234: E70–78.
16. Opie LH. Fuels: Carbohydrates and Lipids. In: *The Heart, Physiology and Metabolism*, Opie LH (ed), New York; Raven Press, 1991: 208–246.
17. Sun DQ, Hguyen N, Degrado TR, Schwaiger M, Brosius FC. Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 to plasma membrane of cardiac myocytes. *Circulation* 1994; 89: 793–798.
18. Hicks RJ, Herman WH, Kalff V, Molina E, Wolfe ER, Hutchins G, et al. Quantitative evaluation of regional substrate metabolism in the human heart by positron emission tomography. *J Am Coll Cardiol* 1991; 18: 101–111.
19. Ferrannini E, Santori D, Bonadonna R, Natali A, Parodi O, Camici PG. Metabolic and hemodynamic effects of insulin on human heart. *Am J Physiol* 1993; 264: E308–315.
20. Knuuti MJ, Yki-Jarvinen H, Voipio-Pulkki LM, Maki M, Ruotsalainen U, Harkonen R, et al. Enhancement of myocardial [fluorine-18]fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 1994; 35: 989–998.
21. Sugden MC, Holness MJ, Liu YL, Smith DM, Fryer LG, Kurszynska YT. Mechanisms regulating cardiac fuel selection in hyperthyroidism. *Biochem J* 1992; 286: 513–517.
22. Bonen A, Megeney LA, McCarthy SC, McDermott JC, Tan MH. Epinephrine administration stimulates GLUT4 translocation but reduces glucose transport in muscle. *Biochem Biophys Res Commun* 1992; 187: 685–691.
23. Mooradian AD. Effect of ascorbate and dehydroascorbate on tissue uptake of glucose. *Diabetes* 1987; 36: 1001–1004.
24. Paternostro G, Pagano D, Gnecchi-Ruscone T, Bonser RS, Camici PG. Insulin resistance in patients with cardiac hypertrophy. *Cardiovasc Res* 1999; 42: 246–253.