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We report a case of delayed enhancement of myocardial FDG uptake in NIDDM patient after oral glucose loading. A 65-year-old man who had a past history of NIDDM received FDG-PET examination during fasting and glucose loading. In neither condition, was an accumulation of FDG in the myocardium, and myocardial blood flow was normal. An oral glucose tolerance test (OGTT) was performed to find the best time for FDG injection and 3 hours after loading, the serum insulin concentration was increased significantly. When the interval between glucose loading and the injection of FDG was set at 3 hours, enhancement of myocardial FDG uptake was demonstrated. To know the best time for the FDG injection in advance is thought to be important in obtaining better image quality and interpreting the myocardial viability when FDG-PET examination during glucose loading is performed in NIDDM patients.

Key words: FDG-PET, NIDDM, glucose transporter

INTRODUCTION

FDG has been widely used for the detection of viable ischemic myocardium. Diabetes Mellitus (DM) complicates the evaluation of myocardial viability by deteriorating image quality during fasting or oral glucose loading.[1,2] To enhance myocardial FDG uptake, oral glucose loading is a simple method, but its image quality is poor with the conventional interval between loading and the injection.[3] We report a case of delayed enhancement of myocardial FDG uptake detected by changing the interval between glucose loading and injection in a patient with non-insulin dependent diabetes mellitus (NIDDM).

CASE REPORT

A 65-year-old man complained of chest oppression and was admitted to our hospital. In an electrocardiogram

(ECG), II, III, and aV_F leads demonstrated ST increase. Acute myocardial infarction was suspected and emergency coronary angiography (CAG) was performed. Though significant stenosis was demonstrated in segment 2 of the right coronary artery (90%) and segment 11 of left circumflex artery (75%), it was eliminated by intra-coronary infusion of nitroglycerine and thought to be caused by vasospasm. Abnormal wall motions were not observed in left ventriculography.

He had a history of diabetes mellitus (DM), and sulfonylurea therapy had been performed. His fasting glucose level at admission was 149 mg/dl (reference value 65–110 mg/dl) and hemoglobin A_{1c} (HbA$_{1c}$) was 6.9% (reference value 4.3–5.9%).

To examine myocardial viability, an FDG-PET study was performed during fasting and glucose loading following the protocol shown in Figure 1. Approximately 55.5 MBq (1.5 mCi) of FDG was injected and a fasting FDG image was obtained 1 hour later with a 3-dimensional acquisition mode. Then 75 gram of oral glucose loading (Toleran G) was performed and myocardial blood flow was measured with N-13 ammonia. One hour after glucose loading, approximately 370 MBq (10 mCi) of FDG

was injected and a glucose loading FDG image was obtained 1 hour after FDG injection with a 2-dimensional acquisition mode.

The results are shown in Figure 2. There was no apparent decrease in myocardial blood flow. In both FDG-PET examination conditions, no FDG accumulation in
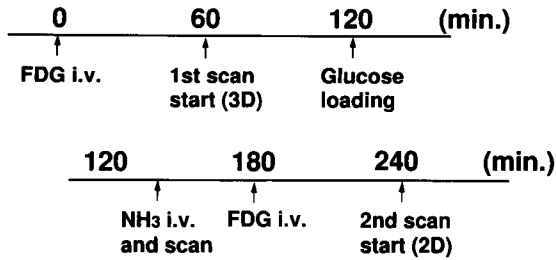

Fig. 1   Protocol for fasting-glucose loading FDG-PET examination.

myocardium was apparent. The serum glucose and insulin levels were 132 mg/d*l* and 9.9 mU/*l* (reference value 5–25 mU/*l*) in the fasting and 293 mg/d*l* and 14.3 mU/*l* in the glucose loading condition, respectively. To find the best tome for enhancement of myocardial FDG uptake after glucose loading, an oral glucose tolerance test (OGTT) was performed. Serum glucose and insulin were measured at the point of pre-loading and the 1 hour, 2 hours and 3 hours after loading. After glucose loading, the serum glucose concentration was noticeably increased. In contrast, the serum insulin concentration was within the normal range 1 hour and 2 hours after loading, then increased up to 37 mU/*l* 3 hours after loading. We thought that in this case the best time for injection was 3 hours after oral glucose loading.

Based on the result of this test, the FDG-PET examination was performed according to the following the proto-
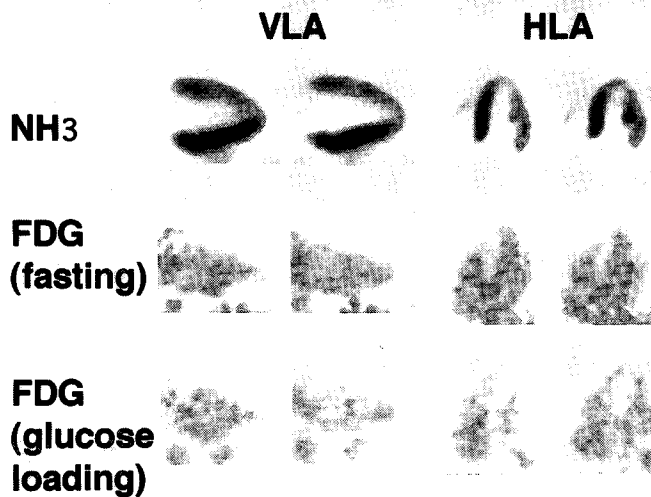

Fig. 2   The results of the first examination. In myocardial perfusion study using N-13 ammonia, no apparent decreased flow area was detected. During fasting and glucose loading state, no significant myocardial uptake of FDG was observed.
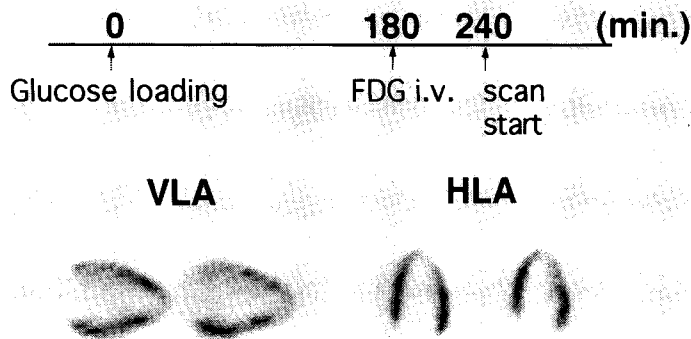

Fig. 3   Protocol of the second examination and its result. After setting the interval between glucose loading and FDG injection to 3 hours, enhanced FDG uptake in myocardium was demonstrated.

col. Three hours after oral glucose loading, approximately 370 MBq (10 mCi) of FDG was injected, then 1 hour later data acquisition was performed. The protocol and results are shown in Figure 3. Enhanced myocardial FDG uptake was demonstrated in diffuse left ventricular myocardium.

DISCUSSION

FDG is widely used to detect ischemic myocardium in the fasting state and myocardial viability in the glucose loading state. In myocardial ischemia, lesions are demonstrated as high FDG uptake areas. Stanley et al. reported that diabetes does not affect the rate of glycolysis during myocardial ischemia.[4] Sun et al. reported that ischemia induces the translocation of glucose transporter 4 (GLUT4) from an intracellular component to the plasma membrane of cardiac myocytes,[5] so that the detection of ischemia in a diabetic patient seems to be possible in the fasting state. In contrast, enhancement of myocardial FDG uptake is necessary to know the myocardial viability. To enhance myocardial FDG uptake, several methods directly associated with glucose metabolism, including oral glucose loading and the euglycemic-hyperinsulinemic method (insulin clamp method) has been applied[6,7] in non-diabetic patients. In diabetic patients, euglycemic-hyperinsulinemic method was applied and its feasibility was reported.[3,8,9]

Three major metabolic abnormalities which contribute to hyperglycemia in NIDDM are defective glucose-induced insulin secretion (impaired insulin secretory responses to glucose), increased hepatic glucose output and the impaired ability of insulin to stimulate glucose uptake in peripheral target tissues (insulin resistance).[10] Impaired insulin secretion is caused by the depletion of glucose transporter 2 (GLUT2) which exists in the β-cells in the pancreas. Insulin resistance is a major pathophysiological characteristic of NIDDM,[11,12] and the most immediate manifestation of insulin resistance is fasting hyperinsulinemia in conjunction with normo- or hyperglycemia. This is caused by the abnormality of GLUT4 which exists in the skeletal muscles and myocardium. Both abnormalities are improved after a period of euglycemic therapy with insulin,[13-16] weight loss,[17,18] and sulfonylurea.[19,20] In this case, impaired insulin secretion was observed but the insulin level in the fasting state was not high even though mild hyperglycemia was detected. The sulfonylurea therapy he received several years might have improved his insulin resistance and only impaired insulin secretion might be revealed.

Recently, a new method for enhancement of myocardial FDG uptake which is not directly associated with glucose metabolism was proposed. The concept of new method is that by lowering the free fatty acid level, myocardial glucose uptake is increased. For this method, nicotinic acid derivatives[21,22] and niacin[23] are used. The greatest advantage of this method is that these drugs do not change the glucose and insulin concentration and the insulin-mediated glucose transporter system is not affected, so that enhancement of myocardial FDG uptake may be easily performed in NIDDM patients.

In this case, we changed the time interval between oral glucose loading and FDG injection to obtain the best FDG images during glucose loading. With this method, no quantitative image, such as the myocardial glucose utilization rate, can be obtained because of the instability of the glucose concentration. But our method may make it easy to judge viability by visual assessment or semi-quantitative analysis with a standardized uptake value (SUV).

In conclusion, to find the best time for FDG injection in advance is thought to be important in obtaining better image quality and interpreting myocardial viability when an FDG-PET examination is performed in NIDDM patients during glucose loading.

REFERENCES

1. Prellwitz J, Vatsta M, Sunderland J, Shiue C-Y, Gupta N, Frick M. Investigation of factors influencing FDG myocardial image quality [Abstract]. *J Nucl Med* 32: 1039, 1991.
2. vom Dahl J, Hicks R, Lee K, Eitzman D, Alaouar Z, Schwaiger M. PET myocardial viability studies in patients with diabetes mellitus [Abstract]. *J Am Coll Cardiol* 17: 121A, 1991.
3. Ohtake T, Yokoyama I, Watanabe T, Momose T, Serizawa T, Nishikawa J, et al. Myocardial glucose metabolism in noninsulin-dependent diabetes mellitus patients evaluated by FDG-PET. *J Nucl Med* 36: 456–463, 1995.
4. Stanley CW, Hall JL, Smith KR, Cartee GD, Hacker TA, Wisneski JA. Myocardial glucose transporter and glycolytic metabolism during ischemia in hyperglycemic diabetic swine. *Metabolism* 43: 61–69, 1994.
5. Sun D, Nguyen N, DeGrado TR, Schwaiger M, Brosius FC III. Ischemia induces translocation of the insulin-responsive glucose transporter GLUT4 to the plasma membrane of cardiac myocytes. *Circulation* 89: 793–798, 1994.
6. Hicks R, vom Dahl J, Lee K, Herman W, Kalff V, Schwaiger M. Insulin-glucose clamp for standardization of metabolic conditions during F-18 fluorodeoxyglucose PET imaging. *J Am Coll Cardiol* 17: 381A, 1991.
7. Knuuti MJ, Nuutila P, Ruotsalainen U, Saraste M, Harkonen R, Ahonen A, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 33: 1255–1262, 1992.
8. vom Dahl J, Herman WH, Hicks RJ, Ortiz-Alonso FJ, Lee KS, Allman KC, et al. Myocardial glucose uptake in patients with insulin-dependent diabetes mellitus assessed quantitatively by dynamic PET. *Circulation* 88: 395–404, 1993.
9. Voipio-Pulkki LM, Nuutila P, Knuuti MJ, Haaparanta M, Teras M, Wegelius-U, et al. Heart and skeletal muscle glucose disposal in type 2 diabetic patient as determined by positron emission tomography. *J Nucl Med* 34: 2064–2067, 1993.
10. Garvey WT. Glucose transport and NIDDM. *Diabetes Care* 15: 396–417, 1992.

11. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37: 1595–1607, 1988.
12. Defronzo RA. Lilly Lecture 1988: the triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 37: 667–687, 1988.
13. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes. *Diabetes* 34: 222–234, 1985.
14. Scarlett JA, Gray RS, Griffin J, Olefsky JM, Kolterman OG. Insulin treatment reserves the insulin resistance of type II diabetes mellitus. *Diabetes Care* 5: 353–363, 1982.
15. Ginsberg H, Rayfield EJ. Effect of insulin therapy on insulin resistance in type II diabetic subjects: evidence for heterogeneity. *Diabetes* 30: 739–745, 1981.
16. Andrews WJ, Vasquez B, Nagulesparan M, Klimes I, Foley JE, Unger R. Insulin therapy in obese NIDDM induces improvements in insulin action and secretion that are maintained for two weeks after insulin withdrawal. *Diabetes* 33: 634–642, 1984.
17. Henry RR, Wallace P, Olefsky JM. Effect of weight loss on mechanism of hyperglycemia in obese non-insulin dependent diabetes mellitus. *Diabetes* 35: 990–998, 1986.
18. Zawadzki JK, Bogardus C, Foley JE. Insulin action in obese non-insulin dependent diabetes and in their isolated adipocytes before and after weight loss. *Diabetes* 36: 227–236, 1987.
19. Greenfield MS, Doberne L, Rosenthal M, Schulz B, Widstrom A, Reaven GM. Effects of sulfonylurea treatment on *in vivo* secretion and action in patients with non-insulin-dependent diabetes mellitus. *Diabetes* 31: 307–312, 1982.
20. Kolterman OG, Gray RS, Shapiro G, Scalett JA, Griffin J, Olesky JM. The acute and chronic effects of sulfonylurea therapy in type II diabetic subjects. *Diabetes* 33: 346–354, 1984.
21. Knuuti MJ, Yki-Jarvinen H, Voipio-Pulkki LM, Maki M, Ruotosalainen U, Harkonen R, et al. Enhancement of myocardial [Fluorine-18]Fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med* 35: 989–998, 1994.
22. Monti LD, Lucignani G, Landoni C, Moresco RM, Piatti P, Stefani I, et al. Myocardial glucose uptake evaluated by positron emission tomography and fluorodeoxyglucose during hyperglycemic clamp in IDDM patients. *Diabetes* 44: 537–542, 1995.
23. Stone CK, Holden JE, Stanley W, Perlman SB. Effect of nicotinic acid on exogenous myocardial glucose utilization. *J Nucl Med* 36: 996–1002, 1995.