Re-Evaluation of Myocardial FDG Uptake in Hyperglycemia

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Myocardial [^{18}F] fluorodeoxyglucose (FDG) uptake depends on several metabolic variables in vivo. The effect of different levels of experimentally induced hyperglycemia on myocardial FDG uptake was examined. **Methods:** FDG uptake was studied in young Donryu rats 1 hr after intravenous injection under various pretreatments that increased serum glucose levels. Serum samples were analyzed for glucose, insulin and free fatty acids. Myocardial distribution of FDG was examined with autoradiography. **Results:** Administration of glucose (n = 42), triiodothyronine (n = 7), epinephrine (n = 7), dehydroascorbic acid (n = 5) and 4 mg streptozotocin (Szt, n = 10) increased glucose levels to 120–200 mg/dl. Dexamethasone (Dex, n = 34) and 6 mg Szt (n = 6) increased glucose levels to 200–450 mg/dl. Myocardial FDG uptake increased proportionately with increases in serum glucose level up to 200 mg/dl. In severe hyperglycemia (serum glucose: 200–450 mg/dl), however, the FDG uptake decreased and did not correlate with blood glucose level. A study of fractional FDG uptake calibrated by the arterial FDG curve confirmed the same results. Heterogeneous distribution of FDG was observed in the myocardium, both in fasting and in severe hyperglycemic conditions. The pattern of FDG uptake by skeletal muscles was similar to that of the myocardium, although the uptake was lower than that in the myocardium. Changes in insulin and free fatty acids levels could not explain the FDG uptake pattern in severe hyperglycemia. Blood FDG uptake level remained constant regardless of glucose level. **Conclusion:** Hyperglycemia induced a biphasic pattern of myocardial FDG uptake, common with skeletal muscles. The understanding of myocardial FDG uptake characteristics and their dependence on blood glucose is helpful in interpreting myocardial FDG-PET images.

Key Words: fluorine-18-fluorodeoxyglucose; myocardial metabolism; skeletal muscle; hyperglycemia

PET, using 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), has become a valuable method for assessing various myocardial diseases (*1,2*). In myocardial imaging with FDG, increased myocardial uptake of FDG after glucose loading is well documented. After glucose loading, increased insulin level, coupled with reduced free fatty acid shift the metabolic fuel of the myocardium from fatty acids to glucose, which results in increased FDG uptake (*1-4*). Under fasting conditions, the distribution of FDG in the myocardium is not uniform but becomes homogeneous after glucose loading (*5*). FDG-PET examination of patients during a postprandial state has been recommended to enhance the detection of myocardial metabolic defect (*5*). In hyperglycemic diabetic patients, however, defect in myocardial glucose utilization and nonuniformity of FDG distribution has also been reported (*6*). The exact correlation between myocardial FDG uptake and hyperglycemia is, however, not clear. To understand the effect of hyperglycemia on

myocardial FDG uptake in vivo, the uptake of FDG was studied using in vivo hyperglycemic rats.

MATERIALS AND METHODS

The experimental protocol was approved by the Laboratory Animal Care and Use Committee of Tohoku University, Sendai, Japan.

Induction of Hyperglycemia

Young male Donryu rats weighing 140–180 g were used for radioisotope studies after manipulation of blood glucose level. The control rats (n = 48) were fasted for 12 hr. Rats in the glucose loading group (n = 42) were given an oral dose of 0.6 ml of 50% glucose 15 min before the injection of the radioisotope. Hyperglycemia was also induced using several pharmacological agents listed in Table 1. These agents were obtained commercially. Streptozotocin (Szt) is known to induce experimental diabetes by directly damaging pancreatic beta cells (*7*). We used two doses of Szt: low doses to induce mild hyperglycemia and higher doses to induce severe hyperglycemia (Tables 1 and 2). Dehydroascorbic acid is also known to induce hyperglycemia in vivo (*7*) and inhibit brain uptake of glucose (*8*). Ascorbic acid shares the membrane transport with glucose (*9*). We then tested both the ascorbic acid and dehydroascorbic acid. Dipyridamole, a commonly used coronary dilator, was also used in the study. Additionally, dexamethasone (Dex), triiodothyronine and epinephrine are known to induce hyperglycemia.

FDG Uptake and Serum Glucose

After induction of hyperglycemia, a 1.11-MBq dose of FDG was injected intravenously into each animal. Each animal was killed 1 hr later. Blood samples were then collected for analysis and tissue samples from the myocardium and thigh skeletal muscles were excised and weighed. Radioactivity of tissue and blood was measured using an automated gamma counter. Serum samples were separated and stored at -20°C. Glucose levels were measured by the glucose oxidase method using an autoanalyzer. We expressed FDG uptake as the differential uptake ratio (DUR):

$$DUR = \frac{\text{sample radioactivity/sample weight}}{\text{injection dose/body weight}}. \quad \text{Eq. 1}$$

FDG Fractional Uptake and Serum Glucose

Three control, four glucose loading and three Dex-treated rats were anesthetized by intramuscular injection of 30 mg/kg sodium pentobarbital. In a separate study, we confirmed that this dose of anesthesia did not influence myocardial FDG uptake. A dose of 1.11 MBq FDG in 0.2–0.3 ml saline was injected through a catheter placed in the femoral vein and flushed with 0.3 ml saline. Blood samples, 0.05 ml each, were collected through a catheter placed in the carotid artery sequentially until 60 min after injection. The rats were killed immediately after blood sampling at 60 min by an overdose of anesthesia, and myocardial tissue samples were excised and weighed. A gamma counter was used to count tissue and blood samples. The blood glucose level was measured just before FDG injection. The percent fractional uptake of FDG in the

TABLE 1
Pretreatments Used to Modify Blood Glucose Levels

Drugs	Feeding	Treatment before tracer experiment
Control (Cont)	12-hr fasting	
Glucose load (Glu)	Free feeding	50% Glu 0.6 ml p.o. 15 min before
Dehydroascorbic acid	Free feeding	100 mg i.p. 10 min before
Ascorbic acid	Free feeding	100 mg i.p. 10 min before
Dipyridamole	Free feeding	3 mg i.p. 5 min before
Streptozotocin (Szt)-1	Free feeding	6 mg i.v. 10 days before
Streptozotocin (Szt)-2	Free feeding	4 mg i.v. 10 days before
Dexamethasone (Dex)	Free feeding	0.1 mg s.c. twice a day for 3 days
Triiodothyronine	Free feeding	10 μg p.o. once a day for 3 days
Epinephrine	Free feeding	50 μg i.p. 30 min before

myocardium was calculated according to the following formula (*10*) and plotted against the blood glucose level:

$$\%FDG \text{ fractional uptake} = \frac{C_{FDG}}{\int_0^{60} Cb \, dt} \times 100, \quad \text{Eq. 2}$$

where C_{FDG} is the myocardial activity (cpm/g) of FDG, $_0\int^{60} Cb \, dt$ is the integral of the arterial blood activity (Cb; cpm/g) from the time of injection to the end of the distribution period of 60 min.

Free Fatty Acids and Insulin in Hyperglycemia

A dose of 1.11 MBq FDG was injected intravenously in control (n = 8), glucose load (n = 8), Dex-treated (n = 7) and two groups of Szt-treated rats (Szt-1, n = 6; Szt-2, n = 10). The animals were killed 1 hr later. Blood, myocardium and thigh muscle samples were obtained. Aliquot of whole blood was used for measurement of radioactivity. FDG uptake in each sample was measured by an automated gamma counter. The uptake was also expressed as DUR. Serum samples were separated and stored at -20°C until measurement of glucose, free fatty acid and insulin. Free fatty acid was measured using the acil-CoA synthetase method with autoanalyzer, and insulin was measured by radioimmunoassay. FDG data of the Szt groups were also used in the former section. Differences between data were tested for statistical significance using Student's t-test or one-way analysis of variance test.

Autoradiography

A dose of 63 MBq FDG was injected intravenously in three control and glucose load and four Dex-treated rats. The rats were killed 1 hr later. Their hearts were excised, embedded in a block, frozen and sectioned on a cryostat at -15°C, as previously described (*11*). Serial 30-μm thick transverse sections were placed in contact with ARG film for 9 hr to produce FDG images.

TABLE 2
Effects of Treatments on Serum Glucose

Treatment	Number of rats	Glucose (mg/dl)*
Control	48	105 ± 13
Ascorbic acid	7	104 ± 14
Dipyridamole	7	102 ± 8
Triiodothyronine	7	152 ± 8[†]
Epinephrine	7	163 ± 6[†]
Streptozotocin (Szt)-2	10	165 ± 14[†]
Dehydroascorbic acid	5	173 ± 31[†]
Glucose loading	42	176 ± 41[†]
Streptozotocin (Szt)-1	6	393 ± 64[†§]
Dexamethasone (Dex)	34	308 ± 82[†§]

*Mean ± s.d.
[†]p < 0.001 compared to control (Student's t-test).
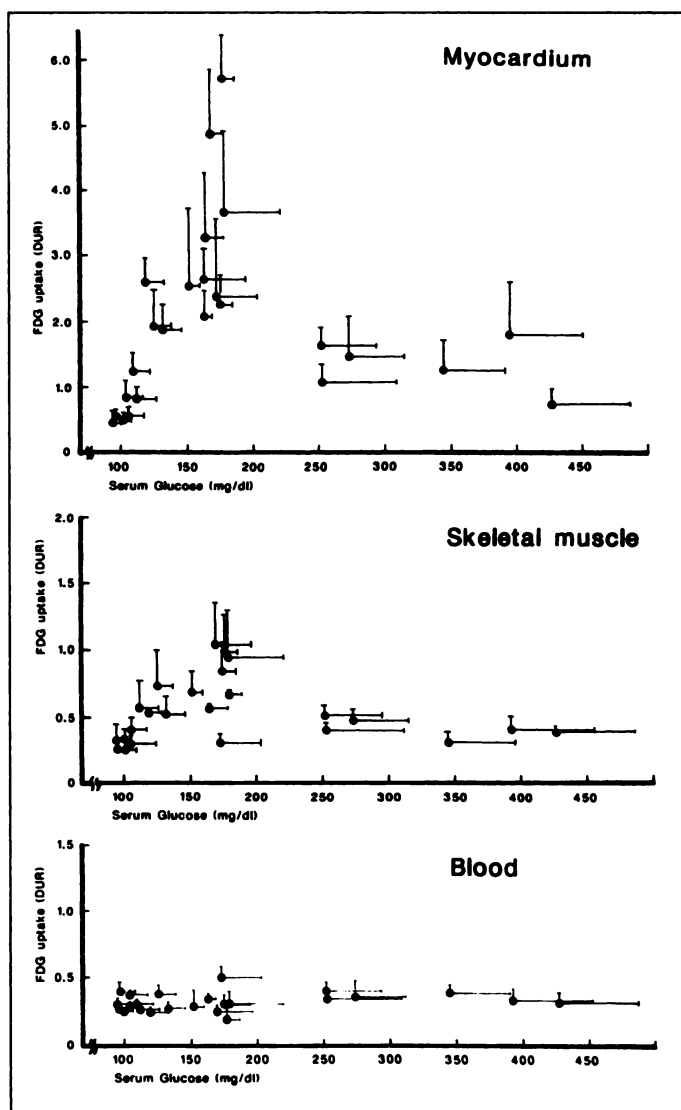[§]p < 0.001 compared to Glucose loading and dehydroascorbic acid.

FIGURE 1. Myocardial FDG uptake (top) and uptake in thigh skeletal muscle (middle) correlated with serum glucose levels. Blood FDG uptake (bottom) was almost constant. Each point represents mean and s.d. of five to eight rats. Data were obtained 60 min after injection of FDG and various pretreatments listed in Table 1. Treatment and blood glucose data are in Table 2.

RESULTS

Effect of Treatment on Serum Glucose Level

Table 2 summarizes the effects of pretreatment regimens on blood glucose level. All pharmacological agents induced significant hyperglycemia, except for ascorbic acid and dipyridamole. The level of hyperglycemia varied according to the drug used, with the highest levels in Szt-1- and Dex-treated animals.

Effect of Hyperglycemia on FDG Uptake

Figure 1 shows the effect of serum glucose level on FDG uptake in different tissues. Myocardial uptake of FDG increased proportionately with the increase in serum glucose level up to 200 mg/dl. The peak uptake occurred at a glucose level of approximately 200 mg/dl. Further increase in serum glucose level (200–450 mg/dl), however, resulted in reduced FDG uptake. At these glucose levels, no relationship between FDG uptake and serum glucose was evident. FDG uptake of skeletal muscle showed a similar pattern, although the uptake was lower than that in myocardium. The blood FDG level was not influenced by serum glucose level.

To confirm the result of the single-point blood and tissue sampling study shown in Figure 1, a more sophisticated
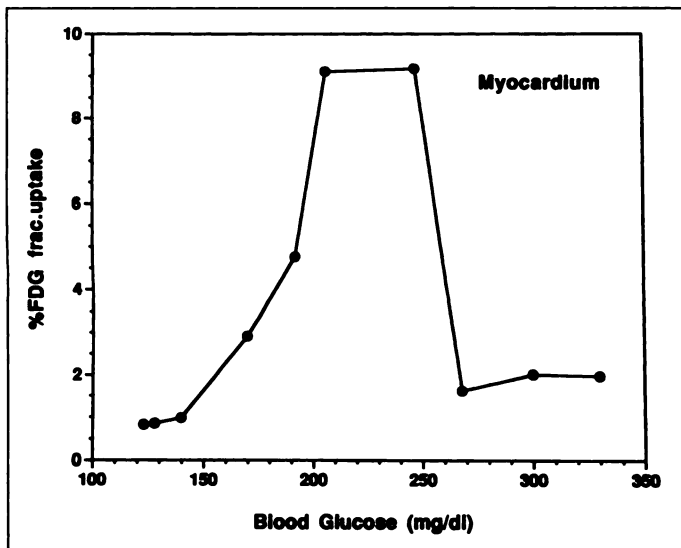
FIGURE 2. Percent FDG fractional uptake in myocardium. FDG uptake fraction over the integral of the arterial blood activity was calculated and plotted against the blood glucose level. Left three points (<140 mg/dl) are fasting condition, middle four points (170–245 mg/dl) glucose loading and right three points (265 mg/dl <) dexamethasone treatment.

approach for quantification of fractional FDG uptake was performed using arterial FDG clearance curve. Figure 2 shows a similar pattern to Figure 1. Three fasting rats showed low fractional FDG uptake at low glucose levels. Four glucose load rats showed increased fractional FDG uptake with increasing blood glucose level. Three Dex-treated rats showed the highest glucose level (>250 mg/dl), but fractional FDG uptake was lower than that of the glucose load.

We also investigated the exact effect of Dex, Szt and glucose load on insulin, FFA levels and on myocardial FDG uptake (Fig. 3). The control group (n = 8) had a glucose level ranging from 80 to 119 mg/dl. The second group included the glucose load and the Szt-2-treated rats with moderate hyperglycemia ranging from 141 to 195 mg/dl. In this group, myocardial FDG uptake was higher (4.00 ± 1.27, n = 18; control: 0.57 ± 0.07, n = 8, p < 0.001), and the free fatty acids were lower than the control group levels (0.51 ± 0.10, n = 18; control: 0.96 ± 0.28, n = 8, p < 0.001), although the insulin level was higher than the control (7.90 ± 1.79, n = 18; control: 4.88 ± 0.84, n = 8, p < 0.001). There were no significant differences between the glucose load and Szt-2-treated rats in each measurement. Both the Dex- and Szt-1-treated rats had severe hyperglycemia ranging from 289 to 488 mg/dl.

The levels of free fatty acids and insulin in Dex-treated rats (1.38 ± 0.42, p < 0.05; 46.50 ± 6.30, p < 0.001) were significantly higher than those in the control rats and those with moderate hyperglycemia. Free fatty acids and insulin levels in rats with severe hyperglycemia and in Szt-1-treated rats (0.55 ± 0.07; 9.50 ± 2.90) were not different from those in rats with moderate hyperglycemia. FDG uptake in rats with severe hyperglycemia (1.26 ± 0.77, n = 13) was lower than that in rats with moderate hyperglycemia (p < 0.001) and was not correlated to the glucose level. Furthermore, FDG uptake was not different between Dex- and Szt-1-treated animals, and no significant correlation was observed between FDG uptake, free fatty acids and insulin levels in rats with severe hyperglycemia. These results suggest that myocardial FDG uptake is enhanced under mild hyperglycemia (glucose load and Szt-2) by interaction with free fatty acids and insulin but decreased under severe hyperglycemia (Dex- and Szt-1-treated rats) irrespective of free fatty acids or insulin levels.
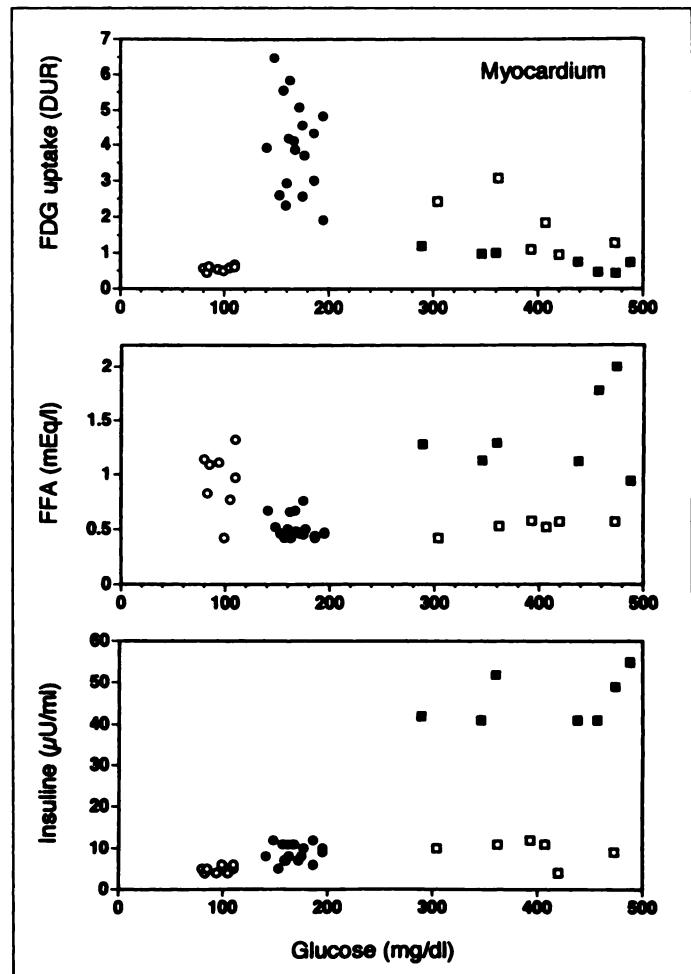

FIGURE 3. Correlation between serum glucose and myocardial FDG uptake (top), serum free fatty acid (FFA) (middle), serum insulin (bottom). (O) Control (fasting), (●) moderate hyperglycemia induced by glucose load or by Szt-2 treatment, (□) severe hyperglycemia induced by Szt-1 treatment and (■) severe hyperglycemia induced by Dex treatment.

Figure 4 shows ARG of the myocardium under glucose loading and the Dex treatment and control conditions. ARG shows a homogeneous high grain density in the myocardium after glucose loading. On the other hand, the ARG of control and Dex-treated rats showed low and heterogeneous grain density in the myocardium.

DISCUSSION

This study's primary finding was that myocardial FDG uptake varied with serum glucose level, which showed a biphasic pattern. A hyperglycemic state increased FDG uptake along with an increase in blood glucose levels, ranging from 100 to 200 mg/dl. Severe hyperglycemia, however, reduced FDG uptake without correlation to blood glucose level. Heterogeneous distribution of FDG was observed in the myocardium, both in fasting and severe hyperglycemic conditions. The change in FDG uptake by heart and skeletal muscle had a similar pattern. The results of the single-point blood and tissue sampling study agreed with the fractional FDG uptake study using the arterial FDG clearance curve. The FDG fractional uptake percent calculation provided a fraction representing the FDG uptake in each myocardial tissue in relation to the delivered dose presented to the heart. This method has been applied and validated in various experimental and clinical studies of myocardial FDG metabolism (10).

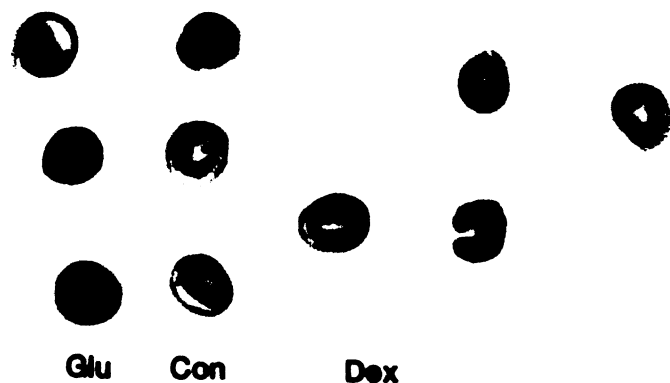Several agents used in the present experiment induced a state

Glu   Con   Dex

of moderate hyperglycemia. Dehydroascorbic acid is known to induce hyperglycemia in vivo (7) and inhibit brain uptake of glucose (8). Our results demonstrated that this compound increased myocardial FDG uptake. Enhanced cardiac glucose utilization under hyperthyroidism is due to secondary changes in glucose-lipid interaction at a tissue level rather than acting through glucose transporter expression (12). In the present study, triiodothyronine induced moderate hyperglycemia and increased myocardial FDG uptake. On the other hand, epinephrine stimulates translocation of glucose transporter into the plasma membrane of muscle (13). When used in the present study, epinephrine caused moderate hyperglycemia and increased FDG uptake by the heart and skeletal muscles. The effect was similar to that observed during glucose loading. Thus, each treatment induced moderate hyperglycemia by a different mechanism. As for the effect of these treatments on myocardial FDG uptake, the latter simply increased with increasing blood glucose levels, with significant interaction with free fatty acids and insulin.

In this study, we demonstrated that the administration of ascorbic acid did not influence glucose levels. On the other hand, dipyridamole inhibits glucose transport in skeletal muscle (14). In the present study, it failed, however, to change either glucose levels or FDG uptake by the heart and skeletal muscles.

Our study examined the effect of acute hyperglycemia induced in young normal rats. It is unlikely that our treatment altered myocardial microcirculation as a result of hyperglycemia, as seen in certain diabetic patients. In severe hyperglycemia, myocardial FDG uptake was inhibited, reaching a level of approximately 1.8–0.7 (DUR) and stabilized at that level independent of blood glucose level. If this phenomenon represented an isotope dilution effect and competition between FDG and glucose, myocardial FDG uptake should have decreased simply in response to increasing levels of blood glucose. Instead, myocardial FDG uptake showed a biphasic response, an initial increase associated with increasing levels of blood glucose, until a level of 200 mg/dl was achieved. A further increase in the glucose level reduced FDG uptake. Furthermore, the blood FDG level was not influenced by the glucose level. The steady level of myocardial FDG uptake at blood glucose levels exceeding 200 mg/dl cannot be explained by the isotope dilution effect. Instead, specific changes in glucose metabolism or transport must occur at blood glucose levels higher than 200 mg/dl. A shift of metabolic fuel from glucose to fatty acid or

impairment of glucose metabolism or transport may explain low and heterogeneous myocardial FDG uptake under severe hyperglycemia.

Glucocorticoid induces insulin resistance and suppresses myocardial glucose extraction in vivo (15,16). Dex also reduces skeletal muscle glucose uptake (17). Dex-induced insulin resistance in rat skeletal muscle is not due to suppression of glucose transporter gene expression. A possible failure of translocation of glucose transporter-4 (Glut-4), containing intracellular vesicles, to plasma membrane has been suggested (17). On the other hand, Szt induces experimental diabetes by selective destruction of pancreatic beta cells (7), probably due to methylation of DNA (18). Several studies indicated that glucose uptake by heart and skeletal muscle is reduced in Szt-induced diabetes (19-22). Recently, a dissociation of reduced glucose uptake rates and unaltered levels of Glut-4 at an early stage (7 days) of Szt diabetes has been reported (20). Furthermore, impaired glucose transporter translocation or activity has also been suggested (20). We demonstrated significantly higher insulin levels in Szt-1- and Szt-2-treated rats compared to the control group. Glucose load and Szt-2-treated rats with mild hyperglycemia showed high myocardial FDG uptake, while Szt-1- and Dex-treated rats with severe hyperglycemia showed significantly lower FDG uptake than the former group. The reduced FDG uptake by the myocardium and skeletal muscle under severe hyperglycemia induced by Dex or Szt treatments may be due to reduced glucose transport. Since we did not examine the mRNA or the protein of glucose transporter of the myocardium, the exact mechanism remains unclear.

A recent study using isolated working rat hearts showed that myocardial FDG uptake was linearly related to glucose utilization only under steady-state conditions. Additionally, under various treatments including insulin, FDG uptake underestimated glucose utilization (23). The myocardial lumped constant relating the steady-state phosphorylation rate of FDG to that of glucose was sensitive to medium glucose level and to insulin stimulation (24). The potential variability of the lumped constant has been considered a limiting factor in the use of FDG as a tracer of glucose metabolism. Since the degree of FDG accumulation in the heart varies for several reasons, FDG may not provide a quantitative measure of the glucose metabolic rate (25). The interaction of free fatty acids and insulin in mild hyperglycemia in our study suggested that enhanced FDG uptake in mild hyperglycemia is linked to glucose utilization. A metabolic fuel shift from fatty acid in the fasting condition to glucose in the mild hyperglycemia may explain the enhanced FDG uptake. On the other hand, reduced FDG uptake in severe hyperglycemia could be explained by a dissociation between FDG and glucose metabolism. Biochemical analysis of FDG and glucose metabolism, however, are necessary to elucidate the exact mechanism. Nevertheless, our observation of biphasic myocardial FDG uptake in response to increasing blood glucose levels is useful information for FDG-PET myocardial imaging in patients with various diseases or medications that may alter blood glucose level.

CONCLUSION

Each hyperglycemic treatment seems to influence the distribution of FDG due to the inherent mechanism inducing hyperglycemia. For FDG-PET imaging, myocardial uptake of FDG showed a simple biphasic response to rising blood glucose levels. In fasting states to mild hyperglycemic states of approximately 200 mg/dl, FDG uptake increased proportionately with increasing blood glucose levels. Severe hyperglycemia (200–450 mg/dl), however, decreased FDG uptake. Heterogeneous

distribution of FDG in the myocardium was observed in fasting and severe hyperglycemic states. FDG uptake by skeletal muscles showed a pattern similar to that of the myocardium. Understanding of these FDG uptake characteristics and their dependence on blood glucose is helpful in interpreting myocardial FDG-PET scans.

ACKNOWLEDGMENTS

REFERENCES

1. Schwaiger M, Hicks R. The clinical role of metabolic imaging of the heart by positron emission tomography. *J Nucl Med* 1991;32:565–578.
2. Camici P, Ferrannini E, Opie LH. Myocardial metabolism in ischemic heart disease: basic principles and application to imaging by positron emission tomography. *Progr Cardiovasc Dis* 1989;32:217–238.
3. Yamada K, Endo S, Fukuda H, et al. Experimental studies on myocardial glucose metabolism of rats with ^{18}F-2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 1985;10:341–345.
4. Knuuti MJ, Nuutila P, Ruotsalainen U, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992;33:1255–1262.
5. Gropler RJ, Siegel BA, Lee KJ, et al. Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal, fasted humans. *J Nucl Med* 1990;31:1749–1756.
6. Voipio-Pulkki LM, Nuutila P, Knuuti MJ, et al. Heart and skeletal muscle glucose disposal in type 2 diabetic patients as determined by positron emission tomography. *J Nucl Med* 1993;34:2064–2067.
7. Rerup CC. Drugs producing diabetes through damage of the insulin secreting cells. *Pharmacol Rev* 1970;22:485–518.
8. Mooradian AD. Effect of ascorbate and dehydroascorbate on tissue uptake of glucose. *Diabetes* 1987;36:1001–1004.
9. Pecoraro RE, Chen MS. Ascorbic acid metabolism in diabetes mellitus. *Ann NY Acad Sci* 1987;498:248–257.
10. Camici P, Araujo LI, Spinks T, et al. Increased uptake of ^{18}F-fluorodeoxyglucose in postischemic myocardium of patients with exercised-induced angina. *Circulation* 1986;74:81–88.
11. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of AH109A tumor and inflammation by radioscintigraphy with L-[methyl ^{11}C]methionine. *Jpn J Cancer Res* 1989;80:778–782.
12. Sugden MC, Holness MJ, Liu Y-L, Smith DM, Fryer LG, Kurszynska YT. Mechanisms regulating cardiac fuel selection in hyperthyroidism. *Biochem J* 1992;286:513–517.
13. Bonen A, Megeney LA, McCarthy SC, McDermott JC, Tan MH. Epinephrine administration stimulates Glut-4 translocation but reduces glucose transport in muscle. *Biochem Biophys Res Commun* 1992;187:685–691.
14. Lozeman FJ, Challiss RAJ, Leighton B, Newsholme EA. Effects of dipyridamole on adenosine concentration, insulin sensitivity and glucose utilization in soleus muscle of the rat. *Eur J Physiol* 1987;410:192–197.
15. Amatruda JM, Livingston JN, Lockwood DH. Cellular mechanisms in selected states of insulin resistance: human obesity, glucocorticoid excess and chronic renal failure. *Diabetes Metab Rev* 1985;1:293–317.
16. Wahlqvist ML, Lim SP, Shanahan EA, Outch K. Role of cortisol in cardiac glucose metabolism in vivo. *Advances in Myocardiology*, 1980;2:39–50.
17. Haber RS, Weinstein SP. Role of glucose transporters in glucocorticoid-induced insulin resistance: Glut-4 isoform in rat skeletal muscle is not decreased by dexamethasone. *Diabetes* 1992;41:728–735.
18. Bennett RA, Pegg AE. Alkylation of DNA in rat tissues following administration of streptozotocin. *Cancer Res* 1981;41:2786–2790.
19. Kahn BB, Flier JS. Regulation of glucose-transporter gene expression in vitro and in vivo. *Diabetes Care* 1990;13:548–564.
20. Kahn BB, Rossetti L, Lodish HF, Charron MJ. Decreased in vivo glucose uptake but normal expression of Glut-1 and Glut-4 in skeletal muscle of diabetic rats. *J Clin Invest* 1991;87:2197–2206.
21. Kainulainen H, Breiner M, Schürmann A, Marttinen A, Virjo A, Joost HG. In vivo glucose uptake and glucose transporter proteins Glut-1 and Glut-4 in heart and various types of skeletal muscle from streptozotocin-diabetic rats. *Biochim Biophy Acta* 1994;1225:275–282.
22. Garvey WT, Hardin D, Juhaszova M, Dominguez JH. Effects of diabetes on myocardial glucose transport system in rats: implications for diabetic cardiomyopathy. *Am J Physiol* 1993;264:H837–H844.
23. Ng CK, Holden JE, DeGrado TR, Raffel DM, Kornguth ML, Gatley SJ. Sensitivity of myocardial fluorodeoxyglucose lumped constant to glucose and insulin. *Am J Physiol* 1991;260:H593–H603.
24. Hariharan R, Bray M, Ganim R, Doenst T, Goodwin GW, Taegtmeyer H. Fundamental limitation of [^{18}F]2-deoxy-2-fluoro-D-glucose for assessing myocardial glucose uptake. *Circulation* 1995;91:2435–2444.
25. Clarke K, Veech RL. Metabolic complexities in cardiac imaging. *Circulation* 1995;91:2299–2301.

Derivation of Input Function from FDG-PET Studies in Small Hearts

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The extraction of pure arterial time-activity curves (TACs) from dynamic PET images of a small animal heart using factor analysis of dynamic structures (FADS) was found to be unsuccessful due to the small size of the cardiac chamber that causes extensive mixture of TACs of different structures. **Methods:** In this study, we used digital phantoms of the left ventricle (LV cavity size: 1–2 cm) and small monkey (LV cavity size: ~ 2 cm) dynamic FDG PET studies to evaluate FADS for extracting the pure blood-pool TACs by adding a single blood sample (taken at a late scan time) constraint. **Results:** In the digital phantom studies, spillover fractions in the extracted blood-pool TACs using FADS without a blood sample constraint (FADS(-)) and with a blood sample constraint (FADS(+)) were 3%–91% and < 3%, respectively. In the monkey studies (n = 4), FADS(+) extracted blood-pool TACs matched well with the arterialized well counter measurements (% differences of curve integration: FADS(-) < 82%; FADS(+) < 9%). The microparameters (K_1^*, k_2^*, k_3^*, k_4^*) and macroparameters (K_{ni}^*), obtained from the FADS(+) blood-pool TACs, were similar to those obtained from plasma samples in a three-compartment model fitting (% differences of K_{ni}^*: phantom studies < 5%; monkey studies < 9%). **Conclusion:** The FADS technique with a single-blood sample has the potential to extract the pure blood-pool TACs directly from dynamic PET images of a small animal without multiple blood sampling, region of interest definition or spillover correction.

Key Words: factor analysis; blood-pool time-activity curve extraction; PET; fluorine-18-FDG