Myocardial Glucose Uptake in Patients With Insulin-Dependent Diabetes Mellitus Assessed Quantitatively by Dynamic Positron Emission Tomography

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Background. Animal studies have demonstrated reduced myocardial glucose utilization in the diabetic heart, suggesting abnormalities in glucose transport. This study was designed to evaluate myocardial glucose uptake as assessed by 2-fluoro-(fluorine-18)2-deoxy-D-glucose (FDG) and positron emission tomography (PET) in patients with insulin-dependent diabetes mellitus (IDDM) under standardized metabolic conditions.

Methods and Results. A hyperinsulinemic-euglycemic clamp technique was used during PET data acquisition in nine healthy male volunteers and seven young male patients with a history of IDDM for less than 5 years. Oxidative metabolism was assessed with C-11 acetate, and glucose uptake was quantitatively measured with FDG using Patlak graphic analysis. Hemodynamic data and C-11 acetate kinetics were comparable. Myocardial glucose uptake averaged 0.44±0.12 μmol·g⁻¹·min⁻¹ in normal subjects and 0.43±0.16 μmol·g⁻¹·min⁻¹ in patients with IDDM (P=NS). Blood tracer clearance was also similar in both groups as determined by the ratio of peak blood tracer activity to the activity at 55 to 60 minutes after tracer injection. F-18 activity ratio between myocardium and blood pool averaged 7.2±3.4 in the normal heart and 7.5±3.0 in the diabetic heart (P=NS).

Conclusions. These data indicate that metabolic standardization and supplementation with insulin in young patients with IDDM is associated with myocardial glucose uptake similar to that observed in the normal heart. Chronic therapy with insulin may prevent the metabolic abnormalities observed in diabetic animal models. (Circulation 1993;88:395-404)

Key Words • myocardial glucose metabolism • positron emission tomography • F-18 deoxyglucose • insulin-dependent diabetes mellitus

Positron emission tomography (PET) provides a unique noninvasive approach for the qualitative and quantitative assessment of tissue perfusion and metabolism. Numerous different radiopharmaceuticals have been introduced for evaluation of carbohydrate (ie, C-11 glucose, F-18 deoxyglucose), lipid (ie, C-11 palmitate), and amino acid (ie, N-13 glutamate, N-13 alanine) metabolism.

FDG (2-fluoro-[fluorine-18]2-deoxy-D-glucose) is a glucose analogue that competes with glucose for transmembranous transport sites at the myocyte membrane and traces the initial phosphorylation of glucose to glucose-6-phosphate. Studies in animals have suggested that FDG can be used to measure quantitatively the rate of exogenous glucose utilization in the heart.¹⁻³ Due to the fact that FDG is a poor substrate for either glycolysis, glycogen synthesis, or pentose phosphate shunt pathways, and dephosphorylation of FDG-6-phosphate is slow, FDG-6-phosphate is virtually "trapped" and accumulates in the myocyte.⁴ Thus, FDG kinetics, derived from dynamic PET imaging, can be used in combination with a tracer kinetic model for noninvasive quantification of myocardial glucose uptake.⁵⁻⁶

Tissue glucose utilization is altered in diabetes mellitus because of either insulin deficiency or insulin resistance. Animal studies have suggested impaired myocardial glucose transport rates in streptozotocin-induced diabetes mellitus.⁷ On the other side, plasma free fatty acid levels may be elevated in diabetic patients as a result of increased lipolysis. In the presence of high plasma free fatty acid and decreased insulin levels, myocardial glucose utilization is depressed, resulting in low myocardial uptake of the glucose analogue FDG.⁸

A retrospective review of clinical tissue viability PET studies after oral glucose load at our institution revealed an incidence of 28% of studies with inadequate myocardial FDG uptake in patients with diabetes mellitus (64% type I and 36% type II) and coronary artery disease as compared with only 3% in patients with coronary artery disease but without known diabetes mellitus.⁹
FIG 1. Protocol and time course of the clamp procedure, plasma sampling, and positron emission tomography data acquisition.

These observations raise the question of whether reduced myocardial glucose utilization in patients with diabetes mellitus represents an intrinsic abnormality of myocardial glucose metabolism or reduced insulin stimulation of metabolic pathways regulating general tissue glucose utilization, including the myocardium.

The purpose of the present study was to address this question by comparing myocardial glucose uptake as assessed quantitatively by FDG in young patients with insulin-dependent diabetes mellitus and in nondiabetic subjects. Overall metabolic conditions were standardized in both groups using the insulin-glucose clamp technique.

Methods

Dynamic PET imaging was performed in young healthy volunteers and subjects with insulin-dependent diabetes mellitus under standardized and controlled metabolic conditions. These studies included the quantitative evaluation of oxidative metabolism with C-11 acetate and glucose metabolism with FDG. C-11 acetate kinetics were used as an indicator of overall myocardial oxygen consumption to document comparable metabolic and hemodynamic conditions in both groups. C-11 acetate clearance rate constants have been shown previously to reflect oxidative metabolism over a wide physiological range, independent of overall substrate utilization. Myocardial glucose uptake was defined by FDG using Patlak's graphic analysis approach.

The protocol and time course of the PET data acquisition are outlined in Fig 1.

Patient Selection and Preparation

The study protocol was approved by the Institutional Review Board of the University of Michigan Medical Center. All subjects were enrolled after granting written informed consent. Studies were performed in nine young healthy male volunteers (group A) and in seven young insulin-dependent diabetic male subjects (group B) drawn from the University of Michigan Hospitals Diabetes Research and Training Center. All subjects were free of clinical and electrocardiographic evidence of ischemic, valvular, or hypertensive heart disease or other major illness and were nonsmokers.

The normal volunteers had a normal oral glucose tolerance test (75 g dextrose) and were within 100±10% of ideal body weight. Subjects with a family history of insulin-dependent diabetes mellitus were excluded.

The diabetic patients were also within 100±10% of ideal body weight. All subjects had duration of diabetes less than 5 years and were treated only with human insulin. Patients with a known diabetic microangiopathy or other metabolic disorders were not included. Also, patients with a history of alcohol or drug abuse were excluded from this study. Baseline characteristics and inclusion and exclusion criteria for both groups are summarized in Table 1.

Hemodynamic and Metabolic Standardization and Measurements

Insulin-glucose clamp. Diabetic patients were admitted to the Clinical Research Center the evening before the study and received intravenous regular human insulin before their dinner and bedtime snack and continuously overnight to maintain plasma glucose levels between 80 and 130 mg%. Normal subjects were studied after overnight fasting without hospitalization.

All subjects were asked to consume a normal diet or their usual diabetic diet and no alcohol for 3 days before the study. All PET studies were carried out in the morning after a 10-hour fast.

The intravenous hyperinsulinemic-euglycemic clamp method, as described previously by DeFronzo et al., was used in all subjects to standardize the metabolic

| Table 1. Baseline Characteristics and Selection Criteria for Normal and Diabetic Subjects |
|---------------------------------|-----------------|-----------------|
| **Group A (normal, n=9)** | **Group B (diabetic, n=7)** |
| Age (y) | 26.7±6.0 | 20.9±2.3* |
| Weight (kg) | 77.6±9.8 | 73.7±4.0 |
| Height (cm) | 179±11 | 179±3 |
| Inclusion criteria | 100±10% of ideal body weight | 100±10% of ideal body weight |
| Normal OGT (75g) | History of stable IDDM <5 y |
| Treatment with human insulin |
| Exclusion criteria | Evidence for heart disease | Evidence for heart disease |
| Hypertension | Hypertension |
| Metabolic disorder | Metabolic disorder other than IDDM |
| Alcohol or drug abuse | Alcohol or drug abuse |
| Family history of IDDM | Diabetic microangiopathy |
| Smoking | Glycosylated hemoglobin >8% |
| Smoking |

OGT, oral glucose tolerance test; IDDM, insulin-dependent diabetes mellitus.

*P<.05 vs group A.
environment. Briefly, a 10-minute priming dose (calculated by the patient's body surface area) of regular human insulin diluted in 0.9% sodium chloride was infused to acutely raise the plasma insulin level. Priming was followed by a continuous insulin infusion at a constant rate of 40 mU/m² body surface area per minute, which was calculated to maintain plasma insulin levels of approximately 80 μU/mL throughout the study.14

Plasma samples for immediate analysis of glucose levels were drawn at 5-minute intervals and measured using an automated glucose analyzer (Beckman Instruments, Brea, Calif). Glucose (20% dextrose with 10 mEq of potassium chloride per liter) was continuously infused beginning 5 minutes after commencement of the insulin infusion using a calibrated infusion pump until a plasma glucose equilibrium of approximately 85 mg% was achieved. Plasma glucose levels were kept constant throughout the study by infusion rate adjustments using the negative feedback principle (for details see Reference 14). Plasma glucose levels were in a steady state in all individuals within 45 minutes after starting the insulin and glucose infusions.

Hemodynamic and metabolic data. Heart rate and blood pressure were recorded frequently, and ECG monitoring was performed throughout the procedure. Venous blood was arterialized by retrograde venous puncture and placing the subject’s hand in a box heated to 60°C to assess arterial substrate and hormone levels without requiring arterial puncture.15–17 This technique minimizes possible effects of tissue extraction of these substrates by increasing cutaneous blood flow and arteriovenous shunting. Blood samples were drawn at baseline, at the beginning and end of the C-11 acetate study and at the beginning, at 30 minutes, and at completion of the FGD study and were frozen at −70°C until analyzed.

Glucose, free fatty acids, insulin, lactate, gluconolactone, human growth hormone, epinephrine, and norepinephrine were analyzed from these samples using previously published standard methods.18–20 These data were assessed to document comparable metabolic conditions during each imaging sequence and to evaluate possible effects of each of these substrates on myocardial FGD uptake.

Positron Emission Tomography

Image acquisition. The imaging studies were performed under resting conditions using a two-ring multislice whole-body PET scanner (ECAT 931 CTI/Siemens, Knoxville, Tenn), allowing simultaneous imaging of fifteen 6.75-mm-thick transaxial slices encompassing the entire heart. All studies were obtained using the following reconstruction parameters: matrix size 128 × 128 pixels, Hanning reconstruction filter, cut-off frequency of 0.30 cycles per pixel, and computed decay correction.

After positioning of the patient in the scanner gantry and during stabilization of the plasma glucose levels, a transmission scan for attenuation correction was performed for 15 to 20 minutes using a retractable germanium-68 ring source. During the entire study, the subjects were not moved out of the scanner.

C-11 acetate studies were started approximately 45 minutes after beginning the insulin-glucose clamping procedure, when plasma glucose levels had reached a steady state at the target of about 85 mg%. After the intravenous bolus administration of 20 mCi C-11 acetate, dynamic PET imaging was performed over 31 minutes with 10 frames each of 90-second duration followed by 5 frames each of 120-second duration and 2 frames each of 180-second duration.

After the C-11 decay, 10 mCi FGD diluted in 10 mL was injected as an intravenous bolus by hand over 15 seconds, and dynamic PET images were obtained for 1 hour with 12 frames of 5-minute duration each. The time course of the PET studies is outlined in Fig 1.

Image processing and analysis. A reorientation algorithm as described previously was used to generate a dynamic series of 12 short-axis cardiac planes from the dynamic series of 15 transaxial planes obtained after C-11 acetate and FGD injections.27 It involves a linear interpolation of activity data. The reoriented short-axis cardiac images served as input data to semiautomated regional analysis programs to create polar coordinate maps of myocardial C-11 clearance rate constants and of myocardial FGD uptake.

Epicardial and endocardial ellipses were assigned by the operator for each short-axis plane in the frame (a set of 12 simultaneously acquired short-axis planes) with the highest ratio of cardiac to noncardiac activity. In the C-11 acetate study, this was an early frame, soon after rapid blood pool clearance and before significant decrease of myocardial C-11 activity. In the FGD study, the final frame was chosen because of progressive accumulation of activity within the myocardium.

Activity maxima were defined within these ellipses along 60 radii beginning at the posterior intersection of the left and right ventricular free walls. Then, a 3 × 3-voxel region of interest around each area of maximal activity was used to define myocardial regions of interest representing 60 regions for each plane. Finally, using the spatial coordinates of these regions of interest, regional tissue tracer activity was determined for all frames yielding time-activity curves for 60 circumferential regions in each short-axis cardiac plane.

Calculation of Tracer Kinetics

C-11 acetate. From the resultant decay-corrected C-11 acetate time-activity curves, C-11 clearance rate constants (k/min) were calculated by least-squares, monoexponential curve fitting.12 Comparison of C-11 clearance rate constants obtained using the described reorientation and regional analysis algorithms with those derived from analysis of the primary transaxial data revealed concordant results, validating this approach.27

F-18 FGD. Using the analysis approach proposed by Patlak13 and adapted for quantification of myocardial FGD uptake by Gambhir,4 blood pool and myocardial FGD time-activity curves were used to calculate myocardial glucose uptake. This approach applies a graphic analysis of F-18 activity in blood pool representing the arterial input function and the myocardium. The blood pool region of interest was defined in the first frame of the dynamic series and was confined to the two most basal planes covering the entire heart to reduce myocardial spillover in this region at late time points. The right ventricle was chosen to minimize myocardial spillover from the usually small left ventricular chambers in this subject population. In addition, the dynamic FGD images were acquired in frames of 5 minutes and the calculation of the Patlak slope included only the linear part, which
TABLE 2.  Hemodynamic Data for Normal Subjects and Diabetic Patients Before and During C-11 Acetate and F-18 FDG Positron Emission Tomography Imaging

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (normal, n=9)</th>
<th>Group B (diabetic, n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline C-11 acetate</td>
<td>F-18 FDG</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>59±8</td>
<td>57±8</td>
</tr>
<tr>
<td>Mean</td>
<td>57±8</td>
<td>60±7</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>114±5</td>
<td>114±5</td>
</tr>
<tr>
<td>Mean</td>
<td>114±6</td>
<td>117±6*</td>
</tr>
<tr>
<td>RPP (beats · mm Hg⁻¹ · min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>6798±1168</td>
<td>6501±924</td>
</tr>
<tr>
<td>Mean</td>
<td>6592±891</td>
<td>7010±862</td>
</tr>
</tbody>
</table>

Baseline values were measured at the beginning of the study before start of the clamping procedure. Basal values are those at the start of each tracer imaging sequence. Mean values represent the average values calculated from measurements at the beginning, during, and at the end of each tracer imaging sequence (see “Methods”: “Hemodynamic and Metabolic Data”). F-18 FDG, F-18 deoxyglucose; bpm, beats per minute; RPP, rate-pressure product.

*P<.05 vs mean values during C-11 acetate imaging.

started in all cases with the second or third frame. Therefore, early timing differences between the right ventricular chamber and the left ventricular myocardium were mostly excluded.

The analysis describes the correlation between C_i/C_o and \( \int_0^t C_d dt/C_o \), where C_i is the decay-corrected myocardial activity and C_o is the decay-corrected blood pool activity at any given time t. \( \int_0^t C_d dt \) is the integral of blood pool activity from time zero to time t and serves as an index of the arterial FDG input function into the myocardium. Since F-18 FDG-6-phosphate accumulates in tissue as a function of uptake and phosphorylation of FDG, this relation becomes linear after equilibration of free tissue FDG.

Myocardial glucose uptake rates were derived by multiplying the slope of this linear part of the plot by the average of three plasma glucose measurements obtained at the beginning, midpoint, and end of the F-18 FDG study (converted to micromoles per liter) and then dividing by the "lumped constant." This constant has been experimentally derived and reflects the differences in myocardial handling of glucose and F-18 FDG. In our algorithm, this constant was set at 0.67, defined previously in experimental animal studies.² Krivokapich et al³ demonstrated that the "lumped constant" remained stable despite significant changes in flow, glucose concentration, or insulin activity or in the presence of anoxia in rabbit myocardium.

Regional analysis. For regional analysis, C-11 clearance rate constant data and FDG uptake data were averaged for quadrants representing 15 sectors of 6° each and were assigned to the anterior, lateral, inferior, and septal wall using a standardized polar map display format.²²

Peak to end blood activity ratio. The FDG blood clearance during imaging reflects, beside tracer decay, the overall tissue FDG uptake and hence, indirectly, total body glucose utilization. Therefore, the ratio of the mean tracer activity per pixel in the blood pool region in the first imaging frame (0 to 5 minutes) divided by the mean tracer activity in the same region in the last imaging frame (55 to 60 minutes) was calculated.

Myocardial to blood activity ratio. The myocardial to blood pool F-18 activity ratio was calculated as a measure-

ment of the target to background ratio. It serves as an indirect combined parameter of overall blood tracer clearance and myocardial FDG uptake and reflects diagnostic image quality.²⁰ A region of interest covering the entire left ventricular myocardium was drawn on a midventricular short-axis slice to measure the average activity per pixel at the 55- to 60-minute frame, and the result was divided by the mean activity per pixel of the blood pool region at the same time point.

Statistical Analysis

Results are presented as mean±1 SD. For statistical analysis, comparisons between the two groups were made using the Mann-Whitney Wilcoxon U test. Results within one group were analyzed using the Wilcoxon ranking test for paired data sets. Linear regression analysis was used to investigate whether any of the hemodynamic parameters, plasma substrate concentrations, or plasma hormone levels correlated significantly with myocardial glucose uptake. A probability value of <.05 was considered to indicate a significant difference.

Results

Metabolic and Hemodynamic Conditions

Hemodynamic data. The mean values for heart rate, systolic blood pressure, and rate-pressure product for both groups are presented in Table 2. Systolic blood pressure and rate-pressure product were slightly lower in the diabetic patients, but this difference did not reach statistical significance at any time point during the imaging sequences. In both groups, the systolic blood pressure increased slightly by 3% (group A) and 5% (group B) during the FDG imaging procedure. This and the marginal variation in heart rate led to small changes in rate-pressure product that did not reach statistical significance for any time point.

Plasma substrate levels. Fasting plasma glucose levels were in the normal range at the beginning of the study and decreased significantly, as expected, during hyperinsulinemia in group A. In group B, baseline values demonstrated, despite overnight insulin substitution, a larger variation but were within normal limits. There was no significant difference between both groups at any time point during the study.
Table 3. Metabolic Data for Normal and Diabetic Patients Before and During C-11 Acetate and F-18 FDG Positron Emission Tomography Imaging

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (normal, n=9)</th>
<th>Group B (diabetic, n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>C-11 acetate</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>Basal 93±6</td>
<td>85±11</td>
</tr>
<tr>
<td></td>
<td>Mean 86±6†</td>
<td>85±7†</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>Basal 10±7</td>
<td>69±13†</td>
</tr>
<tr>
<td></td>
<td>Mean 71±15†</td>
<td>75±14†</td>
</tr>
<tr>
<td>FFA (mEq/L)</td>
<td>Basal 0.52±0.19</td>
<td>0.14±0.05†</td>
</tr>
<tr>
<td></td>
<td>Mean 0.14±0.05†</td>
<td>0.12±0.04†</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>Basal 0.63±0.17</td>
<td>0.82±0.19†</td>
</tr>
<tr>
<td></td>
<td>Mean 0.79±0.16†</td>
<td>0.75±0.13†</td>
</tr>
<tr>
<td>Glucagon (pg/L)</td>
<td>Basal 56±23</td>
<td>57±19</td>
</tr>
<tr>
<td></td>
<td>Mean 54±18</td>
<td>55±23</td>
</tr>
<tr>
<td>HGH (ng/mL)</td>
<td>Basal 0.99±0.20</td>
<td>0.94±0.25</td>
</tr>
<tr>
<td></td>
<td>Mean 1.11±0.47</td>
<td>4.29±5.14**†</td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>Basal 96±28</td>
<td>82±30</td>
</tr>
<tr>
<td></td>
<td>Mean 84±25</td>
<td>76±14</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>Basal 238±53</td>
<td>261±65</td>
</tr>
<tr>
<td></td>
<td>Mean 279±65†</td>
<td>275±65†</td>
</tr>
</tbody>
</table>

Baseline values were measured at the beginning of the study before the start of the clamping procedure. Basal values are those at the start of each imaging sequence. Mean values represent the average values calculated from measurements at the beginning, during, and at the end of each imaging sequence (see "Methods": "Hemodynamic and Metabolic Data"). FFA, free fatty acids; HGH, human growth hormone. *P<.05 vs mean value during C-11 acetate imaging; †P<.05 vs baseline value; ‡P<.05 vs group A.

Insulin levels were within normal limits under fasting conditions in both groups. The slightly higher baseline levels in group B reflected the effect of overnight insulin administration. The plasma insulin levels increased significantly after the intravenous insulin bolus in both groups, approximating the target levels, and remained stable throughout the study. There was no significant difference in plasma insulin levels during the clamping procedure between the two groups.

Free fatty acids were normal at baseline and decreased significantly, as expected, during insulin administration without differences between both groups.

Lactate levels increased slightly but significantly in group A. In group B, they did not change significantly during the imaging procedure but were between 18% and 29% lower as compared with group A.

Glucagon, norepinephrine, and epinephrine were within normal limits and showed some variation during the study but did not differ between both groups.

Human growth hormone showed moderate fluctuation within both groups, with a significant difference between group A and group B during the C-11 acetate imaging. This probably was due to the fact that some subjects fell asleep during the imaging procedures. There were no significant differences between the groups during FDG imaging.

C-11 Acetate Kinetics

Because of a malfunction of the imaging system, one dynamic C-11 acetate PET study in each group could not be analyzed quantitatively. Therefore, the C-11 results for group A are of eight subjects and for group B, six subjects.

Global C-11 acetate clearance rates were slightly higher in the diabetic subjects, but the difference was not statistically significant (Table 4). They ranged from 0.044/min to 0.064/min in group A and from 0.049/min to 0.081/min in group B.

Myocardial Glucose Uptake

The images in Fig 2 illustrate an example of the dynamic sequence of FDG activity imaged over 12 frames for 5 minutes each in a diabetic patient studied under clamped metabolic conditions. The first frame shows tracer activity in the right and left ventricular chamber, which is then rapidly cleared from the blood pool and accumulates progressively during the 60 minutes of imaging in the left ventricular myocardium.

Global glucose uptake was comparable for both groups, with 0.44±0.12 (0.23 to 0.60) µmol·g⁻¹·min⁻¹ in group A and 0.43±0.16 (0.16 to 0.69) µmol·g⁻¹·min⁻¹ in group B (P=NS) (Table 5).

As expected, within the small range of glucose and insulin plasma levels during clamping, there were no
Table 4. Regional and Global C-11 Acetate Clearance Rate Constants (kl/min) in Normal and Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Group A (normal, n=8)</th>
<th>Group B (diabetic, n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>0.056±0.007</td>
<td>0.064±0.011</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.054±0.007</td>
<td>0.062±0.011</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.052±0.005</td>
<td>0.064±0.011*</td>
</tr>
<tr>
<td>Septum</td>
<td>0.055±0.007</td>
<td>0.065±0.013</td>
</tr>
<tr>
<td>Global</td>
<td>0.053±0.006</td>
<td>0.062±0.01</td>
</tr>
</tbody>
</table>

*P<.05 vs group A.

significant correlations between glucose and insulin levels and glucose uptake in both groups. By testing the correlation of other substrate concentrations, hormone levels, and the rate-pressure product with the myocardial glucose uptake, there were no significant relations under this strictly standardized metabolic condition.

Regional analysis of FDG uptake confirmed the previously reported heterogeneous tracer uptake, particularly with significantly reduced FDG uptake in the septum as compared with the lateral wall (10% lower in group A, 15% in group B).

Peak to End Blood Activity Ratio

The ratio of peak blood tracer activity to the activity at the end of imaging was 7.8±3.7 (2.8 to 14.7) for group A and 8.1±5.5 (2.3 to 17.3) in group B (P=NS). This indicated indirectly comparable overall glucose clearance by glucose utilizing tissue. However, there is a considerable range and variation in both groups. Testing the relation to plasma substrate and hormone levels and hemodynamic data did not reveal significant relations.

Myocardial to Blood Activity Ratio

The F-18 activity ratio between myocardium and the ventricular blood pool at the end of the imaging sequence was 7.2±3.4 (3.3 to 13.9) in group A and 7.5±3.0 (3.4 to 12.8) in group B, which was not significantly different.

There was a significant relation (r=0.9, P=0.0001) for all subjects between the myocardial to blood and the peak to end F-18 activity ratio. To illustrate this close relation better, all data points are presented in one graph (Fig 3). By separate analysis, the relation is expressed as r=.91 (P<.001) for group A and r=.96 (P<.001) for group B.

There was no significant relation between myocardial to blood activity ratio and absolute myocardial FDG uptake in both groups, as illustrated in Fig 4.

Discussion

This study demonstrates that myocardial glucose uptake in young insulin-dependent diabetic patients with-
out evidence for diabetic angiopathy does not differ from that in a group of matching healthy volunteers under standardized metabolic conditions using the insulin-glucose clamp technique. The hemodynamic, metabolic, and hormonal milieu, as documented by several parameters, was comparable in both groups. The only exception was the increase of lactate levels during the clamping and imaging procedure in group A as compared with a slight decrease in group B. Overall tissue FDG uptake and, hence, glucose utilization defined by the FDG clearance from the blood, were similar in both groups although with a considerable interindividual variation.

These data suggest that myocardial glucose uptake in young patients with a history of insulin-dependent diabetes mellitus less than 5 years is comparable to normal subjects if adequate insulin substitution is provided.

**Glucose Uptake in the Normal Heart**

In normal human myocardium, metabolism under resting conditions is primarily oxidative and depends on various substrates such as free fatty acids, glucose, lactate, pyruvate, and ketones. The hormonal factors that regulate myocardial substrate utilization are complex and depend on substrate intake and integrity of feedback mechanisms regulating hormone release.

Under fasting conditions, free fatty acids are the primary fuel for myocardial oxidative metabolism, and glucose utilization is relatively low.\(^8\) Under postprandial conditions, insulin levels are high and stimulate glucose utilization in the hepatocytes, skeletal, and myocardial muscle. Such metabolic versatility has been noninvasively demonstrated by PET using metabolic tracers such as C-11 palmitate and F-18 FDG.\(^{31-33}\)

For the clinical application of FDG imaging in patients with ischemic heart disease, different metabolic protocols have been proposed. Exercise-induced ischemia has been studied under fasting conditions, resulting in relatively increased FDG uptake in ischemic regions compared with normally perfused areas.\(^{34-36}\) However, imaging of normal myocardium with FDG at rest under fasting conditions leads to highly variable and, in some patients, markedly reduced myocardial tracer accumulation.\(^29\)

A postprandial protocol with oral glucose load to augment global myocardial FDG uptake at rest has been proposed for the assessment of tissue viability\(^9\) by increasing the contrast between viable and nonviable cells.\(^{38,39}\) The insulin-glucose clamp used in this study was designed to produce stable insulin plasma levels in the range expected after oral glucose loading.

Previous studies in our institution using the same method of data acquisition and analysis have shown that oral glucose loading in normal volunteers is associated with a myocardial glucose uptake of 0.41±0.15 \(\mu\)mol \cdot g\(^{-1}\) \cdot min\(^{-1}\),\(^40\) which was not significantly different from the values in this study. However, after oral load, the myocardial to blood activity ratio was 4.1±1.4 and the peak to remaining tracer activity was 3.0±0.9, both significantly lower in comparison to each population studied with clamping. These data suggest higher overall tissue glucose utilization and a more rapid FDG blood clearance under clamped conditions without a concordant increase of absolute myocardial glucose uptake. Knutti et al\(^14\) reported similar results in non-diabetic patients with coronary artery disease studied after oral glucose loading and during hyperinsulinemic clamping. This may reflect that the myocardial response to high insulin levels saturates at a lower insulin plasma level than does other tissue such as skeletal muscle or adipocytes. The close relation between both parameters as demonstrated in Fig 3 can be interpreted as higher total body glucose utilization with rapid blood clearance being the major reason for the higher contrast between blood and myocardium, since it was not due to higher absolute values of myocardial FDG utilization.

However, this study was not designed to assess myocardial or other tissue insulin sensitivity or to quantitatively calculate whole-body glucose turnover. The ratios for peak to remaining tracer activity and myocardial to blood tracer activity and the reported metabolic parameters were assessed to show a comparable metabolic environment and similar total tissue insulin responsiveness within both groups studied under clamped conditions.
Glucose Uptake in the Diabetic Heart

Diabetes mellitus is associated with cardiac dysfunction and a markedly increased morbidity and mortality in patients with advanced coronary artery disease. In addition, there is ongoing controversy over the existence of a specific diabetic cardiomyopathy that is not related to epicardial coronary disease. Possible explanations include microangiopathy, diabetic neuropathy, and abnormalities in myocardial energy metabolism in combination with other risk factors.

Experimental data from animal studies support the evidence for dysregulation of glucose metabolism in non-insulin-treated diabetic myocardium. One possible explanation is a decreased rate of transmembranous glucose transport into the cell, which could be demonstrated in experimental studies.

The mechanism by which insulin stimulates glucose transport into muscle and fat is the translocation of glucose transporters from the intracellular membrane pool (microsomes) to the cell surface. This was demonstrated by studies in an isolated, perfused rat heart model. A recent study in the dog heart demonstrated a close correlation between in vivo myocardial glucose uptake and in vitro–measured sarcolemma glucose transporter concentration during hyperinsulinemia.

In the diabetic myocardium, experimental data have further shown that glucose utilization of non-insulin-treated diabetic myocardium differs from nondiabetic myocytes but that the glucose utilization of the diabetic myocardium can be normalized after insulin treatment. Recently, Almira et al. confirmed the decreased insulin binding on membranes of isolated myocytes of streptozotocin-treated rats. Chronic insulin administration for more than 2 weeks in the diabetic rats prevented the reduced insulin binding and stimulated glucose transport rates to a level similar to that observed in nondiabetic control myocytes.

It can be speculated that similar abnormalities may play a role in diabetic patients with insulin deficiency or resistance, demonstrating decreased myocardial glucose utilization as evidenced by reduced FDG uptake. Further studies in poorly controlled patients with diabetes mellitus or in individuals with insulin resistance are required to extend this in vivo investigation of myocardial glucose metabolism in the human diabetic heart.
Limitations of the Study

Only the diabetic subjects were treated with the overnight intravenous insulin infusion. The purpose of this overnight therapy was to achieve normal plasma insulin and glucose levels so that in the morning the clamp studies could be begun promptly without the need to achieve acute euglycemia in the diabetic subjects. Due to ethical considerations, we did not treat the normal subjects with an overnight infusion. However, baseline insulin and glucose levels were comparable in both groups, and previous studies have shown that in non-insulin-dependent diabetic patients, 20 hours of normoglycemia improves B-cell sensitivity to glucose but that up to 10 days of intensive insulin therapy results in no change in tissue insulin sensitivity. Studies that demonstrated improvements in insulin action after intensive insulin therapy in subjects with diabetes have generally involved treatment for 2 weeks or longer.

The studied insulin-dependent diabetic patients represented a strictly controlled and carefully selected subpopulation of young patients with short duration of diabetes mellitus. These patients do not represent the "typical" patient with coronary artery disease and long-standing diabetes mellitus. However, in those patients, myocardial FDG uptake may reflect an indistinguishable mixture of metabolic changes caused by ongoing or recent ischemia, myocardial necrosis, and diabetes mellitus. Therefore, we chose a well-defined patient population without evidence for coronary artery disease to gain insights into metabolic factors influencing myocardial FDG uptake.

Clinical Implications

Based on the presented results, reported experimental data from animals, and our previous observation that image quality is inversely correlated to elevated plasma glucose levels during FDG imaging, all diabetic patients as well as patients with markedly elevated plasma glucose levels now receive intravenous insulin before injection of FDG at our institution. However, metabolic clamping in all patients for routine clinical PET studies may not be feasible because of technical requirements. Therefore, an approach of intravenous bolus insulin administration adjusted to plasma glucose levels has been introduced in the clinical study protocol at our institution. With this regimen, 94% of all studies in diabetic patients were of adequate image quality, which was not different from results in nondiabetic patients. Furthermore, insulin administration was effective in those patients with no history of diabetes mellitus but with an abnormal glucose tolerance after the oral glucose load (Fig 5).

However, some patients with non-insulin-dependent diabetes mellitus demonstrated inadequate myocardial FDG uptake despite insulin administration and effective reduction of plasma glucose levels. Whether or not the reduced myocardial FDG uptake reflected myocardial insulin resistance remained unclear. Further studies using the clamp technique in non-insulin-dependent diabetic patients are necessary to elucidate the importance of this technique for metabolic PET imaging.

Conclusions

Standardization of metabolic conditions with hyperinsulinemic-euglycemic insulin-glucose clamping during FDG imaging resulted in comparable myocardial glucose uptake in young patients with a history of insulin-dependent diabetes mellitus and normal subjects without evidence for coronary heart disease. Metabolic standardization including intravenous administration of insulin is recommended for PET imaging with FDG to optimize image quality in patients with diabetes mellitus.

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