Coronary Artery Disease and Cardiac Metabolism

Myocardial Glucose Transport and Utilization in Patients With Type 2 Diabetes Mellitus, Left Ventricular Dysfunction, and Coronary Artery Disease

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OBJECTIVES
This research was designed to assess the effect of type 2 diabetes mellitus (T2DM) on myocardial glucose utilization in patients with heart failure secondary to coronary artery disease.

BACKGROUND
Patients with T2DM and coronary artery disease have an increased morbidity and mortality compared with patients with coronary artery disease without diabetes that may relate to a reduction in the ability of the myocardium to utilize glucose.

METHODS
Myocardial blood flow and glucose utilization were assessed during a hyperinsulinemic clamp by 18F-flurodeoxyglucose and positron emission tomography in 54 patients (19 with T2DM) with multivessel coronary artery disease and heart failure. In a subgroup of 18 patients, myocardial biopsies were obtained during coronary bypass surgery to assess glucose transporter (GLUT4) distribution and protein concentration, and compared with myocardium from transplant donor hearts.

RESULTS
Myocardial blood flow was similar in patients without diabetes and those with T2DM. Myocardial glucose utilization was lower in patients with T2DM (0.34 ± 0.16 vs. 0.47 ± 0.24 mmol·min⁻¹·g⁻¹, p = 0.0002) despite comparable plasma insulin concentrations and a higher blood glucose concentration. Extraction of glucose by the myocardium was reduced in patients with T2DM (7.1 ± 3.1% vs. 13.5 ± 5.2%, p < 0.01). Myocardial GLUT4 protein was similar in patients with and without T2DM (p = 0.75).

CONCLUSIONS
Patients with coronary artery disease and heart failure exhibit myocardial insulin resistance, and this is greater in those with T2DM. This may limit the ability of the myocardium in patients with T2DM to withstand ischemia and may contribute to the increased cardiovascular morbidity and mortality in such patients. (J Am Coll Cardiol 2006;48:2225–31)

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Type 2 diabetes mellitus (T2DM) is associated with an increased risk of coronary artery disease (CAD). In addition, after an acute coronary syndrome or myocardial infarction, patients with T2DM have a disproportionately higher risk of serious complications and death, (1–3), which suggests that the hearts of these patients are less tolerant to ischemia.

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In the fasting, post-absorptive state, a minority of energy production in the human heart is derived from glucose oxidation. After eating, the release of a number of hormones including insulin influences myocardial metabolism (4). Insulin facilitates myocardium glucose utilization, largely by means of the insulin-dependent translocation of the glucose transporter (GLUT4) from the intracellular pool to the plasma membrane (5). By decreasing plasma free fatty acids (FFA), insulin has also a profound indirect effect on myocardial lipid utilization, which is linearly related to FFA concentration in the bloodstream (6).

Ischemia results in increased myocardial glucose utilization (MGU) derived both from glycogen breakdown and increased utilization of circulating glucose, and such a metabolic shift is mediated by the action of insulin (7). Increased translocation of GLUT4 from intracellular vesicles to the plasma membrane has been demonstrated in models of low flow ischemia and in stunned myocardium (8,9). As knockout mice lacking GLUT4 show a severely impaired response to ischemia, the shift to a glycolytic metabolism is thought to be an adaptive response for myocardial survival.

Insulin resistance is a central feature of T2DM, but the insulin sensitivity of the heart in patients with TD2M with CAD remains the subject of debate. Studies using positron emission tomography (PET) with 18F-flurodeoxyglucose (FDG) have reported reduced MGU during hyperinsulinemia in patients with T2DM (10). Others have not found...
myocardial insulin resistance in patients with T2DM (11), although myocardial insulin resistance has been found in patients with hypertension, heart failure, and myocardial hypertrophy (12–14).

In this study, we investigated the combined effect of T2DM and heart failure secondary to CAD on myocardial glucose during hyperinsulinemia using FDG-PET. In addition, we measured GLUT4 protein in myocardial biopsies obtained at cardiac surgery to gain insight into the molecular mechanism underlying abnormal MGU.

**METHODS**

**Patients.** This was a single-center study of 54 patients (mean age 63 ± 13 years) with heart failure secondary to multivessel CAD who were undergoing assessment of myocardial viability with a view to coronary artery bypass grafting (CABG). Of the 54 patients, 19 had T2DM and 45 were non-diabetic patients (Table 1). Patients with insulin-treated diabetes, a recent history of myocardial infarction, unstable angina, or decompensated heart failure (in the preceding 2 months) were excluded. Viability was defined by preserved utilization of the glucose analogue FDG in at least 6 of the 16 left ventricular (LV) segments (15). The reversibility of LV dysfunction in a segment with preserved viability (hibernation) was confirmed by improved contractile function at 6-month post-operative echocardiography. In a subgroup of 18 patients (6 with T2DM) with viable anterior LV wall myocardium, biopsies were taken at the time of CABG.

**Study protocol.** All medication was withheld on the day of the study. Patients were asked to avoid activities that might precipitate angina for 24 h before the study and to fast from overnight before attending for the study that was commenced between 9 AM and 10 AM. All subjects were asked to consume a diet containing at least 200 g of carbohydrate for 3 days before the study.

The Local Research Ethics Committees of the Queen Elizabeth Hospital, Birmingham, and the Hammersmith Hospital, London, approved the protocol. Radiation exposure was licensed by the United Kingdom Administration of Radioactive Substances Advisory Committee. All patients gave fully informed written consent.

**Assessment of regional LV function.** Global and regional LV function was assessed by resting 2-dimensional echocardiography using conventional views (parasternal long- and short-axis, apical 2- and 4-chamber views). Regional wall motion was scored using the standard 16-segment model by 2 experienced observers who were blinded to the clinical data. Regional wall motion was scored using a 5-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, and 5 = dyskinetic. Segments with a wall motion score ≥ 3 were considered dysfunctional.

**PET: regional myocardial perfusion.** The PET studies were performed using an ECAT 931-08/12 15-slice scanner (CTI/Siemens, Knoxville, Tennessee) after an overnight fast and abstinence from caffeine-containing beverages for at least 24 h. All emission and transmission sinograms were reconstructed using a Hanning filter with a cut-off frequency of 0.5 maximum. A 20-min transmission scan was performed to facilitate subsequent attenuation correction of all emission scans, and the blood pool was imaged by inhalation of tracer amounts of $^{15}$O-labeled carbon monoxide ($^{15}$O) as previously described (16).

**Table 1.** The Demographic Characteristics of the 54 Patients Studied

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>No Diabetes (n = 35)</th>
<th>T2DM (n = 19)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62.3 ± 8.8</td>
<td>61.6 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.1 ± 4.4</td>
<td>71.2 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 ± 5.8</td>
<td>142 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>84.8 ± 6.2</td>
<td>87.3 ± 8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg·beats/min)</td>
<td>9,224 ± 680</td>
<td>10,098 ± 728</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 ± 12</td>
<td>82 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.89 ± 0.17</td>
<td>1.94 ± 0.20</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg·m²)</td>
<td>25.9 ± 3.2</td>
<td>27.7 ± 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.33 ± 0.58</td>
<td>2.36 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26.7 ± 11.0</td>
<td>28.2 ± 11.2</td>
<td>NS</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.37 ± 0.72</td>
<td>2.24 ± 0.67</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD.

BMI = body mass index; BSA = body surface area; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus; WMSI = wall motion score index.
After allowing for the decay of $^{15}$O radioactivity, resting myocardial blood flow (MBF) was measured using oxygen-15-labelled water ($H_2^{15}O$, 700 to 900 MBq), injected intravenously over 20 s at a rate of 10 ml/min with flushing for a further 2 min. The following scanning protocol was used: 14 × 5 s, 3 × 10 s, 3 × 20 s, and 4 × 30 s, for a total scanning time of 310 s.

Hyperinsulinemic glucose clamp. A hyperinsulinemic clamp was performed to determine whole body insulin sensitivity and to provide a standardized metabolic milieu for the measurement of MGU. The subjects were placed in the semirecumbent position, and a cannula inserted into a forearm vein 20 min before drawing venous blood into chilled tubes, that were centrifuged immediately at 4°C and the plasma separated for immediate determination of glucose concentration (by the glucose oxidase technique, YSI 2300 STAT PLUS, Yellow Spring, Ohio). The remaining plasma was frozen in 2 aliquots at −20°C for subsequent insulin and FFA assay. Plasma insulin was assayed by a specific radioimmunoassay and FFA measured in duplicate using a spectrophotometric assay (Wako, Neuss, Germany).

A second cannula was inserted into a superficial vein on the dorsum of the left hand that was arterialized using a heating pad set at 50°C to facilitate blood sampling during the stable state. A primed infusion of insulin was initially infused at a rate of 160 μU·min$^{-1}$·m$^{-2}$ (4 times the final rate) for 4 min, then 80 μU·min$^{-1}$·m$^{-2}$ (twice the final rate) for 3 min and thereafter continued until the end of the study at a constant rate of 40 μU·min$^{-1}$·m$^{-2}$. Four minutes after commencing the insulin infusion, at the same time as reducing the rate to 80 μU·min$^{-1}$·m$^{-2}$, an infusion of 20% D-glucose was commenced at a rate of 0.015 mg·kg$^{-1}$·min$^{-1}$. Samples of arterialized blood were then taken every 5 min through the other indwelling cannula to monitor blood glucose concentration, and the infusion rate of D-glucose was increased as required to maintain euglycemia. Whole-body glucose utilization (M) was computed during the steady-state phase of the clamp. A further blood sample was taken to determine plasma insulin and FFA concentration 90 ± 10 min after commencing insulin.

Regional MGU. The MGU was measured during the equilibrium phase of the previously described hyperinsulinemic clamp. After at least 90 min of hyperinsulinemia, 185 MBq of FDG were injected over a 2-min period and a 36-frame dynamic PET scan acquired (1 × 30 s [background]; 12 × 10 s; 3 × 20 s; 4 × 30 s; 5 × 60 s; 4 × 150 s; 5 × 300 s; 2 × 600 s). The acquired sinograms were corrected for attenuation and reconstructed as previously described. In brief, blood volume quantitative images were calculated using the $C^{15}$O emission data, corrected for the decay, and used to define regions of interest (ROIs) that were projected onto the dynamic $H_2^{15}$O data to generate time-activity curves (TACs) for each ROI. The average of these curves was then used as the arterial input function to calculate MBF. Additional ROIs were positioned on the reconstructed short-axis FDG images and used to define the 16 LV segments and MGU computed from fitted tissue TACs using a linearized approach.

Myocardial glucose use was corrected for perfusible tissue fraction (PTF), an index of tissue viability derived from the $H_2^{15}$O scan, in order to account for the presence of fibrotic tissue (17). Myocardial viability was defined as regional MGU (PTF-corrected) >0.25 μmol/min/g as previously described (18). Serum glucose and FFA were measured at baseline after an 8-h fasting period and immediately before injection of FDG (median of 76 min from commencement of dextrose and insulin infusions).

Myocardial biopsies and immunoblotting. In a subgroup of 18 patients (6 with T2DM) who proceeded to CABG, a Tru-cut biopsy was obtained from the region between the first diagonal branch and the mid-portion of the left anterior descending coronary artery shortly after the institution of cardiopulmonary bypass and before cooling. The biopsy was immediately frozen in liquid nitrogen and stored at −70°C pending analysis. Control biopsies were taken from transplant donor hearts before implantation (n = 7). The primary antibody was a rabbit anti-peptide polyclonal antibody to GLUT4 (AB1346) (Chemicon, Temecula, California). The secondary antibody was a donkey anti-rabbit alkaline phosphatase (Perbio, Hampton, New Hampshire). Labeled blots were scanned by transmission using a Hewlett Packard Deskscan (Palo Alto, California) and the band density was quantified using Sigma Gel software package (Sigma Chemical Co., St. Louis, Missouri). The results were normalized using the density of the myosin band (~200 kDa) identified using a Coomassie blue-stained minigel matching each immunoblot using a sample common to all experiments, and the measurements were expressed as arbitrary units (AU).

Statistical analysis. Data are presented as mean values ± SD and comparison made using paired or unpaired Student t tests. Differences between proportions were compared using the chi-square test with Yates’ correction. A p value <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the patients studied are given in Table 1. Of the 19 T2DM patients, 12 were receiving oral hypoglycemic agents (sulphonylurea alone in 8, combined with metformin in 4), and 7 were treated by diet alone. There was a history of previous myocardial infarction in 13 (36%) of those without diabetes and 6 (31%) of the T2DM subjects. There were no significant differences in weight or body mass index between the patients with and without diabetes, and symptoms (New York Heart Association functional class), LV ejection fraction, and regional wall motion indexes were similar in the 2 groups.

In the patients with T2DM, the fasting plasma glucose was significantly higher and plasma insulin concentration was double that of the patients without T2DM, although...
the plasma FFA concentration was similar (Table 2). During the equilibrium phase of the clamp, immediately before the injection of FDG, plasma insulin concentration had increased to similar levels in the 2 groups, and plasma glucose remained different and comparable to that during fasting (Table 2). The reduction in FFA concentration was greater in those without diabetes (mean fall 0.75 ± 0.37 vs. 0.67 ± 0.35 mEq·ml⁻¹, p = 0.05). Whole body glucose disposal (M) was lower in patients with T2DM (2.24 ± 1.61 vs. 3.74 ± 1.53 mg·kg⁻¹·min⁻¹, p < 0.05).

PET tissue characterization and MGU. There was no evidence for a greater degree of myocardial fibrosis in patients with T2DM as assessed by PTF (an index of the tissue viability derived from the H2¹⁵O scan) or by regional analysis of wall motion at echocardiography (Table 3). Myocardial blood flow was similar in patients with and without T2DM (Table 3), and the distribution of MBF during the clamp was similar in the patients with and without diabetes (Fig. 1A).

Global MGU was lower in patients with T2DM (0.34 ± 0.16 vs. 0.47 ± 0.24 μmol·min⁻¹·g⁻¹, p = 0.0002) despite comparable plasma insulin concentrations and a higher blood glucose concentration. In both T2DM patients and non-diabetic patients, MGU was lower than that of healthy volunteers from our database (0.61 ± 0.07 μmol·min⁻¹·g⁻¹) (19).

In the subjects with T2DM, MGU was globally reduced (p < 0.0001 vs. subjects without diabetes) (Fig. 1B). Combining the blood glucose concentration and MBF provides an estimate of the delivery of glucose to the myocytes, and from the resultant MGU, a glucose extraction fraction can be derived (Table 3). A highly significant reduction in glucose extraction by the myocardium was noted in the myocardium of patients with T2DM (Fig. 1C).

Immunobots. In order to estimate GLUT4 in the myocardium, Western blots were performed on the proteins extracted from the myocardial biopsies. The amount of GLUT4 protein was significantly lower in myocardium from the patients with heart failure compared with samples from donor myocardium (0.93 ± 0.49 AU vs. 1.63 ± 0.30 AU, p = 0.002). Glucose transporter 4 expression was similar in diabetic and non-diabetic patients (0.88 ± 0.43 AU vs. 0.96 ± 0.54 AU, p = 0.75) (Fig. 2).

**DISCUSSION**

This study shows that in patients with heart failure secondary to CAD, T2DM contributes to a further decrease in MGU despite the higher blood glucose concentration and similar MBF. Compared with controls from donor hearts, GLUT4 protein content was lower in patients with heart failure and CAD regardless of the presence of T2DM. In patients with T2DM, the reduced ability of the myocardium to extract glucose is associated with limited suppression of FFA and whole-body insulin resistance.

The ability to increase glycolysis is an important compensatory mechanism to protect the heart against ischemia and infarction (20,21). In previous studies, the hearts of patients with CAD and post-ischemic remodeling have a reduced ability to utilize glucose (13,14), with a direct relationship between contractile function (LV ejection fraction) and myocardial insulin-mediated glucose utilization.

### Table 2. Plasma Glucose, Insulin, and Free Fatty Acid Levels at Baseline and During the Equilibrium Phase of the Hyperinsulinemic Clamp

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>T2DM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting blood results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mmol·l⁻¹)</td>
<td>5.0 ± 0.6</td>
<td>8.0 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma insulin (pmol·l⁻¹)</td>
<td>33 ± 34</td>
<td>66 ± 76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free fatty acid (mEq/ml)</td>
<td>0.98 ± 0.36</td>
<td>0.94 ± 0.26</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Equilibration phase of the clamp before FDG injection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mmol·l⁻¹)</td>
<td>4.87 ± 0.85</td>
<td>7.5 ± 1.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma insulin (pmol·l⁻¹)</td>
<td>351 ± 270</td>
<td>367 ± 282</td>
<td>NS</td>
</tr>
<tr>
<td>Free fatty acid (mEq/ml)</td>
<td>0.20 ± 0.14</td>
<td>0.31 ± 0.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>M value</td>
<td>3.74 ± 1.53</td>
<td>2.24 ± 1.61</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD.

**Table 3. MBF and MGU, Tissue Fraction, and Glucose Extraction in Patients With Normal Glucose Tolerance and Those With T2DM**

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>T2DM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting MBF (ml·min⁻¹·g⁻¹)</td>
<td>0.84 ± 0.29</td>
<td>0.87 ± 0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose · MBF product (mmol·ml·min⁻¹·g⁻¹)</td>
<td>4.03 ± 1.72</td>
<td>5.30 ± 2.41</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MGU (μmol·min⁻¹·g⁻¹)</td>
<td>0.47 ± 0.24</td>
<td>0.34 ± 0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tissue fraction (alpha)</td>
<td>0.54 ± 0.12</td>
<td>0.57 ± 0.13</td>
<td>NS</td>
</tr>
<tr>
<td>WMSI</td>
<td>2.27 ± 1.02</td>
<td>2.28 ± 1.04</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose extraction (%)</td>
<td>13.5 ± 5.2</td>
<td>7.1 ± 3.1</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD.

MBF = myocardial blood flow; MGU = myocardial glucose utilization; other abbreviations as in Table 1.
Insulin resistance is a hallmark of T2DM, and although myocardial insulin resistance may not be a feature of uncomplicated T2DM, such patients are at increased risk of CAD and have a worse outcome than non-diabetic patients after an ischemic event. A number of studies report slight impairment of insulin-stimulated MGU in T2DM without CAD (22,23), whereas others demonstrate normal FDG accumulation in the myocardium of patients with T2DM during physiological hyperinsulinemia (11).

The present study was designed to explore the effect of heart failure secondary to CAD and T2DM on the ability of the heart to utilize glucose. Our findings confirm that patients with treated heart failure and CAD are insulin resistant, and that T2DM confers additional impairment of myocardial insulin sensitivity. This reduction in MGU in patients with heart failure, CAD, and T2DM is not a reflection of lower perfusion because resting MBF was similar in diabetic and non-diabetic subjects. In patients with CAD, abnormalities of myocardial metabolism extend beyond regions with contractile dysfunction, and insulin sensitivity is globally impaired. As myocyte survival during ischemia is dependent on the generation of high-energy phosphates from glucose, the shift toward anaerobic metabolism is a critical adaptive reaction. The association of CAD and T2DM results in a greater degree of myocardial insulin resistance, and may contribute to the increased morbidity and mortality associated with myocardial ischemia in these patients. The present study suggests that patients with T2DM and heart failure secondary to CAD exhibit a greater degree of myocardial insulin resistance.

The main myocyte glucose carrier is GLUT4, and during fasting it is primarily found within intracellular vesicles. Insulin induces a rapid translocation of GLUT4 to the sarcolemma, thereby increasing the cell capacity to take up glucose. Abnormalities of GLUT4 have been demonstrated in hypertrophic cardiac remodeling and the diabetic heart in humans and animal models (24). The reduction of GLUT4 in such conditions is believed to limit the ability of the heart cells to import glucose and to withstand and recover from ischemia. The reduction of GLUT4 protein found in our study is in accord with these previous studies. The lower MGU during hyperinsulinemia in patients with T2DM, despite similar levels of myocardial GLUT4 protein, suggests that GLUT4 expression is not rate-limiting for MGU. Another factor limiting MGU is the higher plasma FFA concentration in T2DM (25). In humans, a highly negative correlation between FFA and net glucose disposal was observed in a large study of more than 500 Europeans during a glucose clamp (26). Using nuclear magnetic resonance spectroscopy, a 50% reduction in insulin-stimulated whole-body glucose metabolism has been reported if FFA is elevated before commencing the hyperinsulinemic euglycemic clamp (27). In a previous study, we reported that FFAs were equally suppressed during an insulin clamp in diabetic and non-diabetic subjects (10); this was not the case in the

**Figure 1.** The distribution of myocardial blood flow (MBF) (A), myocardial glucose utilization (MGU) (B), and glucose extraction (C) during the euglycemic hyperinsulinemic clamp in the patients with and without type 2 diabetes mellitus (T2DM). Ant = anterior regions of the left ventricle; IP = inferoposterior regions of the left ventricle; Lat = lateral regions of the left ventricle.

**Figure 2.** Anti-glucose transporter 4 immunoblot (top) with matching coomassie blue stained gel (bottom) from patients with hibernating myocardium plus in donor myocardium. Immunoblots from diabetic patients are denoted D. Molecular weight standards are shown in the left lane of the gel. Densitometric quantification of the glucose transporter 4 immunoblot was normalized for myosin heavy chain content using the band at 200 kDa on the Coomassie blue stained gel.
present study of patients with heart failure, CAD, and T2DM. The reduced suppression of circulating FFA, despite resting insulinemia, may, therefore, contribute to the reduced ability of the heart to utilize glucose. These findings are of interest in view of the new peroxisome proliferator-activated receptor (PPAR agonists of the thiazolidinediones class, which have been shown to improve post-receptor insulin signaling and insulin sensitivity.

Recent studies have increased our understanding of the effects of selective PPAR-γ ligands (glitazones) with therapeutic effects that extend beyond their use as insulin sensitizers including beneficial effects in conditions associated with ischemia/reperfusion and inflammation (28,29). Currently, these drugs are used in the therapy of patients with T2DM without heart failure. As previously discussed, these patients have a significantly higher incidence of acute myocardial infarction, and the finding that glitazones reduce myocardial infarct size when given before the onset of an ischemic episode (at least in animals) may be clinically important. A number of studies have reported that glitazones exert potent anti-inflammatory effects in animal models of acute and chronic inflammation although the mechanisms underlying the anti-ischemic effects of these agents are not entirely clear.

The administration of systemic glucose-insulin-potassium may protect the myocardium and promote adequate cardiac and hemodynamic performance that would improve recovery after ischemia. Trials that have examined the role of glucose-insulin-potassium in cardiac surgery have been small, open-label, and involved a wide variety of regimens. Recently, a trial of glucose-insulin-potassium or placebo during cardiac surgery has reported an improvement in early post-operative cardiovascular performance, reduced inotrope requirement, and demonstrated less evidence of significant myocardial injury in non-diabetic patients undergoing CABG (29).

**Study limitations.** Hyperglycemia, in addition to its known toxic cellular effects, increases the activity of inducible nitric oxide synthase and promotes inflammation while, in contrast, insulin exerts anti-inflammatory and antia apoptotic effects. The precise benefit of insulin administered either alone to achieve tight glucose control or as a component of glucose-insulin-potassium therapy merits further research. In addition, GLUT4-null mice have been reported to increase MGU in response to insulin in a manner similar to control animals, although with a markedly delayed response. Although we aimed to assess the GLUT1 protein level in the myocardial samples, this analysis was hindered by the contamination of the samples by high amounts of GLUT1 from non-cardiac sources (erythrocytes).

**Conclusions.** Patients with T2DM and heart failure secondary to CAD have lower MGU compared with those without diabetes despite higher plasma glucose and insulin concentrations. The reduced ability of the myocardium to extract glucose in these patients does not appear to be secondary to a reduction in GLUT4 availability.

**Acknowledgments.**

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**References**


