Decreased Myocardial Glucose Uptake During Ischemia in Diabetic Swine

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The purpose of the study was to assess myocardial glucose uptake in nondiabetic (n = 5) and streptozotocin-diabetic (n = 6) Yucatan miniature swine under matched hyperglycemic and hypoinsulinemic conditions. Fasting conscious diabetic swine had significantly higher plasma glucose levels (20.9 ± 2.6 *v* 5.2 ± 0.3 mmol/L) and lower insulin levels (6 ± 1 *v* 14 ± 4 μU/mL) than nondiabetic animals. Myocardial glucose uptake was measured in open-chest anesthetized animals under aerobic and ischemic conditions 12 weeks after streptozotocin treatment. Coronary blood flow was controlled by an extracorporeal perfusion circuit. Ischemia was induced by reducing left anterior descending (LAD) coronary artery blood flow by 60% for 40 minutes. Animals were treated with somatostatin to suppress insulin secretion, and nondiabetic swine received intravenous (IV) glucose to match the hyperglycemia in the diabetic animals. The rate of glucose uptake by the myocardium was not statistically different under aerobic conditions, but was significantly lower in diabetic swine during ischemia (0.20 ± 0.08 *v* 0.63 ± 0.14 μmol · g^{-1} · min^{-1}, $P < .01$). Myocardial glucose transporter (GLUT4) protein concentration was decreased by 31% in diabetic swine. In conclusion, 12 weeks of streptozotocin diabetes in swine caused a significant decrease in myocardial GLUT4 protein and a decrease in myocardial glucose uptake during ischemia.

DIABETIC PATIENTS with coronary heart disease are at greater risk for a fatal coronary event than age-matched nondiabetic patients with a similar severity of coronary heart disease, which suggests that myocardial defects might contribute to the greater mortality in diabetic patients.[1] Several metabolic defects have been identified in animal models of diabetes. Studies on the isolated perfused rat heart have demonstrated that diabetic myocardium has lower rates of glucose uptake under a variety of conditions, including maximal insulin stimulation and anoxia.[2,3] Furthermore, streptozotocin-induced diabetes results in a decrease in glucose transporter protein in rats[4,5] and pigs,[6] suggesting a decreased capacity for glucose transport across the sarcolemmal membrane.

Little is known about the effects of diabetes on myocardial glucose uptake during ischemia in vivo. It is difficult to ascertain the effects of diabetes on cardiac glucose uptake in vivo, due to the confounding effects of unmatched glucose and insulin levels.[7,8] Diabetic patients studied under either hyperglycemic conditions or during a normoglycemic-hyperinsulinemic clamp have a decreased rate of myocardial glucose uptake compared with nondiabetic controls.[9-11] We recently showed that 1 month of streptozotocin diabetes in swine did not affect the rate of glucose uptake by the myocardium in hyperglycemic diabetic animals compared with normoglycemic nondiabetic animals.[6] Clear interpretation of this observation is difficult because hyperglycemia per se results in an increase in interstitial glucose and glucose uptake in ischemic myocardium.[12] Ideally, one would assess the rate of glucose uptake under matched glucose and insulin levels.

The purpose of the present investigation was to assess the effects of streptozotocin-induced diabetes in Yucatan miniature swine on myocardial glucose uptake under hyperglycemic and hypoinsulinemic conditions. It was hypothesized that diabetic animals would have impaired glucose uptake compared with nondiabetic control animals under either aerobic or ischemic conditions.

MATERIALS AND METHODS

Diabetic Model

We induced diabetes with streptozotocin as previously described.[13] Studies were performed on male Yucatan miniature swine (Charles River Laboratories, Wilmington, MA). All animals were received from the vendor at 12 weeks of age. Age-matched nondiabetic control animals (n = 5) and streptozotocin-diabetic animals (n = 6) were studied. The diabetic group received sterile freshly prepared streptozotocin 125 mg/kg intravenously [IV] via the ear vein (Zanosar; Upjohn, Kalamazoo, MI). This dose has been shown to induce basal hyperglycemia and remove the insulin response to an IV glucose load in swine.[6,13,14] Animals were fasted overnight before the injection. Venous blood was drawn from awake, overnight-fasted animals 12 weeks after streptozotocin treatment for measurement of plasma insulin and glucose levels.

Ischemia Studies

Myocardial glucose uptake was assessed in open-chest animals 12 weeks after injection of streptozotocin. Overnight-fasted swine were premedicated with ketamine (10 mg/kg subcutaneously) and anesthetized with halothane (3% to 5%). A tracheostomy was performed under deep general anesthesia, and the animals were ventilated to maintain arterial blood gases in the normal range (P_{O_2} > 100 mm Hg, P_{CO_2} = 35 to 45 mm Hg, and pH 7.35 to 7.45). Anesthesia was maintained with 0.75% to 1.5% halothane. The heart was exposed and instrumented as previously described.[6,15] Coronary blood flow was controlled through an extracorporeal circuit. Briefly, blood was drawn from the carotid artery and passed through a mixing chamber and three independently controlled roller pumps, and into the right main, left circumflex (CFX), and left anterior descending (LAD) coronary arteries. Blood pressure was monitored in the aorta and left ventricle using a manometer-tipped pressure device (Millar Instruments, Houston, TX), and left ventricular free-wall systolic thickening was measured in the LAD perfusion bed using sonomicrometry as previously described.[15] A venous sampling catheter was inserted in the left anterior interventricular vein, which drains the perfusion territory of the LAD coronary artery. Animals were heparinized (20,000 U heparin IV bolus followed by 10,000 U/h).

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Plasma glucose and insulin levels were matched between groups by infusing somatostatin into all animals to suppress insulin secretion (Fig 1). In addition, the nondiabetic group received an infusion of glucose to render them hyperglycemic. The somatostatin infusion (0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ IV) was initiated 60 minutes before the onset of ischemia. Glucose (~0.3 mL/min of 50% glucose) infusion was initiated in the nondiabetic group 50 minutes before the onset of ischemia, and was administered by a syringe pump into the coronary perfusion line just upstream of the mixing chamber. The glucose level in coronary arterial blood was measured at 5-minute intervals during the initial 20 minutes of glucose infusion using a glucose meter (Ames Glucometer III; Miles Diagnostics, Tarrytown, NY), and the infusion rate was adjusted to match glucose levels to those found in the diabetic group.

Ischemia was induced in the LAD perfusion bed by reducing the flow on the LAD perfusion pump by 60%[6,15] (Fig 1). The perfusion system allowed us to control LAD blood flow independently of the CFX and right coronary artery flows, so that ischemia in the LAD perfusion bed was induced without affecting blood flow to the CFX. Blood samples were drawn from the coronary artery perfusion line distal to the mixing chamber and the anterior interventricular vein for determination of the arterial-venous difference for oxygen, glucose, lactate, and free fatty acids (FFAs) at −10, −2, 25, 30, and 35 minutes of ischemia. At time 0, the flow rate on the LAD perfusion pump was reduced by 40%. The total duration of ischemia was 40 minutes. After 40 minutes of ischemia, the animal was euthanized and the heart was removed. A myocardial biopsy was taken from the nonischemic CFX bed and frozen at −70°C until analyzed for GLUT4 glucose transporter protein levels. The LAD perfusion bed was delineated by dye infusion into the left main and right coronary arteries. The LAD bed was dissected out and weighed along with the remaining heart tissue, and the heart weight and heart weight to body weight ratio was calculated.

Analytical Methods

Blood samples for glucose and lactate analysis were immediately deproteinized in ice-cold 7% perchloric acid (1:2 vol/vol), weighed, centrifuged, and stored at −70°C until analyzed in triplicate for glucose and lactate using previously described enzymatic spectrophotometric methods.[16] Blood oxygen concentration was measured using a hemoximeter (OSM 2; Radiometer, Cleveland, OH). Plasma FFA and insulin were assayed as previously described.[6] Myocardial GLUT4 protein were assayed by sodium dodecyl sulfate gel electrophoresis and immunoblotting and expressed relative to an internal standard from swine heart analyzed on each gel, as previously described.[6]

Calculations

LAD bed blood flow ($mL \cdot g^{-1} \cdot min^{-1}$) was calculated as LAD pump flow divided by LAD bed weight. The rates of glucose, lactate, and FFA uptake ($\mu mol \cdot g^{-1} \cdot min^{-1}$) and myocardial oxygen uptake ($\mu L \cdot g^{-1} \cdot min^{-1}$) for the LAD perfusion bed were calculated as the product of the arterial-venous concentration difference and LAD bed blood flow. Percent systolic thickening of the LAD bed was calculated from the end-diastolic and end-systolic thicknesses.[15]

Statistics

Results are presented as the mean ± SE. Values for the aerobic and ischemic periods were taken as the average of two aerobic samples and three ischemic samples. Diabetic and nondiabetic values within a treatment period were compared using nonparametric unpaired *t* tests, and the effects of ischemia within a treatment were assessed using a paired *t* test. A *P* value less than .05 was considered significant.

RESULTS

Fasting conscious streptozotocin-diabetic swine had higher glucose levels (20.9 ± 2.6 *v* 5.2 ± 0.3 mmol/L) and lower insulin levels (6 ± 1 *v* 14 ± 4 μU/mL) than untreated animals. Final body weight was significantly lower in the streptozotocin-diabetic group (31.3 ± 3.0 *v* 43.6 ± 1.1 kg). Absolute heart weight was also lower in the diabetic group (127.2 ± 14.2 *v* 167.1 ± 8.7 g), but was not different when expressed per kilogram body weight (3.81 ± 0.26 and 4.05 ± 0.16 g/kg for nondiabetic and diabetic, respectively). Myocardial GLUT4 protein levels measured in the left ventricular free wall were 31% lower in the diabetic group compared with the nondiabetic group (75.8% ± 4.5% *v* 109.6% ± 8.1% expressed as a percent of the internal standard, $P < .01$).

Cardiac Function

Table 1 shows the values for myocardial blood flow and ventricular function. Diabetes did not result in any significant effects on heart rate, left ventricular peak pressure or maximal dp/dt, or systolic wall thickening during either the aerobic or the ischemic period. Left ventricular end-diastolic pressure was twice as high in the diabetic group than in the nondiabetic group during the aerobic period ($P < .05$); there was no difference during ischemia (Table 1). Ischemia resulted in a 70% to 80% decrease in systolic thickening in both groups ($P < .05$). Maximal dp/dt decreased significantly with ischemia in the nondiabetic group, but not in the diabetic group (Table 1). Ischemia did not result in any significant change in heart rate or peak left ventricular pressure.

Substrate Metabolism

Table 2 presents the glucose, lactate, and FFA arterial levels and uptake values. Arterial substrate levels were matched between nondiabetic and diabetic animals during either period (Table 2). The arterial-venous difference for glucose was significantly lower in diabetic animals during ischemia (Fig 2).

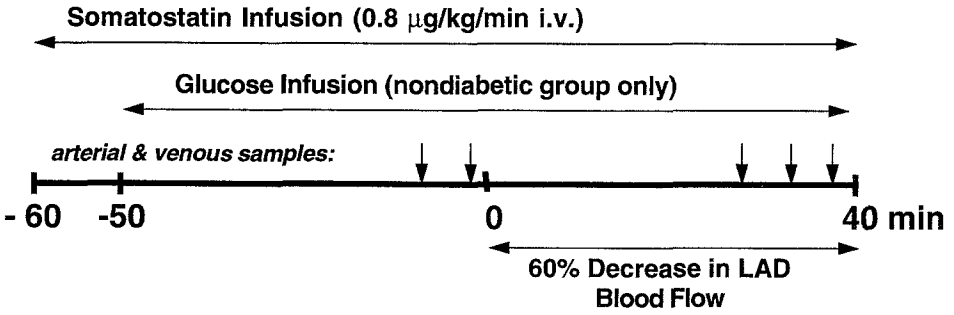

Fig 1. Experimental protocol. Somatostatin was infused in both groups. Glucose was infused in only nondiabetics to match the hyperglycemia observed in diabetics.

Table 1. Hemodynamic and Functional Response Under Aerobic and Ischemic Conditions (mean ± SE)

Response	Aerobic Period	Ischemic Period
LAD bed blood flow ($mL \cdot g^{-1} \cdot min^{-1}$)		
Nondiabetic	1.09 ± 0.06	0.456 ± 0.018†
Diabetic	1.05 ± 0.04	0.449 ± 0.014†
Myocardial oxygen consumption ($\mu L \cdot g^{-1} \cdot min^{-1}$)		
Nondiabetic	101 ± 11	51 ± 6†
Diabetic	96 ± 10	48 ± 6†
Heart rate (beats/min)		
Nondiabetic	111 ± 7	108 ± 11
Diabetic	120 ± 10	116 ± 8
Left ventricular peak systolic pressure (mm Hg)		
Nondiabetic	86.6 ± 1.0	84.0 ± 5.6
Diabetic	77.2 ± 5.2	74.4 ± 0.9
Left ventricular end-diastolic pressure (mm Hg)		
Nondiabetic	6.0 ± 1.9	14.8 ± 4.5†
Diabetic	12.0 ± 2.5*	15.9 ± 0.9
Maximal dp/dt (mm Hg/s)		
Nondiabetic	1,330 ± 176	1,066 ± 167†
Diabetic	1,121 ± 174	868 ± 43
LAD bed systolic thickening (%)		
Nondiabetic	25.1 ± 7.0	5.5 ± 4.5†
Diabetic	21.3 ± 5.3	6.2 ± 3.7†

*$P < .05$ *v* nondiabetic group within the same period.
†$P < .05$ *v* aerobic period within the same treatment group.

Ischemia resulted in a significant increase in the arterial-venous difference for glucose in both groups.

The rate of glucose uptake by the myocardium was not statistically lower in diabetic animals during the aerobic period, but was significantly lower in diabetic swine during ischemia (Table 2). The degree of reduction in glucose uptake in the diabetic group during the aerobic period was similar to that observed during ischemia; however, the difference was not statistically significant, due to the high variability. The high variability during the aerobic period is similar to previously reported values.[6-8,15-17]

Myocardial lactate uptake was significantly lower in diabetic

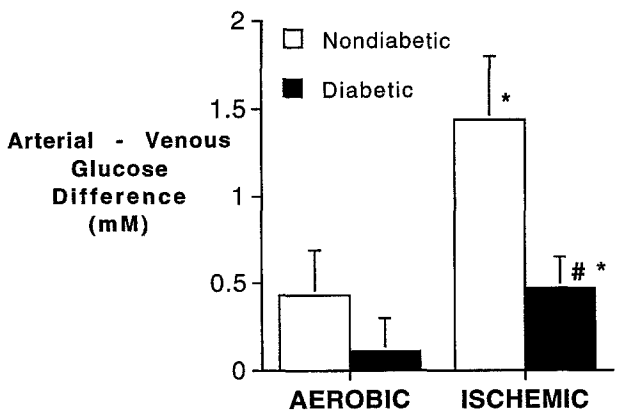

Fig 2. Arterial-venous difference for glucose under aerobic and ischemic conditions (n = 5 nondiabetic and n = 6 diabetic swine). *$P < .05$ *v* aerobic period in the same treatment group. #$P < .05$ *v* nondiabetic group during the ischemic period.

Table 2. Myocardial Blood Flow and Substrate Metabolism Under Aerobic and Ischemic Conditions (mean ± SE)

Parameter	Aerobic Period	Ischemic Period
Arterial insulin concentration (μU/mL)		
Nondiabetic	3.2 ± 0.6	2.8 ± 0.4
Diabetic	2.4 ± 0.3	2.2 ± 0.5
Arterial glucose concentration (mmol/L)		
Nondiabetic	13.9 ± 1.2	17.5 ± 2.2
Diabetic	16.7 ± 2.0	16.8 ± 1.8
Myocardial glucose uptake ($\mu mol \cdot g^{-1} \cdot min^{-1}$)		
Nondiabetic	0.45 ± 0.26	0.63 ± 0.14
Diabetic	0.11 ± 0.20	0.20 ± 0.08†
Arterial lactate concentration (mmol/L)		
Nondiabetic	1.67 ± 0.33	1.68 ± 0.30
Diabetic	2.07 ± 0.61	2.53 ± 0.66
Myocardial lactate uptake ($\mu mol \cdot g^{-1} \cdot min^{-1}$)		
Nondiabetic	0.26 ± 0.03	−0.05 ± 0.04‡
Diabetic	0.12 ± 0.05*	−0.25 ± 0.10‡
Arterial FFA concentration (mmol/L)		
Nondiabetic	0.55 ± 0.12	0.47 ± 0.08
Diabetic	0.67 ± 0.10	0.56 ± 0.04
Myocardial FFA uptake ($\mu mol \cdot g^{-1} \cdot min^{-1}$)		
Nondiabetic	0.15 ± 0.02	0.07 ± 0.01‡
Diabetic	0.11 ± 0.01	0.04 ± 0.01‡

*$P < .05$ *v* nondiabetic group within the same period.
†$P < .01$ *v* nondiabetic group within the same period.
‡$P < .05$ *v* aerobic period within the same treatment group.

swine during the aerobic period (Table 2). Ischemia resulted in a switch from net lactate uptake to net lactate production in both groups, with no difference between groups. Diabetes did not significantly affect FFA uptake during either period. Ischemia resulted in a significant decrease in FFA uptake in both groups.

DISCUSSION

This study is the first to demonstrate that the capacity for glucose uptake during low-flow ischemia is significantly impaired in diabetic myocardium in vivo. Unlike our previous study in diabetic swine,[6] the confounding effects of unmatched glucose and insulin levels were eliminated, allowing for direct assessment of the capacity for glucose uptake. These results extend the findings of Barrett et al,[7] which demonstrated that cardiac insulin-stimulated glucose uptake is impaired in hyperglycemic diabetic dogs compared with acutely hyperglycemic healthy dogs. In the present investigation, we measured the rates of glucose uptake under matched hyperglycemic and hypoinsulinemic conditions. The results clearly demonstrate that streptozotocin diabetic swine have significantly impaired myocardial glucose uptake during ischemia under hyperglycemic conditions.

We recently showed that 1 month of streptozotocin diabetes in swine did not affect the rate of glycolysis in hyperglycemic diabetic animals compared with normoglycemic nondiabetic animals.[6] We also recently observed that hyperglycemia per se results in an increase in glucose uptake in ischemic myocardium in nondiabetic swine.[12] This strongly suggests that the lack of a

difference in glucose uptake between hyperglycemic diabetic animals and normoglycemic nondiabetic animals was at least partially due to the compensatory effects of hyperglycemia. In our previous study,[6] the rates of glucose uptake were 0.26 ± 0.12 and 0.29 ± 0.09 μmol · g^{-1} · min^{-1} in normoglycemic nondiabetic and hyperglycemic diabetic animals, respectively, under ischemic conditions. In the present study, we observed a similar rate of glucose uptake during ischemia in hyperglycemic diabetic animals (0.20 ± 0.08 μmol · g^{-1} · min^{-1}), but a 215% increase in glucose uptake in hyperglycemic nondiabetic animals (0.63 ± 0.14 μmol · g^{-1} · min^{-1}). This demonstrates that hyperglycemia increases glucose uptake during ischemia in nondiabetic myocardium. The results also suggest that hyperglycemia may help compensate for the impaired capacity for glucose uptake in diabetic myocardium. However, the direct effects of hyperglycemia on myocardial glucose metabolism in diabetes have not been reported.

The impaired glucose uptake during ischemia is likely due to a lower concentration of glucose transporter protein. We observed a 31% decrease in GLUT4 protein 12 weeks after streptozotocin injection. We have also recently observed a 65% decrease in myocardial GLUT1 protein in the same swine model[17] and in streptozotocin-diabetic rats.[5] The rate of glucose transport is largely determined by the concentration and activity of glucose transporters in the sarcolemma. One limitation of the present investigation is that we measured myocardial GLUT4 protein levels in tissue homogenates and not in isolated sarcolemmal membranes. Studies in isolated rat hearts[18,19] and in dogs[20] have shown that both GLUT1 and GLUT4 proteins translocate from an intracellular location into the sarcolemmal membrane in response to insulin or ischemia. This translocation of glucose transporters corresponds to an increase in myocardial glucose extraction and uptake. Our results suggest that there was a decrease in glucose transporters in the sarcolemmal membrane in our diabetic animals during ischemia.

The decreased glucose extraction and uptake and elevated left ventricular diastolic pressure in the diabetic group might be due to structural changes (eg, myocardial fibrosis) rather than to metabolic adaptations. We have not histologically evaluated the effects of streptozotocin-induced diabetes on the myocardium, although we did biochemically assess collagen levels in the present investigation, and only saw slight (~10%) increases in myocardial collagen levels (data not shown). We have also assessed the interstitial concentration of glucose and adenine nucleotides in normal and diabetic swine myocardium under aerobic conditions and with dobutamine stress, and observed no differences between diabetic and nondiabetic groups.[17] These results suggest that diabetes does not result in gross fibrosis over a 12-week period in our model, and that the glucose gradient between the capillary lumen and the interstitium is not affected by diabetes. However, these results are far from conclusive. Extensive assessment of the connective tissue architecture and collagen phenotype and cross-linking must be made before this issue is resolved.

Ischemia resulted in similar declines in myocardial systolic thickening in both nondiabetic and diabetic groups. This suggests that the compromised ability for glucose uptake in diabetic animals does not further impair cardiac function during the moderate level of ischemia used in this study. We recently observed in the same ischemic model that enhancing glucose uptake with acute hyperglycemia in nondiabetic swine results in a fourfold increase in the rate of glucose uptake but does not improve left ventricular systolic pressure or peak dp/dt.[12] Furthermore, increasing glucose oxidation and decreasing lactate production with intracoronary treatment with dichloroacetate did not result in improved systolic shortening in ischemic swine myocardium.[21] These findings suggest that the rate of contractile work during moderate ischemia in vivo is not directly regulated by glycolysis.

Somatostatin may have affected growth hormone levels and perhaps other regulators of myocardial metabolism besides insulin. We have not assessed the effects of somatostatin alone on myocardial glucose metabolism; however, we treated all animals with an infusion of somatostatin and made the assumption that the effects would not be grossly different between diabetic and nondiabetic groups. It is possible that the hormonal and metabolic responses to somatostatin are different between normal and diabetic swine. However, there is not a clear rationale for this hypothesis, given the short time frame of our study protocol.

In conclusion, myocardial glucose extraction and uptake were impaired after 12 weeks of streptozotocin diabetes in hyperglycemic and hypoinsulinemic swine. We also observed a 31% decrease in myocardial GLUT4 protein, which may partially explain the decreased capacity for glucose uptake during ischemia.

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