PET detection of the impact of dobutamine on myocardial glucose metabolism in women with type 1 diabetes mellitus

Pilar Herrero, ME, MS,[a] Janet McGill, MD,[b] Donna S. Lesniak, RN,[a] Carmen S. Dence, MS,[a] Shalonda W. Scott, MS,[a] Zulfia Kisrieva-Ware, MD, PhD,[a] and Robert J. Gropler, MD[a]

Background. **Our objective was to determine, in the hearts of women with type 1 diabetes mellitus (T1DM), whether the fate of extracted glucose is altered and, if so, what the impact of dobutamine is on myocardial substrate metabolism. In experimental models of T1DM, myocardial glycolysis and glucose oxidation are reduced with the impairment becoming more pronounced with dobutamine. Whether similar changes occur in humans with T1DM is unclear.**

Methods and Results. **Myocardial perfusion, oxygen consumption, and glucose and fatty acid metabolism were measured with positron emission tomography in 19 women, 7 normal volunteers (NVs) and 12 with T1DM. The NVs and 6 T1DM (DM1) patients were studied under baseline metabolic conditions and 6 T1DM patients were studied during hyperinsulinemic-euglycemic clamp (DM1-C), both at rest and during dobutamine. At rest, myocardial glucose uptake, glycolysis, glycogen storage, and oxidation were reduced by similar levels in DM1 patients compared with NVs ($P < .05$). During dobutamine, although myocardial glucose uptake was not different from DM1 patients at rest, fractional glycolysis was lower compared with NVs or DM1-C patients and reflected a lower glucose oxidation rate ($P < .001$). Measurements of myocardial glucose metabolism at rest and during dobutamine were comparable between NVs and DM1-C patients. During dobutamine, myocardial fatty acid uptake and oxidation increased in all 3 groups.**

Conclusions. **In women with T1DM, (1) myocardial glucose metabolism is impaired downstream from initial uptake, (2) these abnormalities become more pronounced with dobutamine and are paralleled by an increase in myocardial fatty acid metabolism, and (3) insulin restores glucose metabolism to levels observed in normal control subjects. (J Nucl Cardiol 2008;15:791-9.)**

Key Words: Diabetes mellitus • metabolism • catecholamines • tomography

The metabolic phenotype of the diabetic heart is an overdependence on fatty acid metabolism that is paralleled by a decline in glucose use, at least under euglycemic conditions.[1-6] Results of studies in a wide range of experimental models of diabetes have documented that in addition to a decrease in glucose uptake, there is a reduction in glycolysis and glucose oxidation.[7-9] Results of studies in patients with either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) have generally confirmed the increase in myocardial fatty acid uptake (MFAU) and myocardial fatty acid oxidation (MFAO) and a decline in myocardial glucose uptake (MGU).[1-3,10,11] However, whether the metabolism of extracted glucose is also reduced in humans with diabetes is not clear.

Moreover, much of what is known about the metabolic perturbations in patients with either T1DM or T2DM is limited to resting conditions. For example, in humans with T1DM, atrial pacing results in an increase in MGU without any change in fatty acid use. However, whether defects are present in glucose metabolism downstream from uptake is unknown.[1] Furthermore, whether these metabolic perturbations are amenable to therapies such as supplemental insulin is unknown. Accordingly, in this study we sought to answer 3 different questions. First, is the metabolism of extracted glucose by the heart reduced in patients with T1DM? Second, is the myocardial metabolic response to dobutamine, particularly as it

From the Division of Radiological Sciences, Mallinckrodt Institute of Radiology,[a] and Division of Endocrinology, Department of Internal Medicine, Washington University School of Medicine,[b] St Louis, Mo.

This work was supported by grants PO1-HL-13851, R01-HL69100, and M01-RR00036 from the National Institutes of Health (Bethesda, Md).

Reprint requests: Robert J. Gropler, MD, Box 8225, 510 S Kingshighway, St Louis, MO 63110; *Groplerr@mir.wustl.edu.*

1071-3581/$34.00

doi:10.1016/j.nuclcard.2008.08.004

relates to glucose uptake and downstream metabolism, different between patients with T1DM and nondiabetic subjects? Third, if differences in metabolism do exist, can they be reduced by the administration of insulin?

METHODS

Study Population

We studied 19 healthy women, 7 normal volunteers (NVs) and 12 with T1DM. We studied only women because we recently reported that gender may impact myocardial substrate metabolism.[12] Although T2DM is more prevalent, we purposefully chose to study only patients with T1DM to avoid the possible confounding effects of obesity and hypertension that often accompany T2DM.[13,14] Nondiabetic women were identified based on clinical evaluation and a normal oral glucose tolerance test. Women were classified as having T1DM based on either the need for supplemental insulin within the first year of diagnosis, a history of ketoacidosis, or a plasma C-peptide level lower than 0.50 μmol/mL. No T1DM subject had active retinopathy, clinically significant autonomic neuropathy (history of gastroparesis, bladder dysfunction, or orthostatic hypotension), or a serum creatinine level greater than 1.5 mg/dL. Sedentary women were chosen to minimize the possible confounding effects of variable levels in training-induced adaptations on myocardial substrate metabolism.[15] All women were nonobese, nonsmokers, normotensive, and without a family history of coronary artery disease. They had a normal physical examination, electrocardiogram, and symptom-limited rest/exercise echocardiogram. The study was approved by the Human Studies and Radioactive Drug Research Committees at Washington University School of Medicine, St Louis, Mo. Written informed consent was obtained from all subjects before enrollment into the study.

Experimental Procedure

All studies were performed on a conventional commercially available tomograph (Siemens ECAT 962 HR+; Siemens Medical Systems, Iselin, NJ). All subjects were admitted overnight to the General Clinical Research Center at Washington University. Two 18- or 20-gauge catheters were placed into two different intravenous sites: one for infusion and one for blood sampling. At 6 PM the night before the study, both diabetic and nondiabetic subjects ingested a standard weight-adjusted meal. In the morning the NVs ingested a second meal 2 hours before starting the positron emission tomography (PET) study. Six diabetic patients (DM1 group) fasted until the following morning, but overnight, they received an insulin drip at physiologic replacement doses (1-2 U/h) and supplemental dextrose 5% in water (D5W) to maintain blood glucose levels of 5 to 7 mmol/L that was maintained until completion of the imaging study the next day. In this way NVs and DM1 patients could be matched for their plasma insulin and glucose levels under resting conditions. The other 6 diabetic patients (DM1-C group) were started on a hyperinsulinemic-euglycemic clamp 2 hours before the PET imaging session via standard methods.[16] In all subjects telemetry was used and blood pressure measurements were obtained routinely throughout the study. The rate-pressure product was calculated as systolic blood pressure multiplied by heart rate. All subjects were studied at 8 AM to avoid circadian variations in myocardial metabolism and function.[17] Each subject underwent PET imaging on 2 separate days. On day 1, the PET study was performed under the metabolic conditions described previously at rest. On day 2, the study was repeated under the same metabolic conditions as day 1 but during the concomitant intravenous administration of dobutamine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

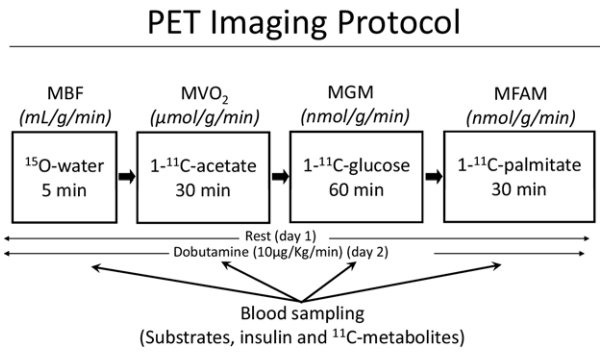

Figure 1. Imaging protocol. *MBF*, Myocardial blood flow; *MVO_2*, myocardial oxygen consumption; *MGM*, myocardial glucose metabolism; *MFAM*, myocardial FFA metabolism; *Substrates*, glucose, fatty acids, and lactate; *C-11-metabolites*, C-11-O_2 and C-11-lactate.

PET Image Acquisition

PET was used to measure myocardial blood flow (MBF) (in milliliters per gram per minute), myocardial oxygen consumption (MVO_2) (in micromoles per gram per minute), glucose metabolism (in nanomoles per gram per minute), and fatty acid metabolism (in nanomoles per gram per minute) using the following PET tracers: oxygen-15-water, 1-carbon-11-acetate, 1-carbon-11-glucose and 1-carbon-11-palmitate, as reported previously.[18-22] During the study, venous blood samples were obtained during each imaging portion of the study (ie, during MBF, MVO_2, and myocardial glucose and fatty acid metabolism imaging) to measure levels of plasma substrates, glucose (in micromoles per minute), fatty acids, lactate (in nanomoles per milliliter), and insulin (in microunits per milliliter) and radiolabeled metabolites.[19-22] The imaging protocol is summarized in Figure 1.

PET Image Analysis

Blood and myocardial PET time-activity curves were used in conjunction with well-established kinetic models to quantify MBF (in milliliters per gram per minute), MVO_2 (in micromoles per gram per minute), MFAU (in nanomoles per gram per minute) and MFAO (in nanomoles per gram per minute), and overall MGU (in nanomoles per gram per minute).[19-21]

Table 1. Clinical characteristics

	NVs	DM1 patients	DM1-C patients
Subjects (women)	7	6	6
Age (y)	27 ± 4	33 ± 9	34 ± 11
BMI (kg/m^2)	23 ± 3	25 ± 3	27 ± 4
TG (mg/dL)	67 ± 18	72 ± 53	58 ± 29
LVEF (%)	67 ± 4	65 ± 6	65 ± 6
DM duration (y)		21 ± 10	17 ± 10
HbA_{1c} (%)		9.1 ± 2.4	9.3 ± 2.9

BMI, Body mass index; *TG*, triglycerides; *LVEF*, left ventricular ejection fraction; *DM*, diabetes mellitus; *HbA_{1c}*, hemoglobin A_{1c}.

Recently, the glucose compartmental model originally developed to measure MGU has been optimized to permit measurements of the metabolic fate of myocardial glucose, including glycolysis, glucose oxidation, and glycogen storage.[22]

Measurement of Plasma Insulin and Substrate Levels

Plasma insulin levels were measured by radioimmunoassay. Plasma glucose and lactate levels were measured by use of a commercially available glucose-lactate analyzer (YSI, Yellow Springs, Ohio). The level of fatty acid in the plasma was determined by capillary gas and high-performance liquid chromatography.

Statistical Analysis

SAS software (SAS Institute, Cary, NC) was used for the statistical analyses. Data are expressed as mean ± SD. All group comparisons for continuous variables were done by use of 2-way analysis of variance for repeated-measurement analyses with rest/dobutamine as the repeated factor (dobutamine) and NV/DM1/DM1-C as the grouping factor (group). Post hoc analyses were done only if $P < .05$ was obtained for dobutamine, group, or their interaction (dobutamine × group).

RESULTS

Clinical Characteristics

The clinical characteristics of the groups are shown in Table 1. The groups were well matched for age, body mass index, plasma lipid levels, and resting left ventricular function (P = not significant). The DM1 and DM1-C groups had a similar duration of disease and level of glycemic control.

Hemodynamics, MBF, and MVO_2

Table 2 shows values for the rate-pressure product, MBF, and MVO_2. There were no differences among groups for values obtained either at rest or during dobutamine. As anticipated, during dobutamine, there was a significant increase in rate-pressure product, MBF, and MVO_2 compared with resting conditions in all 3 groups.

Plasma Insulin and Substrate Levels

Table 3 shows the plasma insulin, glucose, fatty acid, and lactate levels for the 3 groups. As anticipated by the intervention, plasma insulin levels were significantly higher in the DM1-C patients than in NVs and DM1 patients, both at rest ($P < .05$) and during dobutamine ($P < .05$). On average, plasma glucose levels were higher in DM1-C patients than in DM1 patients and NVs and were higher in DM1 patients than in NVs both at rest and during dobutamine ($P < .05$). Glucose levels did not change with dobutamine in any of the 3 groups. Plasma fatty acid levels were higher in DM1 patients when compared with NVs and DM1 patients, both at rest ($P < .05$) and during dobutamine ($P < .01$). On average, fatty acid levels increased in all groups with dobutamine ($P < .01$). At rest, plasma lactate levels were highest in DM1-C patients and lowest in DM1 patients ($P < .05$). On average, plasma lactate levels increased with dobutamine ($P < .05$), but no differences were noted among the 3 groups.

Myocardial Fatty Acid Metabolism

Figure 2 shows the measurements of myocardial fatty acid metabolism in the 3 groups. MFAU at rest was highest in DM1 patients (102 ± 42 $nmol \cdot g^{-1} \cdot min^{-1}$), followed by NVs (60 ± 0.21 $nmol \cdot g^{-1} \cdot min^{-1}$), and was lowest in the DM1-C patients (17 ± 9 $nmol \cdot g^{-1} \cdot min^{-1}$) ($P < .05$). During dobutamine, a similar pattern was found, with DM1 patients having the highest MFAU (213 ± 78 $nmol \cdot g^{-1} \cdot min^{-1}$), followed by NVs (142 ± 92 $nmol \cdot g^{-1} \cdot min^{-1}$), with the lowest MFAU in DM1-C patients (61 ± 49 $nmol \cdot g^{-1} \cdot min^{-1}$) ($P < .05$ vs DM1 patients). Of note, MFAU significantly increased with dobutamine in all 3 groups ($P < .001$).

MFAO at rest was highest in DM1 patients (99 ± 42 $nmol \cdot g^{-1} \cdot min^{-1}$) ($P < .01$) when compared with NVs (43 ± 24 $nmol \cdot g^{-1} \cdot min^{-1}$) and DM1-C patients (18 ± 30 $nmol \cdot g^{-1} \cdot min^{-1}$). During dobutamine, MFAO was similar between DM1 patients (191 ± 75 $nmol \cdot g^{-1} \cdot min^{-1}$) and NVs (133 ± 79 $nmol \cdot g^{-1} \cdot min^{-1}$) but was lower in DM1-C patients

Table 2. Rate-pressure product, MBF, and MVO_2

	NVs		DM1 patients	
	Rest	Dob	Rest	Dob
RPP (beats/min · mm Hg)	6,943 ± 1,230	12,275 ± 2,013*	8,901 ± 2,138	14,194 ± 7,082*
MBF ($mL \cdot g^{-1} \cdot min^{-1}$)	1.07 ± 0.13	2.08 ± 0.37*	1.20 ± 0.27	2.83 ± 0.74*
MVO_2 ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	4.91 ± 0.94	12.7 ± 1.64*	6.10 ± 1.61	18.6 ± 11.8*

Dob, Dobutamine; *RPP*, rate-pressure product; *NS*, not significant.
*$P < .01$ versus rest.

Table 3. Plasma insulin and substrates

	NVs		DM1 patients		DM1 patients		
	Rest	Dob	Rest	Dob	Rest	Dob	*P* value
Insulin (μU/mL)	12.6 ± 10.3	33.4 ± 33.1	25.0 ± 40.7	62.9 ± 86.0	95.5 ± 21.3*†	105.0 ± 31.7*†	Dob, $P = .07$; group, $P < .005$
Glucose (μmol/mL)	4.96 ± 0.73	5.16 ± 0.46	5.74 ± 0.76*	5.64 ± 0.45*	6.17 ± 0.76*†	6.22 ± 0.67*†	Dob, $P =$ NS; group, $P < .005$
Free fatty acids (nmol/mL)	227 ± 137	426 ± 162‡	582 ± 284*	1,044 ± 475*	82 ± 87†	357 ± 372†	Dob, $P < .01$; group, $P < .0001$
Lactate (nmol/mL)	866 ± 141	996 ± 256	564 ± 119*	989 ± 425	1,128 ± 144†	1,177 ± 319	Dob, $P < .05$; group, $P < .05$

Dob, Dobutamine; *NS*, not significant.
*$P < .05$ versus NVs.
†$P < .05$ versus DM1 patients.
‡$P < .05$ versus rest.

(44 ± 46 nmol · $g^{-1} \cdot min^{-1}$) ($P < .05$). There was a significant increase in MFAO with dobutamine in all groups ($P < .0005$).

At rest, the fraction of extracted fatty acid that was oxidized (%MFAO) was similar between NVs (72% ± 26%) and DM1 patients (97% ± 2%) but was significantly lower in DM1-C patients (33% ± 30%) ($P < .005$). However, during dobutamine, no differences were noted among the NV (93% ± 6%), DM1 (90% ± 10%), and DM1-C (79% ± 14%) groups. Of note, there was a significant increase in %MFAO with dobutamine compared with resting conditions in the DM1-C patients ($P < .05$). However, no increases were observed in DM1 patients or NVs.

Myocardial Glucose Metabolism

Figure 3 shows MGU, glycolysis, and glycogen synthesis for the 3 groups, both at rest and during dobutamine. At rest, the MGU level was comparable between the NV (493 ± 188 nmol · $g^{-1} \cdot min^{-1}$) and DM1-C (693 ± 353 nmol · $g^{-1} \cdot min^{-1}$) groups but significantly lower in the DM1 group (186 ± 76 nmol · $g^{-1} \cdot min^{-1}$) ($P < .05$). A similar pattern was observed during dobutamine, with MGU values being comparable between the NV (478 ± 205 nmol · $g^{-1} \cdot min^{-1}$) and DM1-C (820 ± 536 nmol · $g^{-1} \cdot min^{-1}$) groups but significantly lower in the DM1 group (154 ± 105 nmol · $g^{-1} \cdot min^{-1}$) ($P < .05$). Of note, MGU did not increase with dobutamine in any of the groups. Under resting conditions, glycolysis and glycogen synthesis were lower in DM1 patients (76 ± 47 and 110 ± 41 nmol · $g^{-1} \cdot min^{-1}$, respectively) compared with either NVs (292 ± 143 and 201 ± 82 nmol · $g^{-1} \cdot min^{-1}$, respectively) or DM1-C patients (348 ± 259 and 345 ± 133 nmol · $g^{-1} \cdot min^{-1}$, respectively) ($P < .05$). These differences were commensurate with differences in MGU among the groups. During dobutamine, rates of glycolysis were lower in DM1 patients (61 ± 75 nmol · $g^{-1} \cdot min^{-1}$)

Table 2. Continued

DM1-C patients		
Rest	**Dob**	***P* value**
9,221 ± 2,100	21,406 ± 12,567*	Dob, $P < .0005$; group, P = NS
1.08 ± 0.17	2.73 ± 0.69*	Dob, $P < .0001$; group, P = NS
7.34 ± 3.28	14.74 ± 5.82*	Dob, $P < .0001$; group, P = NS

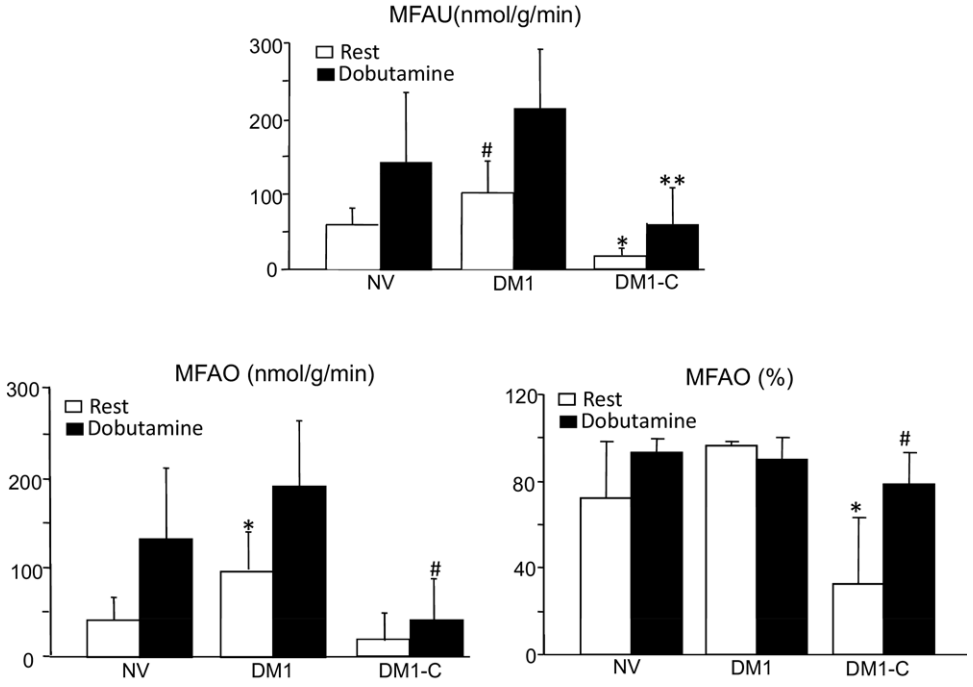

Figure 2. Measurements of myocardial fatty utilization (MFAU), oxidation (MFAO), and fraction of extracted fatty acid that undergoes β-oxidation (MFAO [%]). For MFAU, $P < .001$ for rest versus dobutamine; $P < .05$ versus NVs (rest) (*pound sign*); $P < .05$ versus NVs (rest) and DM1 patients (rest) (*1 asterisk*); $P < .05$ versus DM1 patients (dobutamine) (*2 asterisks*). For MFAO, $P < .0005$ for rest versus dobutamine; $P < .01$ versus NVs (rest) and DM1-C patients (rest) (*1 asterisk*); $P < .05$ versus NVs (dobutamine) and DM1 patients (dobutamine) (*pound sign*). For MFAO (%), P = not significant for rest versus dobutamine; $P < .005$ versus NVs (rest) and DM1 patients (rest) (*1 asterisk*); $P < .05$ versus DM1-C patients (rest) (*pound sign*).

compared with either NVs (320 ± 175 nmol · g^{-1} · min^{-1}) or DM1-C patients (562 ± 525 nmol · g^{-1} · min^{-1}) ($P <$ .05). Rates of glycogen synthesis were also lower in DM1 patients (93 ± 51 nmol · g^{-1} · min^{-1}) compared with DM1-C patients (252 ± 91 nmol · g^{-1} · min^{-1}) ($P < .05$) but similar to those in NVs (148 ± 36 nmol · g^{-1} · min^{-1}). However, the glycolysis fraction (relative to total glucose uptake) was significantly lower in the DM1 group (30% ± 23%) compared with either the NV (59% ± 17%) or DM1-C (62% ± 15%) group ($P < .05$). Paralleling this pattern was the higher glycogen synthesis fraction in the DM1 group (70% ± 23%) compared with either the NV (41% ± 17%) or DM1-C (38% ± 15%) group ($P < .05$).

Figure 4 shows the rates of glucose oxidation for the 3 groups. At rest, glucose oxidation rates were lower in DM1 patients (53 ± 32 nmol · g^{-1} · min^{-1}) compared with either NVs (226 ± 140 nmol · g^{-1} · min^{-1}) or DM1-C patients (312 ± 224 nmol · g^{-1} · min^{-1}) ($P < .05$). These differences paralleled the differences in MGU among the groups. Similar patterns were observed during dobutamine, with rates of glucose oxidation being lower in DM1 patients (38 ± 47 nmol · g^{-1} · min^{-1}) compared with either NVs

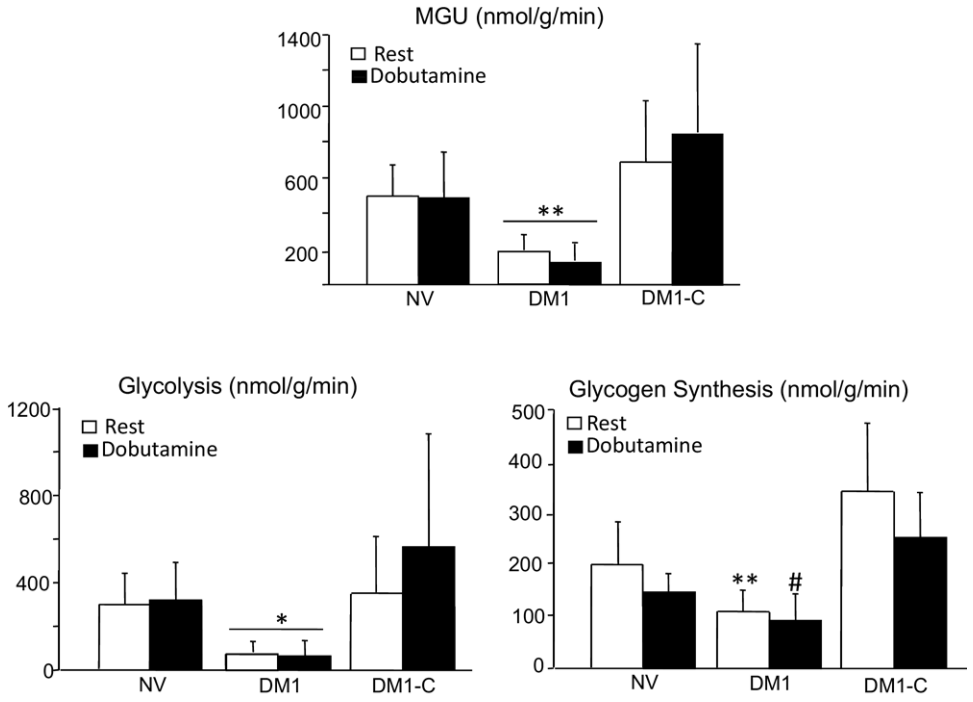

Figure 3. Measurements of myocardial glucose utilization (MGU) glycolysis, and glycogen synthesis. For MGU, P = not significant for rest versus dobutamine; $P < .05$ versus NVs (rest and dobutamine) and DM1-C patients (rest and dobutamine) (*1 asterisk*). For myocardial glycolysis, $P = .09$ for rest versus dobutamine; $P < .05$ versus NVs (rest and dobutamine) and DM1-C patients (rest and dobutamine) (*1 asterisk*). For myocardial glycogen synthesis, $P = .07$ for rest versus dobutamine, $P < .05$ versus NVs (rest) and DM1-C patients (rest) (*2 asterisks*); $P < .05$ versus DM1-C patients (rest) (*pound sign*).

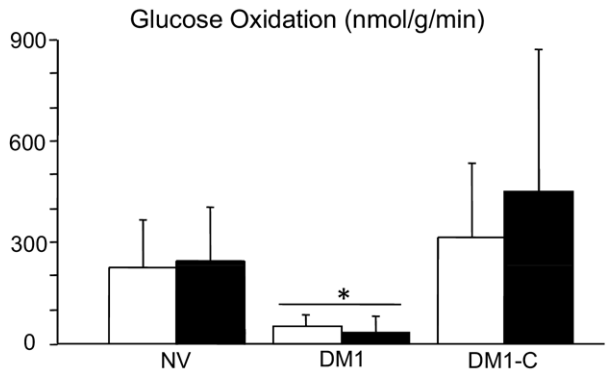

Figure 4. Measurements of myocardial glucose oxidation: P = not significant for rest versus dobutamine; $P < .05$ versus NVs (rest and dobutamine) and DM1-C patients (rest and dobutamine) (*asterisk*).

(250 ± 160 nmol $\cdot$ g^{-1} $\cdot$ min^{-1}) or DM1-C patients (451 ± 423 nmol $\cdot$ g^{-1} $\cdot$ min^{-1}) ($P < .05$). Of note, during dobutamine, fractional glucose oxidation was lower in DM1 patients ($18\% \pm 12\%$) when compared with either the NVs ($48\% \pm 0.12\%$) or DM1-C patients ($50\% \pm 12\%$) ($P < .001$), suggesting greater impairment in glucose oxidation relative to glucose uptake in DM1 patients.

DISCUSSION

The findings of this study in female patients with T1DM are as follows: (1) under resting conditions, myocardial glycolysis, glucose oxidation, and glycogen synthesis are reduced in proportion to the decline in glucose uptake; (2) during dobutamine, glycolysis and glucose oxidation are reduced relative to uptake, resulting in a greater fraction of extracted glucose undergoing glycogen synthesis, whereas there is an increase in MFAU and MFAO; and (3) the impairment in glucose uptake, glycolysis, and glucose oxidation both at rest and during dobutamine can be restored by the administration of high-dose insulin. These results provide complementary evidence that many of the abnormalities in myocardial glucose metabolism obtained in experimental models of T1DM are applicable to humans with the disease.

Myocardial Substrate Metabolism Under Resting Conditions

Consistent with the results of prior studies in experimental models of T1DM and patients with the disease, myocardial fatty acid metabolism was increased in the

DM1 patients compared with NVs, most likely because of the increase in plasma fatty acid levels. The findings of reduced myocardial glycogen synthesis, glycolysis, and glucose oxidation rates commensurate with the decline in glucose uptake confirm that the perturbations in myocardial glucose metabolism in the human diabetic heart are similar to that observed in experimental models of the disease.[4,23-26] In an earlier study in humans with T1DM, arterial–coronary sinus balance measurements were performed, showing that in addition to the decline in MGU, myocardial glucose oxidation was reduced.[27] Our study extends these observations by showing that reductions in glycolysis and glycogen synthesis exist as well. Likely components of the glucose metabolic pathway targeted by diabetes include a decline in myocardial glucose transporter function (eg, glucose transporters 1 and 4) and a decline in activity of hexokinase and 6-phosphofructo-2-kinase (glycolysis) and pyruvate dehydrogenase complex (oxidation).[4,23-26]

In this study the administration of pharmacologic doses of insulin reversed most of these abnormalities. The decrease in MFAU, MFAO, and %MFAO (Figure 2) likely reflects the combined effects of reduced fatty acid delivery to the myocardium (resulting from decreased peripheral lipolysis) and increased myocardial malonyl coenzyme A levels. Conversely, the increase in MGU likely reflects the increased translocation of insulin regulated glucose transporter 4 (GLUT-4) to the sarcolemma.[28,29] Increases in glycolysis and glucose oxidation are consistent with the effects of reduced peroxisome proliferator–activated receptor α activation leading to reduced pyruvate dehydrogenase kinase 4 activity, as well as direct effects of insulin on glycolysis (ie, 6-phosphofructo-2-kinase) and oxidative components (pyruvate dehydrogenase complex).[4,9] Similarly, the increase in glycogen synthesis likely reflects the effects of increased glycogen synthase activity due to the stimulatory effects of insulin and the loss of inhibition by the reduction in cellular fatty acids levels.

Myocardial Substrate Metabolism During Dobutamine

MFAU and MFAO increased during dobutamine to similar levels and by equivalent amounts in T1DM patients when compared with nondiabetic subjects (Figure 2). This increase in fatty acid metabolism appeared to be driven primarily by the increase in plasma fatty acid levels, likely reflecting the lipolytic effects of β-adrenergic stimulation in peripheral adipose tissue by hormone-sensitive lipase.[30] In isolated perfused nondiabetic hearts, catecholamine stimulation results in an increase in MGU, glycolysis, and oxidation.[31] In nondiabetic humans studied under fasting conditions, dobutamine infusion resulted in a significant increase in plasma insulin levels, which in turn was associated with an increase in MGU.[32] The lack of an increase in MGU in our study, as compared with the increase in MGU reported previously, may simply reflect differences in the experimental conditions. For example, in this study normal subjects were studied in the fed state, which leads to an increase in plasma insulin levels. As a consequence, a significant increase in plasma insulin levels with dobutamine was not observed and may have contributed to the lack of increase in MGU.

With dobutamine, the metabolic fate of extracted glucose differs between the NV and DM1 groups. The fraction of glucose metabolism representing glycolysis was significantly lower in the DM1 group and, moreover, tended to be lower when compared with resting conditions. This reduction in glycolysis reflected primarily a reduction in glucose oxidation. As a consequence, the fraction of extracted glucose undergoing glycogen synthesis was increased. Given that plasma fatty acid levels increased with dobutamine, these results are consistent with those of prior studies in various experimental models of T1DM showing that in the setting of increased myocardial fatty acid delivery, the impairment in myocardial glucose oxidation appears to be greater than the impairment in glycolysis, which in turn is greater than the impairment in glucose uptake, leading to a relative increase in glycogen stores.[4,23-26] The impairment in glucose oxidation with dobutamine is consistent with a defect in pyruvate oxidation.[23]

At pharmacologic doses of insulin (DM1-C), myocardial uptake of glucose did not increase during dobutamine (Figure 3). However, an increase in MFAU and MFAO was seen, although at lower levels than that observed under baseline metabolic conditions (DM1) (Figure 2). These data suggest that the lipolytic effects of dobutamine can overcome the lipogenesis effects of insulin to increase the levels of plasma fatty acid delivered to the myocardium and thus stimulate myocardial fatty acid metabolism. In addition, it appears that the administration of insulin was also able to overcome the reduction in glucose oxidation during dobutamine.

Limitations

It is unlikely that the differences in myocardial substrate metabolism were attributable solely to the differences in the plasma substrate and insulin environment between the 3 groups. For example, at rest, DM1 patients exhibited lower levels of glucose oxidation compared with NVs despite, on average, higher (but not significant) plasma insulin levels. Moreover, at rest, even though DM1-C patients exhibited approximately 8 times higher plasma insulin levels than NVs, the level of

glucose oxidation was similar between the groups, further emphasizing the impairment of myocardial carbohydrate oxidation in T1DM. The results of this study can only be applied to female patients with and without T1DM. Further studies will be required to determine the applicability of these observations in male patients and in patients with T2DM. The compartmental modeling method used to estimate glycogen synthesis is based on the fraction of tracer that enters slow turnover pools and thus remains within tissue. There are other glucose intermediates such as those of the pentophosphate pathway that may also show a slow turnover pool pattern. Thus it is possible that the fraction of extracted glucose that entered glycogen synthesis was overestimated in our study.

CONCLUSIONS

The results of this study further complete the picture of the myocardial metabolic phenotype in humans with T1DM. More specifically, reductions in myocardial glucose use extend beyond initial uptake and include various aspects of downstream glucose metabolism that become more pronounced with dobutamine. In contrast, the overdependence by the heart on fatty acid metabolism is increased during dobutamine. Further studies will be required to determine the extent to which these metabolic alterations may contribute to the cardiac abnormalities typically observed in diabetes mellitus, making these alterations potential targets for metabolic therapies in this disease.

Acknowledgment

The authors have indicated they have no financial conflicts of interest.

References

1. Avogaro A, Nosadini R, Doria A, Fioretto P, Velussi M, Vigorito C, et al. Myocardial metabolism in insulin-deficient diabetic humans without coronary artery disease. Am J Physiol 1990;258: E606-18.
2. Doria A, Nosadini R, Avogaro A, Fioretto P, Crepaldi G. Myocardial metabolism in type 1 diabetic patients without coronary artery disease. Diabet Med 1991;8 Spec No:S104-7.
3. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. J Am Coll Cardiol 2006; 47:598-604.
4. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;13:785-9.
5. Rodrigues B, Cam MC, McNeill JH. Myocardial substrate metabolism: implications for diabetic cardiomyopathy. J Mol Cell Cardiol 1995;27:169-79.
6. Severson DL. Diabetic cardiomyopathy: Recent evidence from mouse models of type 1 and type 2 diabetes. Can J Physiol Pharmacol 2004;82:813-23.
7. Duncan JG, Fong JL, Medeiros DM, Finck BN, Kelly DP. Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1alpha gene regulatory pathway. Circulation 2007;115:909-17.
8. Finck BN, Han X, Courtois M, Aimond F, Nerbonne JM, Kovacs A, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: Modulation by dietary fat content. Proc Natl Acad Sci U S A 2003;100:1226-31.
9. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest 2002;109:121-30.
10. Monti LD, Lucignani G, Landoni C, Moresco RM, Piatti P, Stefani I, et al. Myocardial glucose uptake evaluated by positron emission tomography and fluorodeoxyglucose during hyperglycemic clamp in IDDM patients. Role of free fatty acid and insulin levels. Diabetes 1995;44:537-42.
11. Voipio-Pulkki LM, Nuutila P, Knuuti MJ, Ruotsalainen U, Haaparanta M, Teras M, et al. Heart and skeletal muscle glucose disposal in type 2 diabetic patients as determined by positron emission tomography. J Nucl Med 1993;34:2064-7.
12. Peterson LR, Soto PF, Herrero P, Schechtman KB, Dence C, Gropler RJ. Sex differences in myocardial oxygen and glucose metabolism. J Nucl Cardiol 2007;14:573-81.
13. de las Fuentes L, Herrero P, Peterson LR, Kelly DP, Gropler RJ, Davila-Roman VG. Myocardial fatty acid metabolism: independent predictor of left ventricular mass in hypertensive heart disease. Hypertension 2003;41:83-7.
14. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation 2004;109:2191-6.
15. Takala TO, Nuutila P, Knuuti J, Luotolahti M, Yki-Jarvinen H. Insulin action on heart and skeletal muscle glucose uptake in weight lifters and endurance athletes. Am J Physiol 1999;276:E706-11.
16. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-23.
17. Young ME. The circadian clock within the heart: Potential influence on myocardial gene expression, metabolism, and function. Am J Physiol Heart Circ Physiol 2006;290:H1-162.
18. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. J Am Coll Cardiol 1989;14:639-52.
19. Bergmann SR, Weinheimer CJ, Markham J, Herrero P. Quantitation of myocardial fatty acid metabolism using positron emission tomography. J Nucl Med 1996;37:1723-30.
20. Buck A, Wolpers HG, Hutchins GD, Savas V, Mangner TJ, Nguyen N, et al. Effect of carbon-11-acetate recirculation on estimates of myocardial oxygen consumption by PET. J Nucl Med 1991;32:1950-7.
21. Herrero P, Kisrieva-Ware Z, Dence CS, Patterson B, Coggan AR, Han DH, et al. PET measurements of myocardial glucose metabolism with 1-^{11}C-glucose and kinetic modeling. J Nucl Med 2007;48:955-64.
22. Herrero P, Weinheimer CJ, Dence C, Oellerich WF, Gropler RJ. Quantification of myocardial glucose utilization by PET and 1-carbon-11-glucose. J Nucl Cardiol 2002;9:5-14.
23. Hall JL, Stanley WC, Lopaschuk GD, Wisneski JA, Pizzurro RD, Hamilton CD, et al. Impaired pyruvate oxidation but normal

glucose uptake in diabetic pig heart during dobutamine-induced work. Am J Physiol 1996;271:H2320-9.
24. Vadlamudi RV, Rodgers RL, McNeill JH. The effect of chronic alloxan- and streptozotocin-induced diabetes on isolated rat heart performance. Can J Physiol Pharmacol 1982;60:902-11.
25. Chatham JC, Gao ZP, Forder JR. Impact of 1 wk of diabetes on the regulation of myocardial carbohydrate and fatty acid oxidation. Am J Physiol 1999;277:E342-51.
26. Chatham JC, Gao ZP, Bonen A, Forder JR. Preferential inhibition of lactate oxidation relative to glucose oxidation in the rat heart following diabetes. Cardiovasc Res 1999;43:96-106.
27. Ungar I, Gilebrt M, Siegel MS, Blain JM, Bing RJ. Studies on myocardial metabolism. IV. Myocardial metabolism in diabetes. Am J Med 1955;18:385-96.
28. Desrois M, Sidell RJ, Gauguier D, King LM, Radda GK, Clarke K. Initial steps of insulin signaling and glucose transport are defective in the type 2 diabetic rat heart. Cardiovasc Res 2004; 61:288-96.
29. Huisamen B, van Zyl M, Keyser A, Lochner A. The effects of insulin and beta-adrenergic stimulation on glucose transport, glut 4 and PKB activation in the myocardium of lean and obese non-insulin dependent diabetes mellitus rats. Mol Cell Biochem 2001; 223:15-25.
30. Lipworth BJ. Clinical pharmacology of beta 3-adrenoceptors. Br J Clin Pharmacol 1996;42:291-300.
31. Goodwin GW, Ahmad F, Doenst T, Taegtmeyer H. Energy provision from glycogen, glucose, and fatty acids on adrenergic stimulation of isolated working rat hearts. Am J Physiol 1998;274:H1239-47.
32. Soto PF, Herrero P, Kates AM, Dence CS, Ehsani AA, Davila-Roman V, et al. Impact of aging on myocardial metabolic response to dobutamine. Am J Physiol Heart Circ Physiol 2003;285:H2158-64.