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

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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 (DMI-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. 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. 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). 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. 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...
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. 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. 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. 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.

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. 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 μg·kg⁻¹·min⁻¹).

**PET Image Acquisition**

PET was used to measure myocardial blood flow (MBF) (in milliliters per gram per minute), myocardial oxygen consumption (MVO₂) (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. During the study, venous blood samples were obtained during each imaging portion of the study (ie, during MBF, MVO₂, 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. 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), MVO₂ (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).