Sex differences in myocardial oxygen and glucose metabolism

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Background. **Both physiologic and pathophysiologic conditions affect the myocardium's substrate use and, consequently, its structure, function, and adaptability. The effect of sex on myocardial oxygen, glucose, and fatty acid metabolism in humans is unknown.**

Methods and Results. **We studied 25 young subjects (13 women and 12 men) using positron emission tomography, quantifying myocardial blood flow, myocardial oxygen consumption (MVO_2), and glucose and fatty acid extraction and metabolism. MVO_2 was higher in women than in men (5.74 ± 1.08 $\mu mol \cdot g^{-1} \cdot min^{-1}$ vs 4.26 ± 0.69 $\mu mol \cdot g^{-1} \cdot min^{-1}$, $P < .005$). Myocardial glucose extraction fraction and utilization were lower in women than in men (0.025 ± 0.019 vs 0.062 ± 0.028 [$P < .001$] and 133 ± 96 $nmol \cdot g^{-1} \cdot min^{-1}$ vs 287 ± 164 $nmol \cdot g^{-1} \cdot min^{-1}$ [$P < .01$], respectively). There were no sex differences in myocardial blood flow, fatty acid metabolism, or plasma glucose, fatty acid, or insulin levels. Female sex was an independent predictor of increased MVO_2 ($P = .01$) and decreased myocardial glucose extraction fraction and utilization ($P < .005$ and $P < .05$, respectively). Insulin sensitivity was an independent predictor of increased myocardial glucose extraction fraction and utilization ($P < .01$ and $P = .01$, respectively).**

Conclusions. **Further studies are necessary to elucidate the mechanisms responsible for sex-associated differences in myocardial metabolism. However, the presence of such differences may provide a partial explanation for the observed sex-related differences in the prevalence and manifestation of a variety of cardiac disorders. (J Nucl Cardiol 2007;14:573-81.)**

Key Words: Sex • myocardial metabolism • glucose • myocardial oxygen consumption

Myocardial metabolism and cardiac function are inextricably linked: the myocardium metabolizes substrates to generate adenosine triphosphate, the hydrolysis of which allows for cardiac function. In the postnatal myocardium, metabolism of fatty acids provides most of the energy required; glucose and, to a lesser degree, lactate, ketones, intracellular triglyceride, and glycogen also provide energy. However, the myocardium may switch its preference away from free fatty acids and toward glucose depending on physiologic or pathophysiologic conditions and substrate availability.[1-5] The myocardium's choice of substrate affects its oxygen consumption and efficiency, as well as the metabolic regulatory signals generated.[6] Thus the heart's ability to switch from using one substrate to another impacts its ability to cope with different conditions. For example, in ischemia β-oxidation of fatty acids is halted and glucose, the more oxygen-efficient substrate, is preferred.[7] Consequently, conditions that detrimentally affect the myocardium's ability to use glucose may adversely alter the myocardium's ability to adapt to ischemia. For example, humans with type 1 diabetes have an increased reliance on fatty acid metabolism, which may detrimentally affect the diabetic myocardium's ability to adapt to ischemia and survive.[4]

There are also data that show that sex affects myocardial metabolism in animal models and skeletal muscle and liver substrates in humans under a variety of conditions.[8-13] Whether sex affects myocardial metabolism in young, fasting humans is not clear;

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however, it is clear that there are sex-related differences in morbidity and mortality rates from various cardiovascular diseases, and given the known link between metabolism and function, it is reasonable to theorize that sex-related differences in myocardial metabolism may be playing a role.[14] Although sex hormone levels and other differences between men and women are potential effectors or confounders of sex-related differences, the purpose of this study was to test the hypothesis that sex itself is related to and affects myocardial substrate metabolism in vivo in humans and, in so doing, to lay the foundation for further investigation of sex-related differences in metabolism.

METHODS

Study subjects

Young, healthy, nonobese, sedentary subjects, 13 premenopausal women and 12 men, aged 20 to 44 years, participated in this prospective study. All subjects completed a comprehensive medical evaluation, including a history, physical examination, electrocardiogram, routine blood tests, an oral glucose tolerance test, lipid profile, and a rest/stress echocardiogram. Those who had impaired fasting glucose levels, glucose tolerance, or diabetes during an oral glucose tolerance test; hypertension; a history of coronary artery or other cardiac disease; a history of smoking cigarettes within the last 12 months; or an abnormal rest/stress echocardiogram were excluded; those who performed routine aerobic exercise for 30 minutes per day or more for more than 2 days per week were excluded from the study to minimize any potential confounding effect of aerobic training on myocardial metabolism, as training has known effects on hemodynamics and cardiac structure. Subjects also underwent dual-energy x-ray absorptiometry by use of a Hologic Discovery QDR No. 70570 system and Hologic software (version 12.4) (Hologic, Bedford, Mass) for body composition measurement. Of the women, 5 were using contraceptive measures (oral agents in 4 and intramuscular agents in 1). Serum progesterone, estradiol, and estrone levels were measured and the last menstrual dates were recorded in all of the women for the determination of cycle phase. No data on any subject have been previously published. All participants signed the written informed consent form, which was approved by the Institutional Review Board, the General Clinical Research Center, and the Radioactive Drug Research Committee at the Washington University School of Medicine, St Louis, Mo.

Experimental procedure

Subjects fasted overnight (12 hours) and were studied the following morning (to avoid possible confounding effects of interindividual differences in postprandial absorption rates). On the morning of the study, an 18- or 20-gauge catheter was inserted into an antecubital vein for radiopharmaceutical infusion. All subjects underwent positron emission tomography (PET) imaging at 8:00 AM to avoid circadian variations in hormone levels, myocardial metabolism, and function.[15] All studies were performed on a conventional commercially available tomograph (Siemens ECAT 962 HR+; Siemens Medical Systems, Malvern, PA). Blood pressure and heart rate were obtained throughout the study. PET was used to measure myocardial blood flow with oxygen-15-water, myocardial oxygen consumption (MVO_2) with 1–carbon 11–acetate, myocardial glucose extraction fraction and utilization with 1–C-11–glucose, and fatty acid extraction fraction, utilization, and oxidation with 1–C-11–palmitate. During the study, venous blood samples were obtained at predetermined intervals to measure levels of plasma substrates (glucose, fatty acids, and lactate) and insulin levels, as well as radiolabeled metabolites, which are required for compartmental modeling of the kinetics of the metabolic tracers.[16-18] Plasma substrate levels were determined from venous rather than arterial samples; however, because our subjects were in the resting state, differences in substrate concentrations between the 2 sample sites would be expected to be negligible. Radiolabeled metabolites were also determined by use of venous rather than arterial samples; we have used venous C-11–labeled carbon dioxide based on the results of previous studies and have shown that, under resting conditions, the differences in arterial and mixed venous C-11–labeled carbon dioxide levels were minimal and in post hoc analyses did not contribute to a significant difference in MVO_2 or myocardial fatty acid or glucose utilization.[16-18]

Image analyses

PET image analysis for the quantification of myocardial blood flow (in milliliters per gram per minute), MVO_2 (in micromoles per gram per minute), and glucose and fatty acid metabolism was performed by use of well-validated techniques.[16-19] In brief, the myocardial glucose or fatty acid extraction fraction is the fraction of glucose or fatty acid extracted by the myocardium. Myocardial glucose or fatty acid utilization (in nanomoles per gram per minute) represents the total amount of glucose or fatty acid used per minute by the myocardium. Myocardial fatty acid oxidation (in nanomoles per gram per minute) represents the total amount of fatty