Impact of hormone replacement on myocardial fatty acid metabolism: Potential role of estrogen

Pilar Herrero, MS,[a] Pablo F. Soto, MD,[b] Carmen S. Dence, MS,[a] Zulfia Kisrieva-Ware, PhD,[a] Deborah A. Delano, RN, MHS,[a] Linda R. Peterson, MD,[b] and Robert J. Gropler, MD[a,b]

Background. **Estrogen increases fatty acid utilization and oxidation and may decrease glucose use in human skeletal muscle, whereas these effects are attenuated by progesterone. Whether these ovarian hormones exhibit similar effects on myocardial metabolism is unknown.**

Methods and Results. **Myocardial blood flow and oxygen consumption, as well as glucose and fatty acid metabolism, were examined retrospectively by use of positron emission tomography in 24 postmenopausal women receiving estrogen (n = 7), estrogen plus progesterone (n = 8), or no hormone replacement (n = 9) and in 22 age-matched men. Myocardial blood flow was higher in women regardless of hormone replacement status. Myocardial oxygen consumption was higher in women taking estrogen only when compared with men (7.3 ± 1.6 $\mu mol \cdot g^{-1} \cdot min^{-1}$ vs 4.6 ± 1.2 $\mu mol \cdot g^{-1} \cdot min^{-1}$, $P < .001$). Glucose utilization was not affected by gender or hormone replacement. Whereas fatty acid levels and the degree of myocardial fatty acid uptake were not distinguished by gender or hormone use, myocardial fatty acid utilization was higher in women taking estrogen when compared with men (259 ± 68 $nmol \cdot g^{-1} \cdot min^{-1}$ vs 176 ± 50 $nmol \cdot g^{-1} \cdot min^{-1}$, $P = .01$) and trended higher when compared with women not receiving hormonal therapy (185 ± 46 $nmol \cdot g^{-1} \cdot min^{-1}$, $P = .07$) but was not different from that of women taking estrogen plus progesterone (205 ± 58 $nmol \cdot g^{-1} \cdot min^{-1}$, $P =$ not significant).**

Conclusions. **In postmenopausal women, estrogen use is associated with increased myocardial fatty acid utilization. Thus, when the cardiac effects of hormone replacement therapy are being assessed, alterations in myocardial substrate metabolism should be considered. (J Nucl Cardiol 2005;12:574-81.)**

Key Words: Hormone replacement therapy • myocardial fatty acid • estrogen • progesterone

It is becoming increasingly apparent that the ovarian hormones—particularly estrogen and, to a lesser extent, progesterone—play a role in regulating cellular substrate metabolism. For example, in rats subjected to exercise, estrogen supplementation stimulates lipolysis, increasing fatty acid availability.[1] Conversely, estrogen decreases the rate of glucose oxidation and gluconeogenesis, as well as the rate of glycogenolysis, in skeletal muscle and in the liver.[2-5] These metabolic effects are attenuated by the concomitant administration of progesterone.[2,6] Estrogen increases fatty acid oxidation in skeletal muscle, particularly during exercise.[2] In ovariectomized female rats, estrogen replacement increases the activity of carnitine palmitoyltransferase I and β-3-hydroxylacyl coenzyme A dehydrogenase, key enzymes in the oxidation of fatty acids, to levels comparable to those observed in non-ovariectomized animals. Conversely, the addition of progesterone attenuates the effects of estrogen on the activity of these enzymes.[7]

The effect of ovarian hormones on myocardial substrate metabolism is less clear. In animal studies estrogen-signaling pathways have been implicated in the control of myocardial lipid metabolism.[8] Moreover, in isolated perfused hearts from ovariectomized rats chronically treated with estrogen, fatty acid oxidation is higher after ischemia compared with hearts from either ovariectomized controls or age-matched non-ovariectomized rats. However, under normoxic conditions, the rates of fatty acid oxidation were no different between the 3

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

This work was supported in part by National Institutes of Health grants R01-AG15466, P01-HL13851, M01-RR00036, and K23-HL077179, as well as the Robert Wood Johnson Foundation's Amos Medical Faculty Development Award (No. 051893).

Received for publication May 12, 2004; final revision accepted May 17, 2005.

Reprint requests: Robert J. Gropler, MD, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, 510 S Kingshighway Blvd, St Louis, MO 63110; *groplerr@mir.wustl.edu.*

1071-3581/$30.00

doi:10.1016/j.nuclcard.2005.05.009

groups. In addition, the impact of progesterone was not assessed.[9] Furthermore, the effect of these hormones on myocardial substrate metabolism in human beings is unknown. We hypothesized that estrogen will increase myocardial fatty acid metabolism and decrease glucose utilization and that progesterone will attenuate this effect. Accordingly, this study was performed to determine whether estrogen and progesterone alter myocardial substrate metabolism in human beings. Measurements of myocardial fatty acid and glucose metabolism performed with positron emission tomography (PET) were compared between postmenopausal women receiving hormone replacement therapy (HRT) containing either estrogen alone or estrogen plus progesterone, postmenopausal women not receiving HRT, and older men.

METHODS

Study Population

PET imaging data and ovarian hormone use were examined retrospectively in 52 older people who had previously undergone assessment of myocardial glucose or fatty acid metabolism as part of 3 studies of healthy aging conducted at the Mallinckrodt Institute of Radiology, St Louis, Mo. Data from some of these individuals have been published previously.[10-12] Exclusion criteria for these studies were identical and included (1) personal or family history of coronary artery disease, (2) active or recent smoking history, (3) hypertension (average systolic blood pressure >160 mm Hg or average diastolic blood pressure >90 mm Hg), (4) hypercholesterolemia (total cholesterol >260 mg/dL), (5) glucose intolerance, or (6) other systemic illness. All subjects had previously undergone a screening physical examination and rest-exercise echocardiography. Metabolic determinations were performed while fasting in only 49 of these subjects. One was subsequently determined to have hypertension, and another had left ventricular hypertrophy, and they were excluded from the analysis. Also excluded was a woman taking a vaginal estrogen preparation. The remaining 46 older volunteers (aged 60-75 years) consisted of 22 men, 9 women not receiving hormone replacement, 7 women taking estrogen alone, and 8 women taking combined estrogen and progestin. Each study protocol was approved by the Human Studies and Radioactive Drug Research Committees at the Washington University School of Medicine, St Louis, Mo, and written informed consent was obtained from all volunteers before enrollment.

Imaging Protocol

All studies were performed on conventional commercially available tomographs (Siemens ECAT EXACT; Siemens Medical Systems, Iselin, NJ). After an overnight fast, all 46 volunteers underwent PET imaging to measure myocardial blood flow (MBF), myocardial oxygen consumption (MVO_2), and myocardial fatty acid utilization (MFAU), as well as the portion of the fatty acid utilized that undergoes oxidation (MFAO). Because of technical difficulties with radiotracer production, 1 volunteer did not complete MFAU and MFAO determination. In addition, 42 of 46 individuals underwent PET imaging to measure myocardial glucose utilization (MGU). Throughout each imaging study, all volunteers were monitored on telemetry and blood pressures were obtained at 5-minute intervals. The rate-pressure product (RPP), calculated as the product of systolic blood pressure and heart rate, was used as an index of myocardial work and oxygen demand. First, a 2-minute positioning scan was obtained with a rotating germanium 68/gallium 68 sector source and reconstructed to verify proper positioning on the gantry. After completion of the positioning scan, a 15-minute transmission scan was performed for generation of attenuation correction factors used in emission image reconstruction. To measure MBF, an intravenous bolus of 14.8 MBq/kg (0.40 mCi/kg) (up to 925 MBq [25 mCi]) oxygen 15 water was administered, followed by the immediate collection of a 300-second dynamic scan. To measure MVO_2, an intravenous bolus of up to 11.1 MBq/kg (0.30 mCi/kg) carbon 11 acetate was given, followed by a 30-minute dynamic data collection scan for measurement of C-11 acetate myocardial kinetics. All C-11 tracers were labeled in the 1 position. Volunteers were then removed from the tomograph to allow sufficient time for the decay of C-11 acetate (70 minutes). To measure MGU, an intravenous bolus of up to 11.1 MBq/kg (0.30 mCi/kg) C-11 glucose was then administered, followed by 60 minutes of dynamic data collection for measurement of C-11 glucose myocardial kinetics. After sufficient time was again allowed for decay, MFAU and MFAO were determined by use of an intravenous bolus of up to 11.1 MBq/kg (0.30 mCi/kg) C-11 palmitate, followed by a 30-minute dynamic data collection scan for measurement of C-11 palmitate myocardial kinetics. Venous blood samples were obtained at the midpoint of each scan to measure plasma substrates. Plasma samples were also collected every 5, 10, or 20 minutes during PET imaging of the C-11 metabolic tracers to correct blood time-activity curves for the presence of C-11 tracer metabolites. Blood C-11 activity during C-11 acetate and C-11 palmitate imaging was corrected for the presence of $^{11}CO_2$, and blood C-11 activity during C-11 glucose