Exercise training impacts the myocardial metabolism of older individuals in a gender-specific manner

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Soto PF, Herrera P, Schechtman KB, Waggoner AD, Baumstark JM, Ehsani AA, Gropler RJ. Exercise training impacts the myocardial metabolism of older individuals in a gender-specific manner. Am J Physiol Heart Circ Physiol 295: H842–H850, 2008; doi:10.1152/ajpheart.91426.2007.—Aging is associated with decreased aerobic capacity, cardiac function, and insulin sensitivity as well as alterations in myocardial substrate metabolism. Endurance exercise training (EET) improves cardiac function in a gender-specific manner, and EET has been shown to improve whole body glucose tolerance, but its effects on myocardial metabolism are unclear. Accordingly, we studied the effect of EET on myocardial substrate metabolism in older men and women. Twelve healthy older individuals (age: 60–75 yr; 6 men and 6 women) underwent PET with [15O]water, [11C]acetate, [11C]glucose, and [11C]palmitate for the assessment of myocardial blood flow (MBF), myocardial O2 consumption (MVO2), myocardial glucose utilization (MGU), and myocardial fatty acid utilization (MFAU), respectively, at rest and during dobutamine infusion (10 μg·kg−1·min−1). Measurements were repeated after 11 mo of EET. Maximal O2 uptake (V̇O2max) increased (P = 0.005) after EET. MBF was unaffected by training, as was resting MVO2; however, posttraining dobutamine MVO2 was significantly higher (P = 0.05), as was MGU (P < 0.04). Although overall dobutamine MFAU was unchanged, posttraining dobutamine MFAU increased in women (P = 0.01) but decreased in men (P = 0.03). Thus, EET in older individuals improves the catecholamine response of myocardial glucose metabolism. Moreover, gender differences exist in the myocardial fatty acid metabolic response to training. These findings suggest a role for altered myocardial substrate metabolism in modulating the cardiovascular benefits of EET in older individuals.

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Although physiological LV hypertrophy (LVH) and an enhanced response to catecholamines have been implicated, the mechanisms responsible for increases in cardiac function in response to EET have been incompletely defined (47). An increasing body of evidence suggests that cardiac metabolism may play an important role in mediating these functional changes. Fatty acid metabolism is downregulated in both the aging heart and LVH, with an increased reliance on cardiac glucose metabolism (11, 30). Moreover, aging is associated with an impaired ability for the heart to increase glucose metabolism in response to catecholamine stress (44). Aging is also associated with a decline in whole body insulin sensitivity, primarily related to increased abdominal adiposity (31). Although exercise training has been shown to have beneficial effects on whole body glucose tolerance and insulin action (29), even among older individuals (16), the effect of exercise training on myocardial metabolism has not been previously described. We hypothesized that EET improves myocardial glucose and fatty acid metabolism in a gender-specific manner.

METHODS

Study population. The study population consisted of 12 healthy, nonobese, older, sedentary individuals (6 men and 6 women) of 60–75 yr in age recruited specifically for this study. All volunteers completed a comprehensive screening medical evaluation, including a medical history, physical examination, electrocardiogram, complete lipid profile, and exercise stress echocardiography for the detection of cardiac abnormalities. Exclusion criteria included an abnormal rest or exercise echocardiogram, elevated fasting glucose (>100 mg/dl), impaired glucose tolerance, diabetes, hypertension, a history of coronary artery or other cardiac disease, a history of smoking within the last 12 mo, or routine aerobic exercise of ≥30 min/day for >2 days/wk. Baseline (pretraining) data from these individuals have been previously published (21, 30, 44). Written informed consent was obtained from all volunteers before participation in this study, which complied with the Declaration of Helsinki and was approved by the Institutional Review Board and General Clinical Research Center of Washington University School of Medicine.

Experimental procedures and cardiac PET imaging. All volunteers fasted overnight for at least 12 h before each PET scan. All PET scans were performed starting at 8:00 AM to avoid circadian variations in myocardial metabolism and function (54). Quantification of myocardial blood flow (MBF), myocardial O2 consumption (MVO2), myocardial glucose extraction fraction (MGEF), and myocardial glucose utilization (MGU) as well as myocardial fatty acid extraction fraction (MFAEF), myocardial fatty acid utilization (MFAU), the oxidative

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component of myocardial fatty acid metabolism (MFAO), and %MFAO were obtained by PET and [15O]water (up to 28 mCi), [1-13C]acetate (up to 21 mCi), [1-13C]glucose (up to 21 mCi), and [1-13C]palmitate (up to 21 mCi), respectively, using well-validated techniques, as previously reported (3–5, 22). Fractional myocardial glucose uptake (MGUp) and fatty acid uptake (MFAUp) (both in \( \text{mmol} \cdot \text{g}^{-1} \cdot \text{min}^{-1} \)) represent the fraction of glucose and free fatty acids (FFA), respectively, extracted by the heart after correction for changes in MFB; these parameters quantify the intrinsic ability of the heart to extract substrate and were calculated as follows:

\[
\text{MGUp} = \frac{\text{MBF} \times \text{MGEF}}{1}
\]

\[
\text{MFAUp} = \frac{\text{MBF} \times \text{MFAEF}}{2}
\]

where MGU and MFAU (both in \( \text{mmol} \cdot \text{g}^{-1} \cdot \text{min}^{-1} \)) represent the total utilization of extracted glucose and FFA, respectively, taking into account substrate levels in the peripheral circulation. %MFAO represents the fraction of extracted fatty acid oxidized and was calculated as %MFAO = MFAO/MFAU \times 100.

To determine the metabolic response to low-level catecholamine stress, volunteers returned for repeat cardiac PET imaging on a separate day. At that time, an identical imaging protocol was performed during continuous intravenous infusion of low-dose dobutamine (10 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) begun 15 min before each PET scan. These procedures were well tolerated by all participants.

**Training program.** Participants first completed 8 wk of daily stretching and flexibility exercises to prepare them for the EET program. After completion of the flexibility exercises, they underwent baseline VO2max testing with a previously described protocol (15). The EET program consisted of walking, running, or cycling exercises 4–5 days/wk for \( \sim \)1 h/session for 11 mo. Exercise intensity was measured with radio telemetry. The initial intensity of the exercise was adjusted to require 60–70% of the participant’s VO2max for the first 3 mo. Thereafter, intensity was increased progressively to 70–80% of VO2max supplemented by additional brief intervals of intense exercise requiring 90–100% of VO2max two or three times per week. VO2max was measured at 3-mo intervals to maintain training intensity relative to the current VO2max. After completion of the training regimen, volunteers returned for repeat rest and dobutamine PET imaging for the determination of MFB, MVO2, and myocardial glucose and fatty acid metabolism. In one female volunteer, posttraining dobutamine PET imaging for the assessment of fatty acid metabolism was unable to be performed due to technical reasons.

**Echocardiography.** All volunteers underwent two-dimensional and Doppler echocardiographic examination with a Sequoia-C256 (Acuson-Siemens, Mountain View, CA) under resting conditions both before and after EET. The echocardiographic examinations and analysis were performed by a single observer (A. D. Waggoner) in all cases. LV ejection fraction was calculated from end-diastolic and end-systolic volumes determined by the modified Simpson’s method. LV mass was determined by the area-length method and indexed to body surface area to calculate the LV mass index, according to the recommendations of American Society of Echocardiography (41).

**Plasma substrate and insulin analyses.** Plasma glucose concentrations (in mg/dl) were determined by the Cobas Mira analyzer (Roche Diagnostics, Indianapolis, IN). FFA concentrations were measured by an enzymatic colorimetric method (NEFA C kit, WAKO Chemicals, Richmond, VA). Lactate was measured with a photometry kit (Sigma Chemicals, St. Louis, MO). Insulin was measured by radioimmunoassay (Linco Research, St. Charles, MO).

**Statistical analysis.** Statistical calculations were performed by SAS version 8.2. Data are means ± SD. Gender differences in baseline parameters were evaluated by unpaired t-tests. Treatment effects of dobutamine and exercise training were determined by two-way ANOVA with repeated measurements. Gender differences in the dobutamine effect and the training effect on myocardial fatty acid metabolism parameters were determined separately by two-way ANOVA. A \( P \) value of <0.05 was considered statistically significant.

**RESULTS**

**Baseline characteristics.** Baseline characteristics of the subjects (6 men and 6 women) are shown in Table 1. No differences were found between men and women regarding age, total cholesterol, LDL, or triglyceride levels. Baseline VO2max values were within 1 SD of expected values for sedentary individuals of comparable age and gender (25). The mean body mass index (BMI) was lower and mean HDL level was higher in women. Volunteers exercised an average of 3.1 days/wk (range: 2.1–4.0 days/wk) for 44 wk (range: 42–44 wk) at 78% of the maximal heart rate (range: 59–94%).

**Impact of EET on hemodynamics, VO2max, BMI, adiposity, LV structure and function, MFB, and MVO2.** The effects of training and dobutamine infusion are shown in Table 2. As expected, systolic blood pressure, heart rate, and the rate-pressure product increased and diastolic blood pressure decreased with dobutamine infusion. Hemodynamic parameters, both at baseline and during dobutamine infusion, were unchanged with EET. VO2max increased after training, as did VO2max normalized to body weight. BMI did not change with EET. Absolute LV mass, LV mass index, and LV ejection fraction were unchanged after training. Of note, there were no gender-specific differences in the response to EET for any of these parameters (data not shown).

As shown in Table 2, MVO2 increased in response to dobutamine both before and after training. Compared with pretraining values, resting MVO2 was unchanged, but dobutamine MVO2 increased by 19%, indicating a training effect. MBF also increased with dobutamine administration both before and after training, but neither rest nor dobutamine values were affected by exercise training. MBF was consistently higher in women, but no gender differences were found in the effect of training or dobutamine on MBF (Table 3) or MVO2 (data not shown).

**Effects of EET on plasma substrate levels and insulin.** Figure 1 shows plasma substrate and insulin levels. Glucose levels were minimally lowered with dobutamine before training, and no dobutamine effect was seen after training; furthermore, no training effect was detectable. Both FFA and insulin levels increased with dobutamine before and after training with no training effect observed. Before training, lactate levels were unaffected by dobutamine but then trended lower with dobutamine after training (Fig. 1). No gender differences were found.

### Table 1. Baseline parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>69±2.5</td>
<td>70±2.5</td>
<td>68±2.6</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±3</td>
<td>27±2</td>
<td>23±3</td>
<td>0.02</td>
</tr>
<tr>
<td>VO2max, l/min</td>
<td>23±3</td>
<td>24±2</td>
<td>22±2</td>
<td>0.24</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>206±35</td>
<td>196±35</td>
<td>216±34</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>128±31</td>
<td>129±31</td>
<td>127±33</td>
<td>0.91</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>53±14</td>
<td>44±10</td>
<td>63±12</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>124±45</td>
<td>116±35</td>
<td>131±56</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n \), numbers of volunteers. BMI, body mass index; VO2max, maximal \( \text{O}_2 \) uptake.
in the effect of training or dobutamine on glucose, lactate, or insulin levels (data not shown).

Effect of EET on myocardial glucose metabolism. Before training, rest and dobutamine MGUp were similar (Fig. 2). Compared with pretraining values, posttraining rest MGUp was unchanged, but dobutamine MGUp was increased ($P = 0.03$). Similarly, dobutamine did not induce any significant change in MGU either before or after training; compared with pretraining values, posttraining rest MGU was unchanged, but dobutamine MGU was increased ($P = 0.04$). No gender differences were found in the effect of training or dobutamine on myocardial glucose metabolism (data not shown).

Effect of EET on myocardial fatty acid metabolism. Dobutamine induced no changes in fatty acid uptake compared with rest conditions either before or after training (Fig. 3). However, because of the catecholamine-induced increase in serum FFA levels, MFAU increased. This increase was similar before and after EET. MFAU demonstrated a similar pattern of response to dobutamine, both before and after training. Before training, %MFAU remained unchanged with dobutamine. After EET, dobutamine induced a decline in %MFAU. Moreover, dobutamine %MFAO posttraining was lower compared with pretraining values, suggesting a training effect toward reduced percentage of fatty acid oxidation with dobutamine.

Effects of gender on myocardial fatty acid metabolism. Table 3 shows gender-specific data for parameters of myocardial fatty acid metabolism as well as gender differences by two-way ANOVA in both the response to dobutamine and to EET. Before training, men exhibited a more pronounced MFAU and MFAO response to dobutamine primarily as a result of an augmented response of serum FFA levels. A gender difference in the dobutamine response also was seen after training; however, it was the reverse of what was seen at baseline. Men now had a diminished MFAU and MFAO response to dobutamine, primarily due to a diminished response in FFA levels. For the most part, no gender differences were found in the training effect on resting values of fatty acid metabolism, although a trend toward a differential EET response of resting fatty acid uptake was seen; absolute values of fatty acid uptake increased in men and decreased in women (gender difference in training effect: $P = 0.06$; Table 3). Interestingly, although no gender differences were seen in the training effect of resting FFA levels, a posttraining gender difference developed ($P = 0.05$) that mirror gender differences in posttraining MFAU and MFAO ($P < 0.01$ for both; Table 3). Finally, a gender difference in the training effect on dobutamine MFAU and MFAO was seen that was not evident in the pooled data shown in Fig. 3; training induced an overall decline in these parameters in men, whereas they were increased in women. These changes corresponded to changes in FFA levels.

DISCUSSION

We evaluated the effect of EET on myocardial substrate metabolism in healthy, older individuals. The results demonstrate that after 11 mo of EET, $V_{O2max}$ increased 17% in tandem with $I$ a 19% increase in $MV_{O2}$ and $2$ a 50% increase in overall MGU at a fixed dose of dobutamine. These increases were not driven by changes in serum glucose or insulin levels, suggesting a training-induced increase in intrinsic MGU. Moreover, a gender difference was detected in the cardiac metabolic response to exercise training. In women, MFAU and MFAO levels during dobutamine were augmented by training, whereas in men dobutamine MFAU and MFAO declined after EET. These differences in myocardial fatty acid metabolism reflect primarily differential responses in plasma fatty acid levels to dobutamine before and after exercise training. Gender differences were not seen in the myocardial glucose metabolism response to training.

Myocardial glucose metabolism. The aging heart experiences a decline in MFAU and MFAO with an increase in the relative contribution of MGU (30). In addition, older individuals are not able to increase MGU in response to catecholamine stress (44). In the present investigation, post-EET rates of dobutamine MGU increased. Moreover, they approached levels seen in younger individuals, both in terms of absolute value (221 ± 104 vs. 209 ± 78 nmol·g⁻¹·min⁻¹) and response to...
Table 3. Gender-specific effects of exercise training on myocardial fatty acid metabolism

<table>
<thead>
<tr>
<th></th>
<th>Before Training</th>
<th>After Training</th>
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<tbody>
<tr>
<td></td>
<td>Dobutamine</td>
<td>Dobutamine</td>
</tr>
<tr>
<td></td>
<td>Rest</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Free fatty acid levels, nmol/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>552±28</td>
<td>1,324±150 (p = 0.01)</td>
</tr>
<tr>
<td>Women</td>
<td>599±139</td>
<td>1,002±194</td>
</tr>
<tr>
<td>MBF, ml·g(^{-1})·min(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.91±0.23</td>
<td>1.57±0.35 (p = 0.04)</td>
</tr>
<tr>
<td>Women</td>
<td>1.25±0.34</td>
<td>2.22±0.57</td>
</tr>
<tr>
<td>MFAU, ml·g(^{-1})·min(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.31±0.09</td>
<td>0.35±0.07</td>
</tr>
<tr>
<td>Women</td>
<td>0.38±0.08</td>
<td>0.31±0.11</td>
</tr>
<tr>
<td>MFAO, nmol·g(^{-1})·min(^{-1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>173±76</td>
<td>462±121 (p = 0.01)</td>
</tr>
<tr>
<td>Women</td>
<td>226±68</td>
<td>297±66</td>
</tr>
<tr>
<td>%MFAO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>79±22</td>
<td>94±9</td>
</tr>
<tr>
<td>Women</td>
<td>86±13</td>
<td>86±19</td>
</tr>
</tbody>
</table>

Values are means ± SD and represent metabolic parameters measured before and after 44 wk of endurance exercise training both at rest and during an intravenous infusion of 10 µg·kg\(^{-1}\)·min\(^{-1}\) dobutamine.

MFAU, myocardial fatty acid uptake; MFAU, myocardial fatty acid utilization; MFAO, myocardial fatty acid oxidation; NS, not significant. \(p < 0.01\), \(p = 0.06\), \(p < 0.05\), \(p = 0.09\), and \(p = 0.08\) vs. corresponding rest values.
dobutamine (+50 vs. +60 nmol·g⁻¹·min⁻¹) (44). These results suggest that exercise in older individuals may reverse some of the age-related changes in cardiac metabolism.

With aging comes a decline in the insulin sensitivity of skeletal muscle that improves with exercise training (13, 26). One mechanism that mediates this effect is an increase in the concentration of insulin-sensitive glucose transporter 4 (GLUT4) (7). Exercise training in patients with dilated cardiomyopathy has been shown to improve insulin-stimulated MGUp, as measured with [¹⁸F]fluorodeoxyglucose (50). Although quantitative measures of whole body insulin sensitivity were not part of the present study, the lack of change in glucose and insulin levels with training, in the setting of a higher dobutamine MGU, is consistent with a training-induced improvement in myocardial insulin sensitivity. Indirect effects of improved insulin sensitivity also can be seen in the pattern of myocardial fatty acid metabolism. %MFAO is increased with the relative insulin resistance of Type 1 diabetes mellitus (20); in the present study, EET induced a decline in dobutamine %MFAO compared with pretraining values, suggesting an improved insulin effect. The lack of an increase in MGU at rest post-EET may simply reflect the difficulty in detecting differences in MGU when it is at a low level, such as occurs under the fasting conditions used in this study. However, this absence of a similar increase in rest MGU suggests that the impact of EET on metabolism may be primarily due to improved myocardial metabolic sensitivity to dobutamine stimulation.

**Myocardial fatty acid metabolism: gender differences at rest.** Before training, women showed a trend toward a higher resting MBF (P = 0.07), consistent with previously published findings (21). We have previously demonstrated that hormone replacement therapy containing solely estrogen in postmenopausal women increases MFAU and MFAO, most likely as a combined effect on both increasing serum FFA levels (peripheral effect) and myocardial fatty acid extraction (central effect) (21). However, the addition of progesterone counterbalanced this effect. Although half of the women in the present study were on hormone replacement therapy, baseline resting MFAU and MFAO were not significantly different compared with men.

**Gender differences during dobutamine infusion.** At baseline, male subjects increased FFA levels with inotropic stimulation to a greater extent than did women, resulting in higher MFAO and MFAU. Release of FFA from adipose tissue is regulated by the sympathetic nervous system, and numerous examples exist of gender differences in sympathetic nervous system activity (51). In young women, the catecholamine response to stress is lower compared with men, but women have a similar or greater rate of lipolysis, suggesting they may be more sensitive to the lipolytic action of catecholamines (24). Thus,
with inotropic stimulation, women should have higher FFA levels than men, assuming similar rates of clearance. However, rest and exercise studies of whole-body metabolism in an older population have demonstrated no gender differences in plasma FFA levels either at rest or with exercise. Nevertheless, overall rates of fat oxidation are higher in older men at rest, although with exercise these gender differences disappear (51). Potential explanations for our observed gender dimorphism at baseline may include gender differences in rates of clearance or catecholamine sensitivity, some of which may manifest only with advanced age or with sedentary status.

Gender difference and exercise training. Evidence from experimental models has shown that exercise training improves the age-related decline in cardiac fatty acid metabolic capacity (10, 36, 39, 49). This mechanism is potentially an attenuation of the aging-induced decrease of mRNA and protein expression of peroxisome proliferator-activated receptor (PPAR)-α (27). However, these studies were primarily conducted in male animals. In humans, as little as 12–16 wk of EET increases fat oxidation from endogenous sources in skeletal muscle of older adults (37, 43). No gender differences were described in these investigations.

The mechanism responsible for the observed gender differences in the FFA response to dobutamine after training is unclear. Catecholamine-induced increases in FFA levels are mediated through stimulation of adipose tissue β-adrenergic receptors, resulting in lipolysis; thus, the observed gender dimorphism could be attributable to sex-specific changes in tissue sensitivity to β-adrenergic stimulation with training. In a cross-sectional study of adipocytes in younger individuals, endurance training led to better lipid mobilization, an effect that was greater in women than in men (8). The gender-specific FFA levels in the present study are consistent with this mechanism. Recent studies have indicated that both acute and chronic reductions in nitric oxide (NO) bioavailability can alter myocardial substrate consumption (9, 38); moreover, numerous age and gender effects on NO availability have been shown. In studies of vasomotor kinetics, advancing age produces a sex difference that is partially explained by a greater reduction in NO availability in males (1). Exercise training has been shown to increase plasma NO in humans (34). Moreover, adaptations of vascular reactivity in response to EET have been shown to greater in females than in males, though these results vary by anatomic location (33). A gender-specific improvement of cardiac NO availability in response to EET has yet to be demonstrated, but such a mechanism could explain the findings of the present study.

Gender differences in levels of certain adipokines have been observed both at rest and in response to exercise training. Adiponectin and leptin both increase skeletal muscle fatty acid oxidation by activating AMP-activated protein kinase (53). In a middle-aged insulin-resistant cohort, adiponectin has been shown to be higher in women, but no training effect was seen in either sex (35). Leptin has also been shown to be higher in sedentary women, and EET reduced these levels exclusively in women, but not down to levels observed in age-matched men (23). Neither of these mechanistic explanations alone would explain the present findings. IL-6 has also been shown to mediate skeletal muscle metabolism. IL-6 levels are increased during bouts of acute exercise, increasing fatty acid oxidation by stimulating lipolysis and thus increasing lipid availability (2, 52). While no gender difference in this response has been observed, an observational study (18) in males has suggested that EET may attenuate this response. To our knowledge, gender differences in this training effect on the IL-6 response to exercise have not been investigated. Measurements of circulating adipokine levels were not part of the present study, but a gender-specific response of IL-6 levels to EET could explain the observed sex-specific response in FFA levels, MFAU, and MFAO. The potential role of adipokines, particularly IL-6, in the regulation of myocardial metabolism deserves further study.

Study limitations. Despite the increase in dobutamine MGU after training, estimates from stoichiometric calculations indi-
cate that this increase did not account entirely for the increase in dobutamine \(\text{MV}_2\) post-EET. The overall change in dobutamine \(\text{MV}_2\) after EET was 1.8 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) (Table 2). Using stoichiometry, we can calculate the contribution of fatty acid metabolism to this overall change (\(\Delta \text{MV}_{2\text{PAL}}\)) and estimate the remaining component (\(\Delta \text{MV}_{2\text{nonPAL}}\)) from the following equation:

\[
\Delta \text{MV}_2 = \Delta \text{MV}_{2\text{PAL}} + \Delta \text{MV}_{2\text{nonPAL}}.
\]

As 23 molecules of \(\text{O}_2\) are consumed for each molecule of palmitate, a decline after training in dobutamine MFAO from 364 \(\pm\) 137 to 314 \(\pm\) 136 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) (Fig. 3) represents a change in \(\text{MV}_2\) (\(\Delta \text{MV}_{2\text{PAL}}\)) of \(-0.57 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), that is, the contribution from fatty acids to overall oxidation actually declined. The remaining \(\text{O}_2\) consumption (\(\Delta \text{MV}_{2\text{nonPAL}}\)) is therefore \(+2.37 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), for which we need to account.

As we did not measure the oxidative component of MGU, it is unclear what percentage of MGU taken up is oxidized during dobutamine infusion. Even if we assume a 100% rate of oxidation, as 6 molecules of \(\text{O}_2\) are consumed for each glucose molecule, the contribution of MGU to \(\Delta \text{MV}_2\) is only 0.44 \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), leaving unaccounted the majority of \(\Delta \text{MV}_{2\text{nonPAL}}\). The remaining increase in oxidative metabolism is unlikely to be derived from lactate, as post-training dobutamine lactate levels were actually lower (Fig. 1).

An increase in the recruitment of endogenous substrates such as glycogen has been shown in experimental animals after training (40), but it is unclear whether a similar physiological response is present in humans. As neither lactate metabolism, percent glucose oxidation, nor changes in glycogen and triglyceride metabolism were measured, the conclusions that can be drawn about the relative importance of EET-induced changes in MGU are limited.

Because of the technical limitations to performing cardiac PET during exercise, a continuous dobutamine infusion of 10 \(\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) was used in the present investigation as a surrogate for the stress response of acute exercise; higher doses of dobutamine were not tolerated for the duration of a PET scan. On average, only 61% of the maximal predicted heart rate was achieved; thus, the present findings may represent submaximal exercise physiology. Because of the demanding nature of training protocol our sample size was limited, and neither young nor older untrained control groups were studied. We anticipate that our findings would be similar in a younger cohort, as clinical studies comparing responses to EET in younger and older cohorts have shown similar increases in \(\text{V}O_2\max\), insulin action, and GLUT4 activity (7, 13, 32). EET-induced changes in insulin action can be mediated in part through changes in central adiposity (17); this parameter was not measured, although none of the volunteers was obese. As we did not measure percent body fat, it is possible that there was a gender-specific replacement of adipose tissue with fat-free mass, thus altering adipocyte biology in a sex-specific manner; however, findings from several investigations have suggested that body composition changes in older men and women are similar with EET (6, 42). Finally, our results may not be generalizable to older individuals who are obese, who exhibit significant dyslipidemia or insulin resistance, or who begin at a higher level of fitness, such as masters athletes.

Clinical implications. The observed reversal of the age-related changes in myocardial glucose metabolism suggests a mechanism and further underscores the health benefit of EET in older individuals. Moreover, because glucose is the substrate of choice during periods of ischemia (48), the present results suggest a mechanism by which training may increase the tolerance to myocardial ischemia in older individuals. The present findings may provide a partial explain ation for why men are more prone to develop both physiological (training) and pathological (hypertensive) LVH (12, 46). Both types have been linked to altered myocardial substrate utilization and to variations in PPAR-\(\alpha\) gene expression (22, 28). Moreover, MFAO also is reported to be an independent negative predictor of increased LV mass (11). Thus, the increased delivery of fatty acids in women that occurs as a result of exercise training may prevent physiological myocardial hypertrophy. Combined with the findings of the present study, these data suggest that, at least in the case of physiological LVH, hypertrophy may depend on a permissively low fatty oxidation state predominately seen in men. Although physiological LVH was not induced in the present study, this result is likely attributable to the time frame and intensity of the EET regimen, as volunteers were selected for their sedentary status. Whether clinical interventions that alter myocardial fatty acid metabolism can affect the hypertrophic response to exercise or hypertension remains to be determined.

Conclusions. This study demonstrates that EET in older individuals increases the myocardial glucose response to stress, with no detectible gender difference. However, compared with older men, older women are more likely to improve the myocardial fatty acid metabolic response to \(\beta\)-adrenergic stimulation.

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