Gender differences in glucoregulatory responses to intense exercise

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1McGill Nutrition and Food Science Centre, Royal Victoria Hospital, Montreal, Quebec, Canada H3A 1A1; 2Department of Internal Medicine and Institute of Gerontology, University of Michigan and Veterans Affairs Medical Center, Ann Arbor, Michigan 48109; and 3Departments of Physiology and Medicine, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Marliss, Errol B., Stuart H. Kreisman, Anthony Manzon, Jeffrey B. Halter, Mladen Vranic, and Sharon J. Nessim. Gender differences in glucoregulatory responses to intense exercise. J. Appl. Physiol. 88: 457–466, 2000.—We compared glucoregulatory responses to intense exercise (14 min at 88% maximum O2 uptake) between genders (16 men, 12 women). Analysis of covariance of maximum O2 uptake showed no gender effect, with 82% of variance due to fat-free mass (FFM). Glycemia rose comparably during exercise but was higher in women during recovery (P = 0.02). Glucose production [rate of appearance (Ra); in mg/min] increased markedly in both; stepwise multiple regression and analysis of covariance of Ra (peak and incremental area under the curve) showed no effect of gender, body weight, or FFM. Glucose uptake [rate of disappearance (Rd)] increased less than Ra and slower in women. Rd area under the curve related to FFM (P = 0.01) but not gender or body weight. Norepinephrine and epinephrine responses (13–18-fold) and, consequently, rising glycemia (31, 32, 47, 48). NE and Epi stimulate Ra when infused at rest, and, in IE, both rapidly increase by at least 15-fold and have repeatedly been shown to correlate highly with Rd (26, 31, 32, 47, 48). In contrast, insulin and glucagon changes in IE are of insufficient magnitude and occur with an inappropriate time course to explain the Ra increment (30, 31, 32, 47, 48).

Factors implicated in gender differences in the physiological response to exercise include body size, body composition, muscle characteristics, degree of fitness, hormonal effects, and differences in enzymatic activities and cellular mechanisms. Body fat as a proportion of body mass is higher in women (43). Gender differences in \( \dot{V}O_2 \)max, commonly reported when factored for body weight (BW), disappeared when a regression-based approach correcting for fat-free mass (FFM) was used (53). In women, total muscle cross-sectional area is reportedly 60–85% that of men, and although absolute strength corresponds to this difference, when calculated per FFM it virtually disappears (43). Uncertainty remains as to gender differences in the proportions of type 1 and type 2 muscle fibers (27, 36, 41, 43, 50).

Several exercise-related parameters have been shown to vary with the phase of the menstrual cycle (4), and estrogen has been shown to have an apparent tissue-specific effect on glucose transport (34, 45). Estrogen increased plasma free fatty acid (FFA) and lowered lactate levels, with greater lipid availability and lesser tissue glycogen utilization in exercised rats (24, 25). Estradiol administration to amenorrheic women lowered glucose \( R_a \) and \( R_d \) during moderate-intensity exercise, without an effect on relative muscle glycogen contribution to carbohydrate oxidation or respiratory exchange ratio (RER) (42). Estradiol had no impact on lipid or carbohydrate metabolism during 90-min 60% \( \dot{V}O_2 \)max exercise in men (52).

Most prior studies of gender differences have addressed moderate-intensity exercise, and only two measured glucose turnover. Although methodological con-
We hypothesized that, in IE in women, the glucose Ra body composition. Those in men but quantitatively different because of exercise intensities (11, 16). This gender difference in the sympathetic response is more apparent in isometric exercise (9, 18, 44).

Glucose turnover and its regulation in IE have not been addressed in female subjects to our knowledge. We, therefore, studied glucose turnover and its regulation in fit, young, postabsorptive subjects, 12 women and 16 men, exercising at >80% Vo2max for 14–15 min. We hypothesized that, in IE in women, the glucose Ra response would be catecholamine mediated and that Ra and Rd responses would be qualitatively similar to those in men but quantitatively different because of body composition.

METHODS

Participants were 28 lean, weight-stable, fit individuals, aged 18–35 yr: 12 women and 16 men. All engaged in regular activity, such as running, cycling, swimming, soccer, basketball, or rowing, combined in some with resistance training. Anthropometric and exercise data are presented in Table 1. Screening before the study included medical history, physical examination, hemogram, blood biochemistry, urinalysis, hepatitis B and human immunodeficiency virus serology, electrocardiogram, and chest roentgenogram, to exclude any significant diseases. All were nonsmokers and were taking no medications. In female subjects, a negative pregnancy test was required for participation. Subjects were informed of the purpose of the study and of the possible risks and gave signed consent as prescribed by the institutional human ethics committee. FFM was assessed in all female and in eight of the male subjects by using a four-terminal bioimpedance analyzer (103, RJL Systems, Detroit, MI) by using the procedures and anatomic sites described by Lukaski et al. (29) and their equations for young adults.

Vo2max was determined with breath-by-breath analysis during an incremental workload test (starting at 0 and increasing by 20 W/min) with the subject sitting on an electrically braked cycle ergometer (Collins Metabolic Cart, Collins, Braintree, MA). Oxygen uptake (Vo2, STPD), carbon dioxide output (STPD), ventilation (l/min, BTPS), and RER were calculated and recorded at 30-s intervals. Heart rate was displayed electrocardiographically. Exhaustion was defined by the subject at the time at which he or she was unable to continue cycling, uniformly reported as being due to leg muscle fatigue. On a separate occasion at least 2 days after the Vo2max test, each subject underwent a test without blood sampling at 50% for 30 s, followed by ~80% of the previously established maximum workload. This test was done to familiarize the subjects with the workload protocol, to ensure a uniform 12- to 15-min duration and that they would reach ~85% Vo2max within 6–7 min. The workloads that achieved these and points were then used for the subsequent study involving glucose turnover.

The studies with glucose-turnover measurements began between 0800 and 0900, with subjects in the 12-h overnight fasting state without having undergone any significant exercise in the preceding 24 h. All female subjects were in the follicular phase of their menstrual cycle at the time of the study. A 20-gauge Cathlon IV intravenous cannula (Critikon Canada, Markham, Ontario) was inserted into one antecubital vein for sampling and another into a forearm vein of the other arm for infusion. After 20–30 min, a preinfusion blood sample was drawn. A priming bolus of 22 µCi of HPLC-purified [3-3H]glucose tracer (DuPont-NEN, Billerica, MA) was followed by a constant infusion of 0.22 µCi/min in 0.9% saline for 150 min before, and continued for 120 min after, exercise. Blood was sampled at seven 10-min intervals before time 0 (beginning of exercise) to ensure a steady state of plasma glucose specific activity (SA). Glucose SA was adequately maintained by increasing and decreasing the tracer infusion incrementally during the exercise and the immediate recovery period only; it then returned to the preexercise rate until 120 min of recovery. The goal was to introduce labeled glucose into the circulation at a rate proportional to endogenous Ra, thereby attenuating changes in [3H]glucose SA to <25% during the rapid changes in glucose kinetics (31, 32, 47–49). This ensures the validity of glucose turnover calculations (12). The tracer infusion was increased 7.5-fold (in five 3-min steps: 2, 2.75, 4, 5.4, and 7.5× the initial rate) followed by the same stepwise decreases beginning at 3 min of recovery. Blood samples were drawn on a total of 30 occasions (including at 10-min intervals before exercise, 2-min intervals during exercise and early recovery, and 5- to 20-min intervals in later recovery).

Samples for glucose-turnover measurements were placed into tubes containing heparin and sodium fluoride and were processed as described previously (32). Heparinized plasma was collected with aprotinin (Trasylol; 10,000 kallikrein-inactivating units/ml; FBA, New York, NY) in a volume 1:10 that of the added blood for subsequent insulin-[immunoreactive insulin (IRI)] and glucagon-[immunoreactive glucagon (IRG)] and FFA assays. For catecholamine measurements, blood was added to EGTA- and GSH-containing tubes, and the plasma was frozen at −70°C until assay. One aliquot of

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whole blood was immediately deproteinized in an equal volume of cold 10% (wt/vol) perchloric acid, kept on ice until centrifuged at 4°C, and then frozen at −20°C for later lactate and pyruvate assays.

Glucose was measured by the glucose oxidase method by using a GlucoseAnalyzer II (Beckman, Fullerton, CA). Blood lactate and pyruvate were measured by enzymatic microfluorometric methods previously detailed (47). Plasma IRI was determined by RIA by using an anti-beef insulin antiserum, purified human insulin standard (27.3 µU/ng), 125I-labeled dextran-coated charcoal separation. Pancreatic IRG was measured on plasma by double-antibody RIA (Linco). Plasma FFAs were estimated by the method of Ho as cited previously (31). All assays that were performed on aprotinin-containing plasma were corrected for the plasma dilution introduced by the concurrently measured hematocrit. Plasma NE and Epi concentrations were measured by using a radioenzymatic technique (sensitivity <50 pM) (10). The intra- and interassay coefficients of variation for all assays were <10% for the enzymatic assays, they were <5%. Ra and Rd were calculated from the variable isotope dilution protocols according to the one-compartment model (39), with data systematically smoothed by using the optimized optimal segments program (5). Glucose metabolic clearance rate (MCR) was calculated for each time point by dividing Ra by the plasma glucose concentration.

Baseline characteristics were analyzed by using one-way ANOVA. Certain results are presented with denominators of BW and FFM, as these are conventionally used in this type of study. Plasma glucose, SA, glucose turnover, MCR, lactate, pyruvate, FFA, and hormone results were analyzed separately by ANOVA for repeated measures for different periods (baseline, exercise, and recovery). Intergroup differences found to be significant (taken at $P < 0.05$) were subsequently analyzed by the Student-Newman-Kuels $t$-test. Linear correlations were calculated by using the Pearson correlation coefficient. Individual correlation coefficients were calculated for each individual by using all nine data points at which catecholamines were measured in the stated interval. This correlation coefficient was then treated as a continuous variable on which means and SE were calculated, and intergroup differences were assessed by using one-way ANOVA, ANOVA for repeated measures, and the Student-Newman-Kuels tests. Stepwise multiple-regression analyses were performed for selected variables that were significantly correlated. Analysis of covariance (ANCOVA) was also used to seek effects of gender and body composition, as well as putative regulators, on Ra and Rd. The SAS-STAT software package (SAS Institute, Cary, CA), SPSS-Windows Release 6.0 software package (SPSS, Chicago, IL), Microsoft Excel 5.0 Analysis ToolPak (GreyMatter International, Cambridge, MA), and Primer Biostats (McGraw-Hill, New York, NY) were used. Data are presented as means ± SE.

RESULTS

No untoward effects were experienced during or after any of the tests. Anthropometric measures and study data are presented in Table 1. Female subjects had significantly lower height, total weight, and FFM ($P < 0.05$). They also had lower $V_{O2max}$ and study $V_{O2}$ (the mean of the last one-half of the exercise period) when expressed as total values or per kilogram BW ($P < 0.05$ for all) but not when expressed per kilogram FFM. Percent $V_{O2max}$ reached during the study, exercise duration, and heart rate at exhaustion was not significantly different between groups. Significant individual correlations ($P < 0.003$) were present for the whole group between gender and BW, FFM, $V_{O2max}$, and study $V_{O2}$; between BW and FFM, $V_{O2max}$, and study $V_{O2}$; and between FFM and $V_{O2max}$ and study $V_{O2}$. For $V_{O2max}$, ANCOVA showed no effect of gender, but 82% of the variance was accounted for by FFM ($P < 0.001$, adjusted means 3.88 l/min for men, 3.53 l/min for women). Plasma glucose SA for both groups was at steady state before exercise, rose slightly during exercise, and dropped at 2 min of recovery, followed by a gradual return to a near steady state at or somewhat higher than the highest values reached at exhaustion. None of the exercise- or recovery-related changes in SA within subject groups exceeded 25%. SA was, however, significantly higher (~25%) in women at all time points (data not shown).

Plasma glucose concentrations (Fig. 1A) were not significantly different between groups at baseline (men: 4.87 ± 0.10 mM, women: 4.69 ± 0.11 mM). It rose comparably during exercise ($P < 0.01$) to 6.33 ± 0.29 mM in men and 7.11 ± 0.50 mM in women ($P = 0.05$) at exhaustion but became significantly different at peak values at 4 min of recovery (men: 7.23 ± 0.34 mM, women: 8.66 ± 0.48 mM; $P =$...
0.02). It remained significantly higher in women for the first hour of recovery (P = 0.002) as levels gradually returned to baseline in both genders by 60 min in men but at 80 min in women.

Baseline Ra, correlated individually (P < 0.03) with gender, BW, FFM, VO2max, and study VO2 for the whole group of subjects. Only gender entered the multiple regression (P = 0.009), accounting for 32% of the variance. By repeated-measures ANOVA, during baseline from -50 min to time 0 and during recovery from 25 to 120 min, Ra was significantly higher in the male subjects (P < 0.001) when expressed in milligrams per minute (Fig. 1B) and milligrams per kilogram BW per minute (baseline: 2.13 ± 0.09 vs. 1.84 ± 0.08 mg·kg BW⁻¹·min⁻¹; P = 0.03), whereas when expressed as Ra per FFM it was not different. Ra is presented during exercise in milligrams per minute only (Fig. 1B), as multiple regression and ANCOVA showed no effect of gender, FFM, or BW with the use of either peak Ra or incremental area under the curve (AUC).

During exercise, Ra rose rapidly and markedly in both genders, becoming significantly different from baseline by 2 min (P < 0.002). By repeated-measures ANOVA, there was no difference in Ra between genders during exercise or as it fell rapidly in the early recovery period, reaching baseline by 20 min in both genders (Fig. 1B). Notably, neither peak Rb attained nor incremental AUC of Ra correlated significantly with BW, FFM, VO2max or study VO2 individually.

Rd is presented in milligrams per minute (Fig. 2A) and in milligrams per kilogram FFM per minute (Fig. 2B). Both baseline and incremental AUC of Rd correlated individually with gender, BW, FFM, VO2max, and study VO2 (all P < 0.033), and additionally baseline Rd correlated with baseline Ra (P < 0.0001). Peak Rd correlated only with gender, VO2max, and baseline Ra (P < 0.04) and with borderline significance with FFM (P = 0.0513). By multiple regression, 86% of the variance in baseline Rd was accounted for by FFM, VO2max, study VO2, and baseline Ra (P < 0.0001), whereas the only variable in the equation for AUC was FFM (P = 0.011), accounting for 36% of the variance. Peak Rd was accounted for only by gender (P = 0.004). By ANCOVA, FFM accounted for the gender Rd difference for both peak and AUC. For the incremental AUC of Rd, the mean areas were 2,207 mg for men and 1,241 mg for women and, when adjusted for FFM, were 1,708 and 1,570 mg, respectively. Baseline Rd (Fig. 2, A and B) corresponded to baseline Ra, in that it was significantly higher in men in milligrams per minute (P < 0.001, repeated-measures ANOVA) and Rd per FFM was not different (2.65 ± 0.15 vs. 2.57 ± 0.10 mg·kg FFM⁻¹·min⁻¹). During exercise, the rise in Rd occurred rapidly in men but was delayed in women. Ra in milligrams per minute was significantly greater in men during exercise (P < 0.001), whereas per FFM it was not different during exercise or at its 2-min recovery peak (9.85 ± 0.54 vs. 10.37 ± 0.72 mg·kg FFM⁻¹·min⁻¹). Rd in milligrams per minute fell rapidly until 20 min of recovery, remaining higher in the men (P = 0.005) and then was not different to 50 min of recovery, and, once baseline values were reached at 60–80 min of recovery, the values in men were again higher (P = 0.008). Rd per kilogram FFM per minute was significantly higher in women only from 20 to 60 min of recovery (P = 0.02).

The difference, Rb - Rd, in milligrams per minute (Fig. 3A), which is responsible for the glycemic changes, was the same in both genders at rest but significantly greater during exercise (P = 0.023) and up to 10 min of recovery (P = 0.006, ANOVA) in the female subjects. Thereafter for the rest of recovery it was not different. MCR (Fig. 3B) in milliliters per minute was significantly higher in male subjects at baseline, during exercise, and during the first hour of recovery (P < 0.001 for each period, repeated-measures ANOVA), reflecting greater glucose extraction independent of concentrations of circulating glucose. Baseline MCR correlated with gender, FFM, VO2max, study VO2, and baseline Rd and Rb (P < 0.008), and MCR at exhaustion correlated with all of these, as well as incremental AUC of both Ra and Rd (P < 0.03). By multiple regression, 70.4% of the variance in resting MCR is accounted for by baseline Rd, whereas, at exhaustion, 74.5% is from FFM and peak Ra.

Mean plasma IRI (Fig. 4A) was not different between groups at baseline. During exercise, it decreased slightly but significantly to a nadir at 10 min in both men (12%,
P = 0.02) and women (24%, P = 0.005) and did not differ between groups. During early recovery, IRI underwent a near doubling in both groups (P < 0.001, exercise vs. baseline). However, it remained significantly higher in women (P = 0.03) from 15 to 100 min of recovery, corresponding to their greater hyperglycemia during this interval.

Mean plasma IRG (Fig. 4B) was not different between groups at baseline, during exercise, or during recovery. Within groups during exercise it remained unchanged in men but increased 21% in women (at exhaustion, P = 0.02). The IRG-to-IRI molar ratio (IRG/IRI) (Fig. 4C) did not differ between groups at baseline (although it did correlate with baseline Ra for the whole group, P = 0.040) or during exercise (P = NS). During exercise, it tended upward by 14% in men at exhaustion (P = NS) and rose a maximum of 39% at 10 min in women (P = 0.04). It dropped significantly in both groups early in recovery (P < 0.001 for both) and was significantly lower in women from 8 to 60 min of recovery (P = 0.04), principally because of the higher IRI. The peak IRG/IRI correlated only with the baseline ratios in the whole group (P < 0.0001) and, notably, not with baseline, peak, or AUC of Ra. Peak IRG/IRI did not enter into the equations of the multiple regressions of peak Ra or AUC of Ra or account for them significantly by ANCOVA.

The plasma catecholamine responses are shown in Fig. 5. Neither NE nor Epi values differed significantly between groups at baseline, during exercise, at their peak values, or during the recovery period. Both plasma catecholamines underwent rapid and marked increases in both groups during the exercise period, peaking at exhaustion, then falling rapidly early in the recovery period, and reaching baseline values by minute 40 of recovery. Mean peak values for NE (Fig. 5A) were
33.62 ± 5.07 nM in men (a 16.7-fold increase from baseline) and 33.26 ± 2.92 nM in women (a 16.2-fold increase) and for Epi (Fig. 5B) were 5,322 ± 927 pM in men (a 14.3-fold increase) and 4,603 ± 343 pM in women (a 13.4-fold increase). The mean correlation coefficient (r values calculated individually for each subject) of NE and Epi with Rₘ in each group, from baseline until return of catecholamines to baseline values, at minute 40 of recovery are summarized in Table 2. In all cases, there was a significant relationship of the catecholamines to Rₘ. In the whole group, peak NE (but not Epi) correlated individually with peak Ra and AUC of Ra (P = 0.009) and with peak Epi (P = 0.003). Neither peak NE nor Epi correlated with peak IRG/IRI. By ANCOVA, 48% of the variance of peak Rₘ was accounted for by peak NE (P = 0.0001), but peak IRG/IRI was not in the equation. In contrast, both contributed to explaining 54% of the variance of the AUC of Rₘ (P = 0.0021).

Neither blood lactate (Fig. 6A) nor pyruvate (Fig. 6B) was different between groups at baseline. Both underwent considerable rises during the exercise period, peaking at, or soon after, exhaustion, and slowly returned toward baseline in the recovery period. Whereas

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Correlation coefficients (r) were calculated for each subject over period of increases and decreases in glucose production rate and catecholamines associated with exercise and recovery period. The r value presented is the mean of those for each subject, and the P value is that of subject with highest value (least significant) in each group.
lactate did not differ between groups during exercise or at its peak, pyruvate was significantly higher in men during the exercise period (P = 0.014), although not at the peak concentrations reached. Recovery-period values did not differ between groups for either metabolite. Plasma FFA levels (Fig. 6C) were significantly higher in women at baseline (P = 0.018), during exercise (P = 0.025), and during recovery (P = 0.016). Levels dropped markedly and comparably (NS) during exercise in both men (P = 0.004) and women (P = 0.002), then rose again during the early recovery period, and fell slowly thereafter at a time that IRI was elevated.

RER (Table 3) was not different between groups either at baseline or at any time during the exercise period. Values rose rapidly to ~1.00 early in the exercise period in both groups and remained near this level throughout the period of exercise.

**DISCUSSION**

The primary goal of this study was to investigate the glucoregulatory response to postabsorptive IE in women and compare it with that in men. Despite several noteworthy quantitative differences discussed below, we have shown that women have a similar pattern of glucoregulatory responses. In both, IE is characterized by a brisk and marked outpouring of glucose into the circulation that exceeds glucose utilization during the period of exercise, leading to rising glycemia. In both, changes in IRG, IRI, and IRG/IRI are small and out of phase with changes in R\text{a}, arguing against major glucoregulatory roles for these hormones in IE. In both, NE and Epi responses are brisk and marked, undergoing rises of ~15-fold, and are highly correlated with R\text{a}, which is consistent with being the primary mediators of R\text{a} in IE for both genders. Most of the R\text{a} increment is likely of hepatic origin, but we cannot exclude a renal contribution, which has not been studied in IE.

The comparison of responses between genders is complicated by the difficulty in matching subjects, for reasons listed in the introduction. This generates the need to perform statistical analyses that first establish whether there is a relationship of the end point measured to the proposed denominator in the whole group and then the most appropriate analyses to establish the possible hierarchy of factors in the response (53). The most intriguing gender similarity revealed in this way in the present study is the magnitude of the R\text{a} response during IE. Gender differences in other exercise parameters, such as V\text{O}_{2}\text{max} and strength, are typically minimized when factored per unit of, or adjusted for, FFM (43, 53), a surrogate for muscle mass, the tissue imposing the increment in metabolic demand. However, this “ratio method” of selection of denominator has been shown, particularly for V\text{O}_{2}\text{max}, to yield spurious results, as the correlations do not have zero intercepts (53). (The present V\text{O}_{2}\text{max} data are consistent with these published findings.) For this reason, we were not justified in using ratios for R\text{a} as the data during exercise and early recovery in milligrams per minute were neither different between genders by repeated-measures ANOVA, nor correlated with BW or FFM. The higher baseline R\text{a} in milligrams per minute in men was significantly related only to gender, not to BW, FFM, or V\text{O}_{2} (Fig. 1A). The IE R\text{a} response thus appears to be similar despite variations in the size of the subjects and their different genders. We interpret these results to mean that R\text{a} is not determined primarily by the demand for circulating glucose imposed by the muscle fuel requirement in IE. That peak R\text{a} and the incremental AUC of R\text{a} were not related to V\text{O}_{2}\text{max} or study VO\text{2} further supports this notion; i.e., variations in size and fitness that influence them do not influence R\text{a}. These observations are compatible with a feed-forward, centrally originating regulatory mechanism that drives the response beyond the increment in fuel requirement. If the main regulators were the catecholamines, then the fact that 1) their responses were the same between genders and 2) R\text{a} and catecholamine responses are tightly correlated provides further support to the feed-forward hypothesis of regulation.

The previous studies that reported R\text{a} by gender found no differences in R\text{a} per kilogram BW, except at exercise intensities between 45 and 65% V\text{O}_{2}\text{max} (14, 15, 34). The analyses did not include the type of approach used in the present study. However, because the male subjects were 15 kg heavier, their R\text{a} (and R\text{d}) in milligrams per minute would have been higher (14, 15). There was no effect of exercise at these intensities on plasma glucose, and, therefore, R\text{a} and R\text{d} were matched. This is consistent with regulation via signals originating in the periphery to match R\text{a} to requirements. Thus the difference between genders based on the greater muscle mass of the male subjects would fit with such feedback regulation. Although estrogens are another potential factor in the female subjects, they are unlikely to account for a difference during moderate exercise. In a study of estradiol replacement in amenorrheic women (with prior plasma estradiol levels within the normal range for men), R\text{a} per kilogram BW (and therefore also total R\text{a}) at 65% V\text{O}_{2}\text{max} decreased by 13.7% (42).

We [and others (11, 16)] found no gender difference in plasma NE and Epi responses to IE, indicating the absence of gender differences in sensitivity of R\text{a} to catecholamines, if they are the principal mediators. Such a difference has been postulated previously (18) to explain lower catecholamine responses in women for a given handgrip strength test, yet with similar plasma FFA and β-hydroxybutyrate elevations. These authors related these responses to inhibitory effects of estrogens on extraneuronal catecholamine uptake (20) and catechol O-methyltransferase-mediated degradation (1). Such effects could result in a greater response for a
given plasma catecholamine concentration, perhaps consistent with the present results in which exercise $R_a$ was not less, despite the predicted 20% smaller liver mass in the women. Others have also found lower Epi (or both Epi and NE) responses to moderate-intensity exercise in female subjects (7, 35, 44, 51), which we did not find in IE. However, catecholamine responses are of lesser importance than those of the IRG/IRI in regulation at moderate-intensity exercise, and differences found at this level are not pertinent to IE.

In certain situations, lipid mobilization may be more sensitive to catecholamines in women than in men (8, 54). Moreover, there are regional differences between genders in adipose tissue responses to systemically infused Epi (23). Among other indexes of sympathetic activity and responses that have been reported are a greater level of muscle sympathetic nerve activity in men (38) and different circulatory responses to intra-arterial agonists (13). However, although FFAs in the present study were higher in the female subjects during all three phases of the experiment, IE is not a setting in which there is an important role for fat in the incremental energy required for exercise.

In contrast to the gender similarity in $R_a$, the $R_d$ showed a relationship with gender and indexes of body composition and $V_O_2$. At rest, it was higher in the male subjects, whether expressed in milligrams per minute or milligrams per kilogram BW per minute, but not in milligrams per kilogram FFM per minute, suggesting it to be largely determined by the difference in muscle mass. The indexes of $R_d$ response to exercise were again largely accounted for by FFM. In absolute terms, there was greater substrate requirement as the workloads and study $V_O_2$ values were higher in the men. The slower rate of $R_d$ rise during exercise in the female subjects, whose pattern of $V_O_2$ response was the same (not shown), is not explained by our data. One explanation could be a more rapid induction of muscle glycogenolysis in the women, such that the need for uptake of circulating glucose would be less at the outset. Estrogen could have contributed, as it has been shown to decrease glucose transport in the rat diaphragm (45), and lowered $R_d$ during moderate-intensity exercise when administered to amenorrheic women (42). As $R_d$ per kilogram FFM was not different between men and women in our study, a higher $R_d$ per kilogram FFM is not a requirement for the women during IE. In contrast, studies of moderate-intensity exercise did suggest a greater reliance on circulating glucose as a proportion of total carbohydrate oxidation in women (15, 35), implying that a higher $R_a$ per kilogram FFM at that intensity could still be consistent with a matched feedback mechanism of glucose regulation.

In IE in the female subjects, the huge magnitude of the $R_a$ response (perhaps the greatest in human physiology) and the greater $R_a$ – $R_d$ difference and consequent greater hyperglycemic response suggest that the liver, exposed to the same high-catecholamine concentrations (necessary for similar cardiovascular responses in both genders), responds by releasing the same amount of glucose, which then has less mass of FFM to take it up than in men (and the study $V_O_2$ was less, indicating lesser total substrate requirement). This would follow if the postulated feed-forward mechanism causes the maximum possible hepatic glycogenolytic response in both genders. As noted, this is interesting in light of liver weights being ~20% less in women (2).

Many of the remaining gender differences can be viewed as the consequence of the greater $R_a$ – $R_d$ imbalance in women. This explains the greater postexercise hyperglycemia, which in turn causes the greater hyperinsulinemia. The greater recovery period $R_d$ per kilogram FFM in women is a predictable consequence of this hyperglycemic, hyperinsulinemic state. This greater $R_d$ would be consistent with more rapid replenishment of muscle glycogen in women, which would be advantageous during repeated bouts of IE with short, intervening periods of rest. In postabsorptive IE in men, we observed a greater reliance on blood glucose during a second bout of IE (32). Women may be innately more efficient at restoring depleted glycogen from endogenous glucose, and, therefore, the effect found in men may be less in women with repeated bouts. If the slower rise in $R_d$ at the outset of IE in the female subjects (Fig. 3A) does reflect greater muscle glycogenolysis contributing to the fuel utilized initially, then this might mandate a greater $R_d$ in recovery to replete.

MCR (ml/min) was higher in men at baseline and during exercise because of their higher $R_d$ (in mg/min) with comparable glycemics and additionally during the first hour of recovery because of their lesser hyperglycemic response. Thus, because both $R_d$ and exercise MCR were accounted for mainly by FFM, this likely explains most of the gender difference. The reasons for the subtly greater changes in women in IRG and IRG/IRI from baseline (significant only when each gender is compared with its own baseline and not when the exercise-related responses are compared with each other) and trend toward such a difference in IRI are not clear. Lower pyruvate levels during exercise in women could potentially be explained by their having a higher proportion of Type 1 (slow-twitch, oxidative) muscle fibers (50), although this difference is still not definitely established. Higher plasma FFA levels at rest in women have been reported previously (11), although not universally (16, 51), and may be estrogen related (42).

Previous studies of gender difference in exercise have suggested that, in moderate exercise, women may have lower RER, greater lipid and lesser muscle glycogen utilization, and a correspondingly greater reliance on circulating glucose (15–17). In the present study, RER was not different between genders, and FFA and $R_d$ data were not supportive of the previous findings obtained during moderate exercise. However, our results are consistent with other studies of IE (17), as well as with the lesser contribution of FFA as energy substrate at greater intensities of exercise (15, 19). This reported gender difference in RER follows the same pattern as postprandial vs. postabsorptive RER in which a difference at moderate intensities of exercise...
would be conditions appropriate for greater muscle to the greater R, in women can be viewed as appropriate responses to increasing glycemia. The equivalent R, responses in plasma catecholamine responses, are likely not medi-

tabolism in women, as well as in RER (8, 15, 16), associated with lesser hyperglycemia and even greater R, per FFM in men and women. and trained. Body composition is one of the principal differences between men and women, and it, therefore, would not be surprising if women with differences in body composition would have quantitative differences in glucoregulatory responses. Training sufficient to result in an increase in VO2max has been associated in moderate-intensity exercise with changes in both carbohydrate and lipid metabolism in women, as well as in RER (8, 15, 16), although not in R, when tested at the same relative workload (15). Second, all our subjects were studied in the follicular phase of their menstrual cycles. Several substrates and hormones are known to differ in response to moderate exercise by menstrual cycle phase (4), and thus we are unable to state whether our results can be extrapolated to the luteal phase. Third, as discussed elsewhere (28), most IE is actually performed in the postprandial as opposed to the postabsorptive state. Extrapolating postprandial IE findings from men, in women one might expect postprandial IE to be associated with lesser hyperglycemia and even greater R, per FFM (than postabsorptive IE and than in men) in the recovery period. Our results do raise the possibility that poorly controlled diabetic women may be at even higher risk of post-IE hyperglycemia than similarly controlled diabetic men. We have already shown such postexercise hyperglycemia, even when IE is commenced at euglycemia, in male Type 1 diabetic subjects in whom the recovery-phase hyperinsulinemia cannot occur (49).

In summary, this study has shown that postabsorptive glucoregulatory responses to IE in fit women in the follicular phase of their menstrual cycles are qualitatively similar to those in men, consisting of a marked and rapid rise in R, which is highly correlated to plasma catecholamine responses, are likely not mediated by the IRG/IRI, and exceed the rise in R, leading to increasing glycemia. The equivalent R, responses in both genders support the notion of a feed-forward mechanism for R, response in IE. Greater recovery-period hyperglycemia, hyperinsulinemia, and R, per FFM in women can be viewed as appropriate responses to the greater R, – R, mismatch during exercise and would be conditions appropriate for greater muscle glycogen resynthesis.

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Results of these studies have been presented in part in abstract form (37).

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