J Appl Physiol 92: 504–512, 2002;
10.1152/japplphysiol.00526.2001.

Gender differences in the endocrine and metabolic responses to hypoxic exercise

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Received 2 May 2001; accepted in final form 18 September 2001

Sandoval, Darleen A., and Kathleen S. Matt. Gender differences in the endocrine and metabolic responses to hypoxic exercise. *J Appl Physiol* 92: 504–512, 2002; 10.1152/japplphysiol.00526.2001.—This study tested the hypothesis that women would have blunted physiological responses to acute hypoxic exercise compared with men. Fourteen women taking oral contraceptives (28 ± 0.9 yr of age) and 15 men (30 ± 1.0 yr of age) with similar peak O_2 consumption ($\dot{V}O_{2\,peak}$) values (56 ± 1.1 vs. 57 ± 0.8 ml·kg fat-free mass^{-1}·min^{-1}) were studied under hypoxic (H; fraction of inspired oxygen = 13%) vs. normoxic (fraction of inspired oxygen = 20.93%) conditions. Cardiopulmonary, metabolic, and neuroendocrine measures were taken before, during, and 30 min after three 5-min consecutive workloads at 30, 45, and 60% $\dot{V}O_{2\,peak}$. In women compared with men, glucose levels were greater during recovery from H ($P < 0.05$) and lactate levels were lower at 45% $\dot{V}O_{2\,peak}$, 60% $\dot{V}O_{2\,peak}$, and up to 20 min of recovery ($P < 0.05$), regardless of trial ($P < 0.0001$). Although the women had greater baseline levels of cortisol and growth hormone ($P < 0.0001$), gender did not affect these hormones during H or exercise. Catecholamine responses to H were also similar between genders. Thus the endocrine response to hypoxia per se was not blunted in women as we had hypothesized. Other mechanisms must be at play to cause the gender differences in metabolic substrates in response to hypoxia.

catecholamines; cortisol; metabolites

LIMITED RESEARCH HAS EXAMINED the impact of gender on hormonal and metabolic responses to acute hypoxic exercise. Recent extensive studies have examined the effects of chronic hypoxia in women during different phases of the menstrual cycle (2, 3, 24). However, these studies were not examining the impact of gender per se, because they lacked a comparably fit male control group. Nevertheless, metabolic differences do seem to exist after acclimatization to 4,300 m, with women shifting toward greater fat (3) and men shifting toward greater carbohydrate use (29) during exercise. In normoxia (≤1,500 m), gender does alter the sympathetic and metabolic responses to prolonged (8, 15, 33) and supramaximal exercise (11). For example, women have a greater reliance on fat oxidation and a blunted plasma catecholamine response during exercise at the same relative intensity compared with men with similar fitness levels (8, 11, 15, 33). In addition, women, compared with men, also have a reduced plasma catecholamine response to hypoglycemic (7) and cognitive stressors (21), possibly due to a direct inhibitory effect of estradiol on the sympathetic nervous system (SNS) (6). Yet it remains unknown whether plasma catecholamine responses differ between comparably fit men and women during acute hypoxic exercise. It seems plausible that SNS response to the stress of acute hypoxic exercise will also be different between genders, with the prediction that women will have a lower plasma catecholamine response compared with men.

The hypothalamic-pituitary-adrenal (HPA) axis is also stimulated in response to stress and, therefore, can influence fuel availability (9). Animal studies suggest a potential stimulatory effect of estradiol and/or progesterone on the HPA axis at rest (4), and this suggests that women have an enhanced responsiveness of the HPA axis compared with men. However, in response to prolonged exercise, Davis et al. (8) and Horton et al. (15) found no differences in cortisol responses between men and women. Exercise under hypoxic vs. normoxic conditions causes greater increases in cortisol levels for a given workload in both men (32) and women (3). However, it remains to be determined whether the magnitude of this response to hypoxic exercise is different between comparably fit men and women.

The purpose of this study was to compare the endocrine and metabolic responses to hypoxic exercise in similarly fit men and women exposed to acute hypoxic exercise under the same experimental conditions. We hypothesized that, because of reduced SNS drive in response to hypoxic exercise, women would have significantly lower plasma catecholamines and, consequently, lower cardiorespiratory, glucose, and lactate, but greater cortisol responses to hypoxic exercise compared with men. Because of the SNS inhibitory effects on insulin and stimulatory effects on growth hormone, we also predicted that the men would have lower insulin but greater growth hormone response to hypoxic exercise compared with women.

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METHODS

Subject Recruitment

Young (20–35 yr of age), healthy, recreationally active women taking oral contraceptives (OC; $n = 14$) and men ($n = 15$) were recruited for this study (Table 1). Women taking OC were recruited to control the hormonal fluctuations of the normal menstrual cycle and because this is the subject pool in which differences have been previously found (31). Because fitness (20) and body fat can affect the sympathetic response to exercise, only subjects with a peak O_2 consumption ($\dot{V}O_{2\,peak}$) of 40–50 ml·kg fat-free mass^{-1}·min^{-1} and average percent body fat [≤23% for women and 15% for men as classified by Heyward (14)] were accepted into the study. $\dot{V}O_{2\,peak}$ is expressed relative to fat-free mass to control fitness for differences in body composition. All subjects signed an informed consent approved by the Institutional Review Board at Arizona State University.

Preliminary Assessments

Before or during participation in this study, subjects reported no exposure to an altitude of >3,000 m within 1 mo before each trial, no history of severe acute mountain sickness, no problems associated with venipuncture, and no medications taken during the experimental trials (besides OC). All female subjects had been taking OC for at least 6 mo before participating in the study and were taking OC for birth control reasons rather than for menstrual cycle regulation.

Body composition analysis was assessed via the skinfold technique using a three-site skinfold equation appropriate for gender [Jackson et al. (17) for men and Jackson and Polluck (16) for women]. Body density was converted to percent body fat using the appropriate age- and gender-specific equation (14).

$\dot{V}O_{2\,peak}$ was measured on a cycle ergometer using a continuous incremental protocol starting at 50 W, with increases in workload by equal increments every 2 min to exhaustion. Respiratory gas exchange data were collected continuously using a Parvo Medics True Max metabolic cart (Consentius Technologies, Sandy, UT). Heart rate was recorded every 5 s with a Polar Vantage XL heart rate monitor (Polar Electro, Port Washington, NY), and the data were downloaded onto a computer for further analysis. All subjects met at least two of the following criteria for the $\dot{V}O_{2\,peak}$ test: respiratory exchange ratio of ≥1.1, maximum heart rate of ±10 beats/min of age-predicted maximum (220 − age), or an increase in O_2 consumption ($\dot{V}O_2$) of ≤150 ml/min with an increase in workload.

Exercise Protocol

Figure 1 illustrates the testing protocol. All subjects were tested on 2 different days: once while breathing room air [normoxia (N)] and once while breathing 13% oxygen [hypoxia (H)], which simulates the hypoxic effect of 2,160-m altitude. The order of H and N trials was randomized. For both men and women, the H and N trials were performed either during the same week or 4 wk apart. However, the women were always tested during the 3rd wk of their pill cycle when the effects and/or dosage of estradiol and progesterone within the OC are maximized.

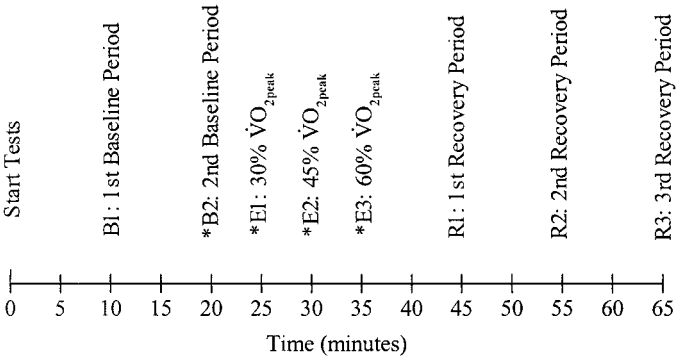

Fig. 1. Timeline for the data collection period. $\dot{V}O_{2\,peak}$, peak O_2 consumption. *Hypoxic or room air.

Table 1. *Subject characteristics*

Variable	Women ($n = 14$)	Men ($n = 15$)
Age, yr	28.0 ± 0.9	29.8 ± 1.0
BMI, kg/m^2	22.1 ± 0.5	24.8 ± 0.6*
Body fat, %	17.6 ± 1.0	13.4 ± 1.1*
Fat-free mass, kg	49.7 ± 1.8	67.8 ± 1.3*
Fat mass, kg	10.9 ± 0.9	10.4 ± 1.1
$\dot{V}O_{2peak}$, l/min	2.7 ± 0.1	3.9 ± 0.1*
$\dot{V}O_{2peak}$, ml·kg^{-1}·min^{-1}	45.4 ± 1.2	49.9 ± 1.1*
$\dot{V}O_{2peak}$, ml·kg FFM^{-1}·min^{-1}	55.3 ± 1.1	57.4 ± 0.8

Values are means ± SE. BMI, body mass index; $\dot{V}O_{2peak}$, peak O_2 consumption; FFM, fat-free mass. *$P < 0.05$, significantly different in men vs. women.

Subjects reported to the laboratory between 5 and 10 AM after an overnight 10-h fast. On repeated trials, subjects were tested at the same time of the morning, and an equal number of subjects in the male and female groups were tested in late vs. early morning hours. A venous catheter was inserted into an antecubital vein by an experienced technician, and subjects then rested for 30 min to ensure accurate baseline hormonal levels. Subjects then moved to the cycle ergometer for resting and exercise data collection. An initial resting baseline period of 10 min (B1) was conducted while subjects breathed room air through an open-circuit system. Subjects remained seated and sedentary on the bike for 10 more min [second baseline period (B2)]. At the start of B2, for both trials, a short hose was connected to the inspiratory side of the Hans Rudolph mouthpiece. This hose was then connected to a two-way valve to allow subjects to breath either room air (N) or from a Douglas bag that was filled with ~13% O_2 from a medical gas tank (H). After B2, the exercise stages began and consisted of three 5-min consecutive cycling workloads corresponding to 30 (E1), 45 (E2), and 60% of $\dot{V}O_{2\,peak}$ (E3) (equals normoxic $\dot{V}O_{2\,peak}$ pedaling at ~70 rpm). Thus subjects performed the same absolute workload in the H and N trials, and the only difference between the trials was that subjects breathed 13% O_2 from B2 through E3 during H. The exercise intensities were chosen to maximize differences between each exercise stage but could not exceed 60% $\dot{V}O_{2\,peak}$ because of the corresponding high relative intensity in the H trial, which would approach hypoxic $\dot{V}O_{2\,peak}$. An exercise duration of 5 min per stage of exercise was used to allow us to study the effect of three different exercise intensities. Because previous studies had shown similar arterial catecholamine levels between 5 and 15 min of exercise (13), we felt 5 min would be long enough to represent the endocrine response at each exercise intensity. Recovery data were collected for 30 min postexercise while the subject remained on the cycle ergometer breathing room air.

Measurements

Heart rate and respiratory gas exchange measurements were measured continuously throughout resting, exercise, and recovery periods with the Polar Vantage XL heart rate

monitor and the Parvo Medics True Max system, respectively. Blood pressure was taken (measured manually) and blood samples were collected with 1 min left in each resting and exercise stage, and at 10 (R1), 20 (R2), and 30 min (R3) of recovery.

Blood samples were analyzed for lactate levels using the YSI 1500 Sport Lactate Analyzer (Yellow Springs Instruments, Yellow Springs, OH) or spun in a cold centrifuge (5°C) for 15 min at 3,000 rpm. A portion of the plasma samples was analyzed for glucose with the Beckman Glucose Analyzer 2 (Fullerton, CA). Metabisulfite was added to a portion of plasma samples taken at B1, B2, E1–E3, and 10 min postexercise and were stored at −80°C for later analysis of norepinephrine and epinephrine. The remaining plasma for each measurement period (B1 through R3) was aliquoted and stored at −80°C for subsequent analysis of cortisol (all subjects), growth hormone, and insulin (n = 8 each for men and women).

Cortisol, growth hormone, and insulin were analyzed using a commercially available radioimmunoassay kit (ICN Biomedicals, Costa Mesa, CA) with an intra-assay coefficient of variation of 1.99, 4.02, and 2.97% and interassay coefficient of variation of 16.3, 6.6, and 9.1% for cortisol, growth hormone, and insulin, respectively.

Catecholamines were analyzed via HPLC (ESA, Chelmsford, MA) with electrochemical detection. Briefly, 1.5 ml of plasma were combined with 10 mg of alumina (BAS). Dihydroxybensylamine was then added as an internal standard to all samples. One milliliter of 2 M Tris·EDTA buffer at pH 8.7 was added to samples to facilitate binding of catecholamines to the alumina, and the vials were then shaken for 15 min. The plasma layer was then discarded, and the alumina was washed three times with deionized and distilled water. Catecholamines were then extracted from the alumina by using 200-μl eluting agent (ESA). Samples were centrifuged at 2,000 rpm for 3 min. Fifty microliters of eluant were then injected into the HPLC column (ESA) for analysis. The interassay coefficient of variation for catecholamine analysis was 19%.

Lactate Threshold Test

Based on the finding that lactate levels were quite variable for a given exercise intensity relative to maximal O_2 consumption ($\dot{V}O_{2\,max}$), it has been suggested that exercise intensity should be expressed relative to the lactate threshold rather than as a percentage of $\dot{V}O_{2\,max}$ (27). Because of this potential impact on our results and because it is unknown whether gender can impact the lactate threshold, a subset of subjects (n = 14: 7 men and 7 women) returned to the laboratory for a lactate threshold test. Data between genders could then be compared relative to the lactate threshold, relative to $\dot{V}O_{2\,peak}$, and with regards to the absolute workload performed. Subjects reported to the laboratory between 6 and 9 AM after an overnight fast. Again, men were tested anytime of the month, and women were tested during the 3rd wk of their pill cycle. A venous catheter was inserted into an antecubital vein, and subjects then rested for 30 min for accurate baseline hormonal levels. Subjects then moved to the cycle ergometer for resting and exercise data collection. An initial resting baseline period of 10 min was conducted while subjects breathed room air through an open-circuit system. The exercise stages then began and consisted of increments of 12.5% of maximum workload (determined from previous $\dot{V}O_{2\,peak}$ protocol) every 2 min to exhaustion.

Heart rate and respiratory gas exchange measurements were measured continuously with the Polar Vantage XL heart rate monitor (Polar Electro) and the Parvo Medics True Max system (Consentius Technologies), respectively. Blood samples were collected, and ratings of perceived exertion were measured within the last 30 s of the resting and exercise stages. Blood lactate was analyzed using the YSI 1500 Sport Lactate Analyzer (Yellow Springs Instruments).

Determination of the Lactate Threshold

The lactate threshold was determined for each individual subject by plotting relative exercise intensity against lactate. Regression analysis was then used to estimate the intensity characterized by a nonlinear increase in lactate (12). This is done by performing separate linear regression analyses on the lactate vs. $\dot{V}O_2$ plot for the first three, four, five, and so on, up to eight data points representing each stage of the $\dot{V}O_{2\,peak}$ test. The lactate threshold was reflected by a decrease in the R^2 and an increase in lactate concentration (nonlinear rise) at the next exercise stage.

Statistical Analysis

All variables were analyzed with a three-way analysis of variance for time (B1 through R3), trial (H and N), and group (men vs. women). All potential interactions were tested, but only significant interactions are reported. Paired contrasts were used as a post hoc test to identify significant differences. Using the change in heart rate during H and N exercise from a pilot study using a similar protocol with $\alpha = 0.05$ and $\beta = 0.80$, we estimated that the number of subjects needed to detect a 20% difference in heart rate is ≥14 per group (men vs. women).

The mean lactate threshold value for the men and women was statistically compared using an unpaired t-test. Statistical significance for all tests was accepted at $P \leq 0.05$.

RESULTS

Physical Characteristics

Because of the experimental design, there were no gender differences in age or $\dot{V}O_{2\,peak}$ relative to fat-free mass (Table 1). There were also no significant differences in fat mass. However, the men had a higher body mass index, fat-free mass, and a greater absolute and relative (to total body mass) $\dot{V}O_{2\,peak}$ (Table 1). Subjects were recreational runners, cyclists, triathletes, and/or mountaineers.

The OC brand name, type of synthetic estradiol and progestin, and length of time on OC for each female subject are listed in Table 2. Most subjects were taking a monophasic pill preparation, which had a constant dosage of estradiol and progestin for 3 wk and placebo for 1 wk. Three subjects were taking a triphasic pill preparation, which contained a constant dosage of estradiol but progressively increased the progestin dosage each week until the placebo week.

Cardiopulmonary Variables

Cardiovascular. Heart rate was greater in H vs. N at all time points except B1 (trial × time interaction, $P < 0.0001$; Fig. 2). As expected, mean arterial pressure increased (main effect of time; $P < 0.0001$; Fig. 2*B*) during exercise workloads vs. baseline and recovery time points.

Table 2. *Type and length of time on OC for female subjects*

Subject No.	OC Brand Name	Ethinyl Estradiol, mg	Synthetic Progestin, mg	Time on OC, yr
1	**Triphasil**	**0.04**	**LN (0.125)**	**0.58**
2	Levlen	0.03	LN (0.15)	4
3	Allesse	0.02	LN (0.1)	0.58
4	Desogen	0.03	DG (0.15)	0.67
5	Orthocept	0.03	DG (0.15)	4
6	Desogen	0.03	DG (0.15)	10
7	Ortho Novum	0.035	NE (1.0)	9
8	**Ortho Novum 777**	**0.035**	**NE (1.0)**	**0.58**
9	Necon	0.035	NE (0.5)	10
10	Modicon	0.035	NE (0.5)	1
11	**Ortho Tri Cyclen**	**0.035**	**NG (0.25)**	**4**
12	Orthocyclen	0.035	NG (0.25)	4
13	Lo Ovral	0.03	DLN (0.03)	5
14	Zovia	0.035	ED (1.0)	1

OC, oral contraceptive; DLN, dextro, levo-Norgestrel; LN, Levo-Norgestrel; DG, desogestrel; NG, norgestimate; NE, norethindrone; ED, ethynodiol diacetate. Subjects in bold were taking triphasic OC. Values in parentheses are concentrations.

Respiratory. H caused a greater increase in ventilation compared with N, and this increase was greater in men vs. women during all exercise time points (gender × time × trial interaction; $P = 0.009$; Fig. 3*A*). When expressed relative to fat-free mass (to control for gender differences in body size), H still caused a significantly greater ventilatory response at B2 and during and 10 min after exercise time points (trial × time interaction; $P < 0.0001$; Fig. 3*B*). However, the gender difference during H was gone, but during N the women had greater ventilatory responses compared with the men (trial × gender interaction; $P = 0.002$; Fig. 3*B*).

Metabolic Variables

Gas exchange. As expected, absolute $\dot{V}O_2$ significantly increased with exercise in H (trial × time; $P < 0.0001$) and was significantly greater in men vs. women (gender × time; $P < 0.0001$; Fig. 3*C*). When expressed relative to fat-free mass, $\dot{V}O_2$ still increased with exercise and was greater in H vs. N (trial × time interaction; $P < 0.001$; Fig. 3*D*), but there was no longer an effect of gender ($P = 0.63$).

Glucose. The women had lower glucose levels at baseline and the first exercise workload (E1) in H and N but had greater glucose levels during recovery from H vs. the men (gender × trial × time interaction; $P = 0.04$; Fig. 4*A*). Because baseline differences existed, percent change from baseline values was also calculated. This analysis showed that glucose levels were significantly elevated over baseline during recovery in women vs. men during H (gender × trial × time interaction; $P = 0.05$; 29.8 ± 2.5, 24.3 ± 4.6, and 20.3 ± 4.7% vs. 14.8 ± 3.2, 7.4 ± 2.3, and 4.3 ± 2.3% in women vs. men for R1, R2, and R3, respectively).

Lactate. As expected, lactate levels increased to a greater extent in H vs. N at E2 through R3 (trial × time interaction, $P < 0.0001$; Fig. 4*B*) and was greater in men vs. women at E3 through R2 (gender × time interaction, $P < 0.001$; Fig. 4*B*).

Neuroendocrine Variables

Growth hormone. The data for the subset of subjects (8 women and 7 men) whose plasma samples were also analyzed for growth hormone and insulin are in Fig. 5, *A* and *B*, respectively. Absolute growth hormone levels significantly increased at E2, E3, and R1 compared with B1, B2, E1, R2, and R3 (main effect of time; $P < 0.0001$) but were not significantly different between trials ($P = 0.89$). In addition, the women had greater growth hormone levels across all time points (main effect of gender; $P = 0.01$).

Insulin. Women had significantly greater insulin levels during H, regardless of time (gender × trial; $P = 0.03$), and women had significantly greater insulin levels than men at R2 and R3, regardless of trial (gender × time; $P < 0.0001$; Fig. 5*B*).

Catecholamines. Norepinephrine levels increased with exercise (main effect of time; E1–E3 > B1 and B2; $P < 0.001$; Fig. 6*A*) and were greater in H vs. N across all time points (main effect of trial; $P = 0.008$), but there was no effect of gender ($P = 0.72$). Epinephrine levels were not significantly different with time or trial or between genders ($P = 0.68$, 0.55, and 0.30 for time, trial, and gender, respectively; Fig. 6*B*).

Cortisol. Cortisol levels did not change with exercise or with H ($P = 0.4$ and 0.5 for time and trial, respectively; Fig. 6*C*). However, across all time points and for both trials, women had greater cortisol levels compared with men (main effect of gender, $P < 0.0001$). When expressed as a percent change from baseline, cortisol was significantly greater during H vs. N at E3 and R1 ($P = 0.03$; 22.4 ± 5.3 and 22.9 ± 6.7% vs.

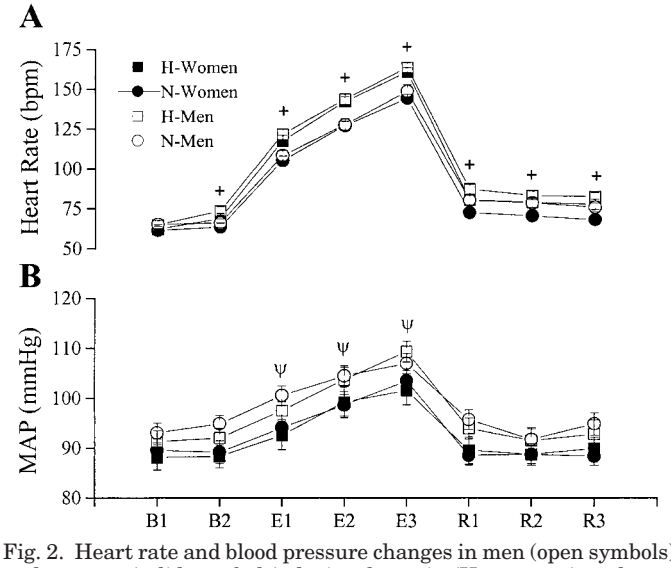

Fig. 2. Heart rate and blood pressure changes in men (open symbols) and women (solid symbols) during hypoxic (H; squares) and normoxic (N; circles) trials. *A*: heart rate showed a significant trial × time interaction ($^{+}P < 0.0001$). *B*: for mean arterial pressure (MAP), there was also a significant main effect of time (exercise greater than baseline and recovery time points; $^{\Psi}P < 0.0001$). Values are expressed as means ± SE. Symbols are occluding error bars where none are visible. bpm, Beats/min. B1 through R3 are as defined in Fig. 1.

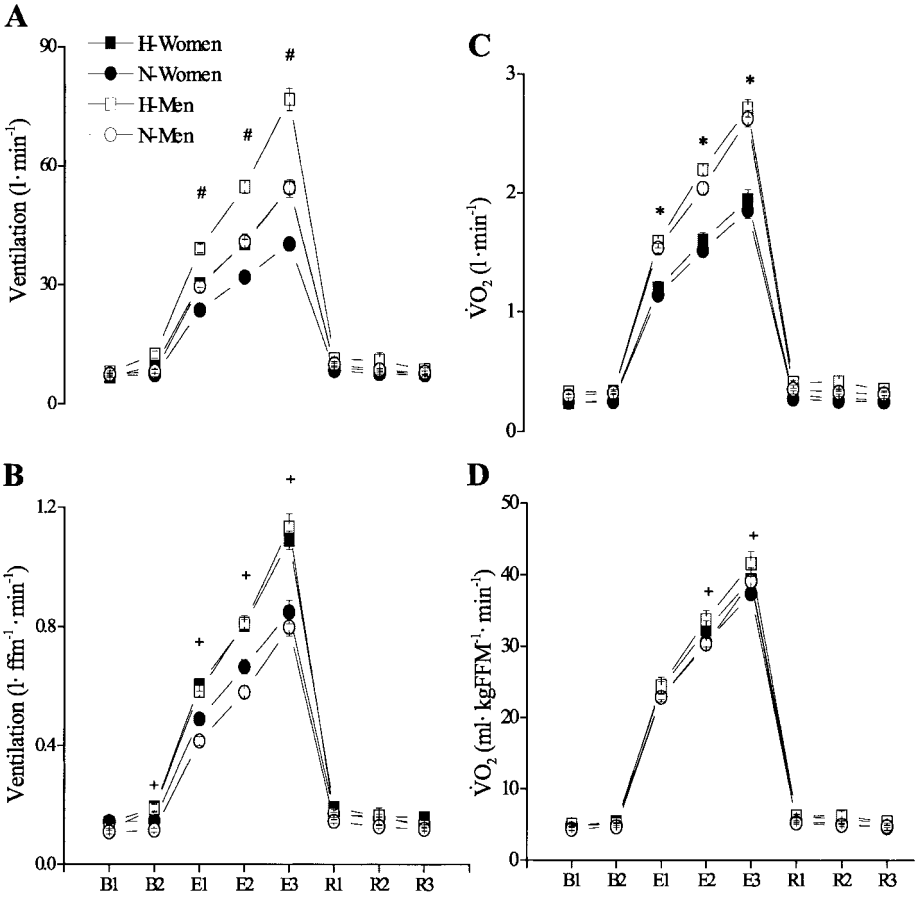

Fig. 3. Ventilatory and oxygen consumption ($\dot{V}O_2$) changes in men and women during H and N trials. *A*: for absolute ventilation, there was a significant gender × trial × time interaction ($^{\#}P = 0.002$). *B*: for ventilation expressed relative to fat-free mass (FFM), there was a significant trial × time ($^{+}P < 0.0001$) and a gender × trial ($P = 0.02$) interaction. *C*: for absolute $\dot{V}O_2$, there was a gender × time interaction ($^{*}P < 0.0001$) and a main effect of trial ($P = 0.0001$). *D*: for relative $\dot{V}O_2$, there was trial × time interaction ($^{+}P < 0.0001$). Values are means ± SE. Symbols occlude error bars where none are visible.

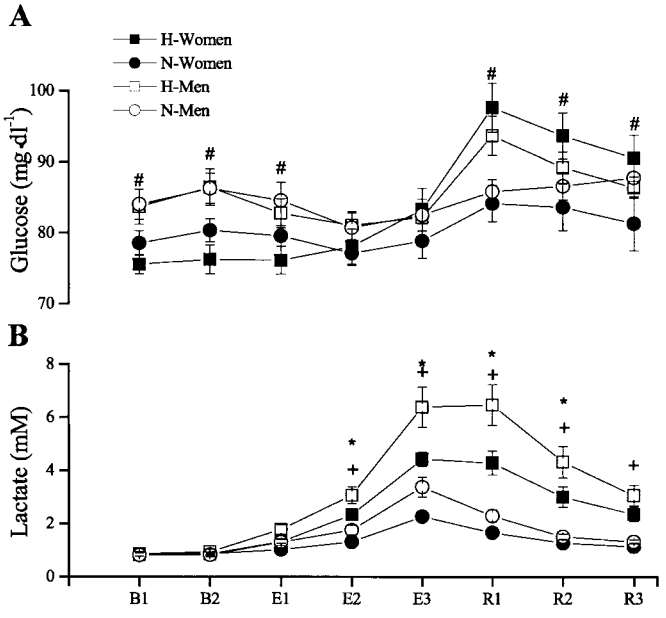

Fig. 4. Plasma glucose and lactate levels in men and women during H and N trials. *A*: for absolute glucose levels, there was a significant gender × trial × time interaction ($^{\#}P = 0.0003$). *B*: lactate responses showed significant trial × time ($^{+}P < 0.0001$) and gender × time ($^{*}P < 0.001$) interactions. Values are means ± SE. Symbols occlude error bars where none are visible.

−0.38 ± 2.9 and −3.9 ± 3.4% change from baseline for E3 and R1, respectively, in H vs. N).

Lactate Threshold Comparisons

Physical characteristics. Physical characteristics of this subset of subjects are summarized in Table 3. Briefly, the men had a higher body mass index, fat-free mass, absolute $\dot{V}O_{2\ peak}$, and maximum workload ($P < 0.05$). However, there were no significant differences between genders in percent body fat, fat mass, or relative $\dot{V}O_{2\ peak}$ (relative to body mass and fat-free mass).

Lactate threshold. The lactate threshold (63.3 ± 4.7 vs. 63.4 ± 3.7% $\dot{V}O_{2\ peak}$; $P = 0.99$; Table 4) was not significantly different between women and men when expressed at the same relative exercise intensity. When expressed as an absolute workload, the women had a significantly lower workload at the lactate threshold vs. the men (135.4 ± 11.2 vs. 184.1 ± 13.9 W for women vs. men; $P = 0.02$).

DISCUSSION

This is the first study to compare comprehensively the endocrine responses to acute hypoxic exercise in similarly fit men and women. The most physiologically significant results of this study were that the men had greater lactate responses during and after hypoxic exercise, the women had greater glucose levels after hypoxic exercise, and that these differences occurred

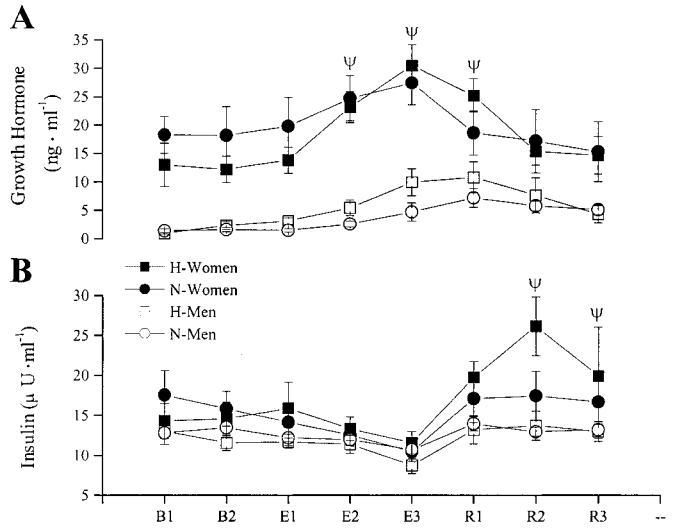

Fig. 5. Plasma growth hormone and insulin levels in men and women during H and N trials. *A*: for absolute growth hormone levels, there was a significant effect of time ($^{\psi}P < 0.001$) and a main effect of gender ($P < 0.0001$). *B*: for insulin levels, there was a significant effect of gender × time interaction with women having greater insulin at R2 and R3 ($^{\psi}P = 0.01$). There was also a trial × gender interaction with women that was greater than all other groups during H ($P < 0.0001$). Values are means ± SE. Symbols occlude error bars where none are visible.

independent of endocrine responses. Thus the endocrine response to hypoxia per se was not blunted in women as we had hypothesized, yet metabolic substrates were still affected by gender.

The additional stimulus of hypoxia during exercise may override gender differences in endocrine response to normoxic exercise. At rest, muscle sympathetic nerve activity was greater in women (no control of menstrual cycle) at 3–7 min but not after 7 min of breathing hypoxic gas compared with men (28). During exercise, both with acute exposure (23) and with chronic exposure to hypoxia (10 days at 4,300 m) (3), women have similar plasma catecholamine responses as that of a group of men previously studied (25). In the acute study, the women had a greater epinephrine excretion rate (23) compared with men previously studied (25). These results support our results and suggest that women may be more sensitive to hypoxia, abolishing the blunted sympathetic response to stress seen in normoxic conditions.

There are a couple of potential caveats to this conclusion. First, plasma norepinephrine levels are susceptible to both changes in spillover from the SNS and clearance from the plasma. A previous study found that 20 min of hypoxic exercise (11% O_2) caused an increase in spillover and arterial norepinephrine levels (19), suggesting that it is not decreased clearance that causes increases in norepinephrine levels found in our

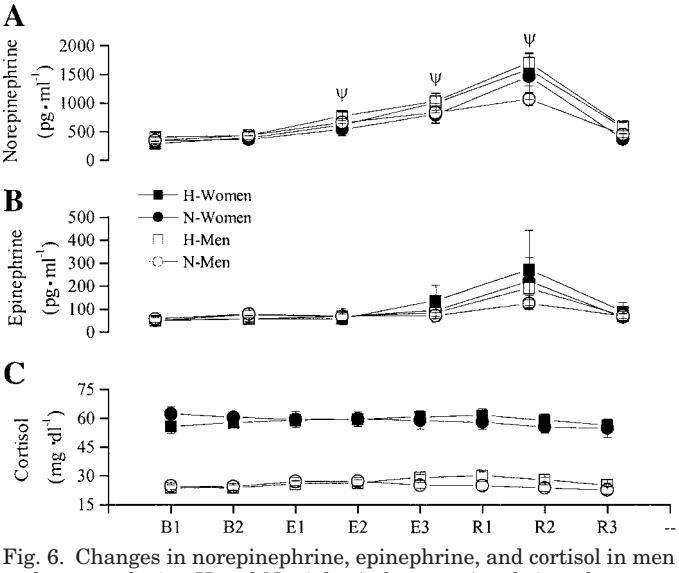

Fig. 6. Changes in norepinephrine, epinephrine, and cortisol in men and women during H and N trials. *A*: for norepinephrine, there was a significant effect of time ($^{\psi}P < 0.0001$), where E1–E3 are greater than B1 and B2, and a main effect of trial ($P = 0.007$). *B*: for epinephrine, there were no significant differences. *C*: for absolute cortisol levels, there was a main effect of gender ($P < 0.0001$). Values are means ± SE. Symbols occlude error bars where none are visible.

Table 3. *Physical characteristics and results for the subset of subjects who performed a lactate threshold test*

Variable	Women	Men
Age, yr	27.4 ± 0.9	30.1 ± 1.1
BMI, kg/m^2	22.2 ± 0.8	24.8 ± 1.1
Body fat, %	17.5 ± 1.6	14.9 ± 1.6
Fat-free mass, kg	50.8 ± 2.6	68.9 ± 1.9*
Fat mass, kg	11.3 ± 1.3	11.6 ± 2.0
$\dot{V}O_{2peak}$, l/min	2.8 ± 0.1	3.9 ± 0.1*
$\dot{V}O_{2peak}$, l·kg^{-1}·min^{-1}	44.7 ± 1.8	48.4 ± 1.8
$\dot{V}O_{2peak}$, ml·FFM^{-1}·min^{-1}	54.5 ± 1.7	56.3 ± 1.4
Maximum workload, W	218.3 ± 10.7	290.6 ± 13.2*
Lactate threshold, %$\dot{V}O_{2peak}$	63.32 ± 4.7	63.39 ± 3.7

Values are means ± SE. *$P < 0.05$, significantly different vs. women.

Table 4. *Individual intensities for E1, E2, and E3 relative to their lactate thresholds in a subset of subjects*

Subject No.	Gender	E1	E2	E3
1	F	53.3	80.0	106.7
2	F	43.6	65.5	87.3
3	F	43.6	65.5	87.3
4	F	43.6	65.5	87.3
5	F	68.6	102.9	137.1
6	F	53.3	80.0	106.7
7	F	36.9	55.4	73.8
Mean ± SE		49.0 ± 3.9	73.5 ± 5.9	98.0 ± 7.9
8	M	43.6	65.5	87.3
9	M	68.6	102.9	137.1
10	M	43.6	65.5	87.3
11	M	43.6	65.5	87.3
12	M	43.6	65.5	87.3
13	M	43.6	65.5	87.3
14	M	53.3	80.0	106.7
Mean ± SE		48.6 ± 3.6	72.9 ± 5.4	97.2 ± 7.2

Data are expressed as a percentage of the lactate threshold. F, females; M, males; E1, E2, and E3: exercise workload at 30, 45, and 60% of peak O_2 consumption. $P > 0.05$ for gender across E1, E2, and E3.

study and others (23). Second, despite the fact that mean epinephrine levels were over three times greater than baseline by E3, this increase was not significant. Thus the possibility exists that the present protocol did not provide enough stimulus to test differences in the sympathoadrenal system between men and women during hypoxic exercise and that differences may, in fact, exist.

The fact that subjects exercised at the same absolute workload rather than the same percentage of $\dot{V}O_{2\,peak}$ between their H and N trials may have contributed to the lack of difference in epinephrine between trials. However, in support of the importance of absolute workload, the SNS has been shown to play a role in the regulation of metabolic responses to the energy requirements of the working muscles (5, 30). In addition, Braun et al. (3) found no significant differences in plasma epinephrine at the same relative exercise intensity and smaller differences in plasma norepinephrine at the same relative vs. absolute exercise intensities between chronic altitude and sea-level trials. Another variable that could have contributed to the lack of epinephrine response could have been that 5 min of exercise may not be long enough to elicit a change in plasma catecholamine levels that are reflective of each exercise intensity. However, others have found no difference in arterial levels of catecholamines between 5 and 15 min of exercise (13). Future studies of acute hypoxic exposure with longer exercise protocols, using both absolute and relative exercise intensities and norepinephrine spillover measures, can address these issues.

Cortisol and growth hormone responses were also not blunted in women in response to H exercise. In fact, at baseline, these hormones were elevated in women vs. men. This is most likely due to estradiol. The synthetic estrogen contained within all OC preparations for subjects in this study increases hepatic synthesis of steroid binding proteins (26), causing increased total cortisol levels (1). Estrogen is also thought to increase growth hormone secretion by increasing sensitivity to pulsatile secretions of growth hormone-releasing hormone (34). However, because these hormonal responses were not different over time or with trial, these hormones are not the mechanisms for the gender differences in lactate and glucose levels.

Despite the absence of a gender effect on endocrine response, women, compared with the men, had significantly greater glucose levels after, and lower lactate levels during and after, H exercise. Others have also shown similar plasma catecholamines but reduced rates of removal of glucose after, but not during, exercise at 88% $\dot{V}O_{2\,max}$ in women during the early follicular phase vs. men (22). Also, after chronic exposure to hypoxia (4,300 m), women did not increase glucose rate of disappearance, as had been previously shown in men (29) during exercise at 65% altitude-specific $\dot{V}O_{2\,max}$.

Others who have reported lower lactate levels during prolonged (10) and supramaximal (11, 35) normoxic exercise also found lower plasma catecholamines in women vs. men. Because the present study did not find differences in plasma catecholamines in response to H exercise, other mechanisms may be at play during H to increase lactate levels during, and decrease glucose uptake after, exercise in men vs. women. One factor is the greater absolute work rates for the men (87.1 ± 2.9, 130.7 ± 4.4, and 174.2 ± 5.8 W vs. 64.2 ± 2.3, 96.4 ± 3.5, and 128.5 ± 4.6 W for E1, E2, and E3, respectively, in men vs. women; gender $\times$ time interaction; $P < 0.0001$). Greater workloads suggest greater energy turnover and more glycolytic flux, leading to greater lactate levels. The signals that stimulate the activation of glycogen phosphorylase to increase glycogenolysis could be inorganic phosphate and calcium, which result directly from muscle contraction. Another factor is estrogen. Administration of estrogen to rats has been shown to spare glycogen during exercise, possibly by increasing lipid availability during exercise (18). However, the route by which estrogen increases lipid availability is unknown. Regardless of the mechanism(s), if women were using less glycogen during hypoxia, they would produce less lactate during exercise. After exercise, the need for glycogen repletion would be less and might contribute to reduced removal and consequently increased plasma levels of glucose. These factors could explain why differences in metabolic responses to hypoxic exercise occurred in the absence of a blunted endocrine response to hypoxic exercise.

Based on the finding that lactate levels were quite variable for a given exercise intensity relative to $\dot{V}O_{2\,max}$, it has been suggested that exercise intensity should be expressed relative to the lactate threshold rather than as a percentage of $\dot{V}O_{2\,max}$ (27). However, the results showed no impact of gender on the lactate threshold expressed as $\%\dot{V}O_{2\,max}$ or power output per kilogram fat-free mass (2.7 ± 0.19 vs. $2.7 \pm 0.23\%$ $\dot{V}O_{2\,max}$ in men vs. women; $P > 0.05$). Despite some variability (ranges from 87.3 to 137.1% lactate threshold vs. 73.8 to 137.1% lactate threshold at E3 in men vs. women), there was no impact of gender on the exercise intensity for E1, E2, and E3 as expressed relative to the lactate threshold in men vs. women (48.6 ± 3.6, 72.9 ± 5.4, $97.2 \pm 7.2\%$ lactate threshold vs. 49.0 ± 3.9, 73.5 ± 5.9, $98.0 \pm 7.9\%$ lactate threshold in men vs. women for E1, E2, and E3, respectively; $P > 0.05$). In addition, the men and women were consuming the same amount of oxygen per kilogram fat-free mass, reflecting very similar relative exercise intensities. Thus the gender differences in this study were most likely not due to the fact that exercise intensity was expressed relative to $\dot{V}O_{2\,peak}$.

The female subjects in this study were all taking OC so that we could avoid the complications of studying women during the menstrual cycle. Because of the difficulty in recruiting subjects, the brand or length of time taking OC was assessed but not controlled. All OC prescriptions used by the subjects in this study contained ethinyl estradiol as the synthetic estrogen, albeit at different dosages in some cases. Estrogen and progestin dosage within each OC may have an independent impact on hormonal and metabolic response to exercise. However, there were no correlations between

baseline cortisol and growth hormone levels and length of time on the pill ($r = 0.35$ and 0.64, respectively) and estrogen ($r = 0.23$ and -0.01, respectively) or progesterone ($r = 0.57$ and 0.05, respectively) dosage ($P > 0.05$ for all correlations). Thus the wide range of time on, and types of, OC prescriptions may not have added any more variation than studying women in different phases of the menstrual cycle when there is wide individual variation in reproductive hormonal levels and sensitivities, yet studying these women added the convenience and ease of OC phase differentiation.

In summary, in contrast to our hypothesis, the women did not have a blunted endocrine response to hypoxia. However, the women did have a lower lactate during hypoxia and greater glucose response during recovery from hypoxia. These differences are most likely due to differences in absolute workload or the presence of estrogen in women vs. men. Less absolute work would lead to less lactate production and glycogen use, and thus less glucose would be taken up by the muscle for refueling glycogen stores after exercise in women. Therefore, the most significant impact of gender on the response to hypoxic exercise may be due to differences in muscle metabolism independent of endocrine drive.

We thank Jeffrey Thresher and Pam Bosch for technical assistance during data collection and analysis. Special thanks to Drs. M. Pagliassotti and R. Roach for critical review of the manuscript. Also, we thank all the research subjects who volunteered to be a part of this study.

This work was supported in part by the American College of Sports Medicine-National Aeronautics and Space Administration Space Physiology Student Research Grant.

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