# Sympathoadrenal Responses to Submaximal Exercise in Women After Acclimatization to 4,300 Meters

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**The purpose of this investigation was to determine the sympathoadrenal response to exercise in women after acclimatization to high altitude. Sixteen eumenorrheic women (age, 23.6 ± 1.2 years; weight, 56.2 ± 4.3 kg) were studied at sea level and after 10 days of high-altitude exposure (4,300 m) in either the follicular (n = 11) or luteal (n = 5) phase. Subjects performed two 45-minute submaximal steady-state exercise tests (50% and 65% peak $O_2$ consumption [$\dot{V}O_2$ peak]) at sea level on a bicycle ergometer. Exercise tests were also performed on day 10 of altitude exposure (50% $\dot{V}O_2$ peak at sea level). As compared with rest, plasma epinephrine levels increased 36% in response to exercise at 50% $\dot{V}O_2$ peak at sea level, with no differences found between cycle phases. This increase was significantly greater (↑44%) during exercise at 65% $\dot{V}O_2$ peak. At altitude, the epinephrine response was identical to that found for 65% $\dot{V}O_2$ peak exercise at sea level (↑44%), with no differences found between phase assignments. The plasma norepinephrine response differed from that for epinephrine such that the increase with exercise at altitude (↑61%) was significantly greater compared with 65% $\dot{V}O_2$ peak exercise at sea level (↑49%). Again, no phase differences were observed. It is concluded that the sympathoadrenal response to exercise (1) did not differ between cycle phases across any condition and (2) was similar to that found previously in men, and (3) the relative exercise intensity is the primary factor responsible for the epinephrine response to exercise, whereas altitude had an additive effect on the norepinephrine response to exercise.**



HIGH-ALTITUDE EXPOSURE is known to elicit sympathoadrenal responses that help to regulate key physiologic and metabolic functions required to adjust to the stress imposed by hypobaric hypoxia.[1-6] We have previously documented the sympathoadrenal responses associated with both acute and chronic exposure to high altitude in men at rest and in response to exercise.[2-4] However, little is known with regard to how women adapt/respond to both acute and chronic high-altitude exposure.

The few studies available have provided evidence to suggest that women may not adapt to altitude in a similar fashion as documented for men. Specifically, differences in substrate metabolism, ventilatory response, arterial oxygen content, and the time course for hematologic changes have been reported during acute and chronic altitude exposure.[7-11] Additionally, the incidence of preeclampsia is also significantly higher among women who reside at high altitude as compared with sea level, and recent studies have suggested an elevation in sympathoadrenal activity as a possible mechanism.[12-14] Thus, there is a need to document the sympathoadrenal responses in women to acute and chronic altitude exposure. Further, how women respond to the added stress of exercise while at altitude remains unknown. As the sympathoadrenal response plays an integral role in the ability to adapt to both high-altitude exposure and exercise, it was a primary purpose of this study to determine if women demonstrate similar sympathoadrenal adjustments during exercise as those previously found in men, and the extent to which these responses contribute to the physiologic and metabolic adaptations associated with their acclimatization to high altitude.

It has also been reported that sympathoadrenal activity can be influenced by the menstrual cycle phase. It is generally found that under sea-level conditions, plasma norepinephrine levels are higher during the luteal phase versus the follicular phase[15,16]; however, a lack of difference in plasma norepinephrine content or urinary epinephrine excretion has also been reported.[16,17] Thus, a second purpose of this study was to examine the interaction between the cycle phase (luteal or follicular) and sympathoadrenal responses at altitude.

## SUBJECTS AND METHODS

### *Subjects*

Sixteen healthy, non-smoking, eumenorrheic sea-level residents (age, 23.6 ± 1.2 years; weight, 56.2 ± 4.3 kg) volunteered to participate in the study. All subjects read and signed an informed-consent form approved by the Human Subjects Committees from the University of Colorado Health Sciences Center and Stanford University and the US Army Surgeon General's Human Use Review Committee.

### *Protocol*

Sea-level measurements (756 mm Hg) were conducted at the Palo Alto Veterans Affairs Health Care System. None of the subjects were currently using oral contraceptives. Based on a prior 3-month diary record and information provided by the subject on her cycle length, each subject began testing for her luteinizing hormone (LH) surge using an ovulation predictor kit (OvuQuick; Becton-Dickinson, Rutherford, NJ) at least 4 days prior to the estimated time of the LH surge. Subjects began their studies at sea level and at high altitude on the day after menses began (follicular) or the day after a LH surge was detected (luteal). Ovarian steroid hormone levels were measured on days 3, 10,

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and 12 at sea level (both follicular and luteal phases), as well as days 3, 6, 9, 10, and 11 at high altitude. Hormone analysis was performed on blood samples using the Diagnostic Products (Los Angeles, CA) "Coat-A-Count" radioimmunoassay, and these data have been previously reported.[5]

Approximately 1 month after sea-level studies, subjects were assigned to arrive at altitude at the beginning of their follicular (n = 8) or luteal (n = 8) phase as already described. Altitude studies were performed while subjects resided at the summit of Pikes Peak, CO (462 mm Hg) for 12 days. Based on both urinary and plasma ovarian hormone measurements during the subjects' 12-day stay at altitude, it was determined that 3 women originally assigned to the luteal phase had crossed over into the follicular phase. Thus, data collected at altitude were analyzed as 11 women in the follicular phase and 5 in the luteal phase. Energy intake was regulated both at sea level and at altitude to avoid weight fluctuations as previously described in men.[18]

### *Catecholamine*

Blood samples for catecholamine analysis were collected both at rest and during submaximal exercise via an indwelling catheter placed in the radial artery. These samples were mixed with reduced glutathione (5 mmol/L) and EGTA and centrifuged, and the plasma was stored in liquid nitrogen until transfer to the Boulder laboratory for storage at −70°C.

Plasma catecholamine levels were determined by high-performance liquid chromatography ([HPLC] BioRad model 1330 pump and model 1340 electrochemical detector; BioRad, Hercules, CA) with electrochemical detection as previously described.[5] Dihydroxybenzylamine (Sigma, St Louis, MO) was used as the internal standard. Catecholamines were absorbed onto acid-washed alumina with 1.5 mol/L Tris buffer at pH 8.6 in 2% EDTA. The alumina was then washed twice with 3 mL distilled water. Catecholamines were extracted with 100 μL 0.1N perchloric acid with 10 minutes of shaking and a final centrifugation at 12,000 × *g*. One hundred microliters of eluant was then injected into the HPLC column (reverse-phase, Bio-Sil ODS-5S; BioRad) and eluted with the mobile phase (6.8 g sodium acetate-anhydrous, 1.0 g sodium heptane sulfonate, 60 mL acetonitrile, and 1.0 g $Na_2EDTA$ in 1.0 L, pH adjusted to 4.8). The flow rate was set at 1.1 mL/min at 2,000 psi at 0.65 V. The chromatogram was integrated on a Shimadzu Integration System (Kyoto, Japan; model C-R3A).

### *Blood Lactate*

Blood lactate was determined spectrophotometrically by the method of Hohorst.[19]

### *Exercise Protocol*

Peak oxygen consumption ($\dot{V}O_2$ peak) was determined from a continuous progressive exercise test on an electrically braked bicycle ergometer (SensorMedics, Anaheim, CA) with 25-W increments every 1 minute. Tests of $\dot{V}O_2$ peak were performed at sea level and on day 5 at altitude. $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ were determined using standard on-line open-circuit techniques (SensorMedics).

Submaximal steady-state exercise testing at sea level involved exercise at an intensity that elicited both 50% and 65% $\dot{V}O_2$ peak obtained during cycling. Subjects were tested at these different exercise intensities on separate days and during both phases of their menstrual cycle. During chronic altitude exposure (day 10), an absolute exercise intensity similar to that of 50% $\dot{V}O_2$ peak determined at sea level was used such that subjects were working at the same absolute $\dot{V}O_2$.

Before submaximal exercise, subjects rested quietly for at least 90 minutes seated in a chair. Subjects then exercised on the bicycle ergometer for 45 minutes at the determined $\dot{V}O_2$. Respiratory measurements and blood samples were collected at rest (−15 and 0 minutes prior to exercise) and at 15, 30, and 45 minutes of exercise.

### *Statistics*

All values reported are the mean ± SE. Differences across all testing conditions, as well as differences between follicular and luteal groups, were determined by a repeated-measures 2-way ANOVA with significance set at a *P* level less than .05. Tukey post hoc comparisons were used to identify significant differences among means. Pearson product correlations were used to assess the relationship between plasma catecholamine content and blood lactate and the respiratory exchange ratio (RER).

## RESULTS

### *$\dot{V}O_2$*

$\dot{V}O_2$ peak was 42.0 ± 1.4 mL/kg/min at sea level. This decreased to 32.2 ± 1.5 mL/kg/min at high altitude. All subjects exercised for 45 minutes at 2 different intensities at sea level. The first exercise intensity resulted in a mean absolute $\dot{V}O_2$ of 21.9 ± 0.6 mL/kg/min, which represents a relative intensity of 52.1% ± 0.8% of the sea-level $\dot{V}O_2$ peak (Table 1). The second submaximal exercise bout elicited an absolute $\dot{V}O_2$ of 27.2 ± 0.7 mL/kg/min corresponding to a 64.8% ± 1.1% relative intensity. The submaximal bout of exercise performed on day 10 at altitude was at the same absolute $\dot{V}O_2$ that elicited the 52.1% ± 0.8% intensity at sea level. This corresponded to a 66.0% ± 1.2% relative intensity at altitude.

### *Plasma Catecholamines*

For a given exercise intensity both at sea level and at altitude, no differences were observed between cycle phases for plasma epinephrine levels (Fig 1A and B). Thus, follicular and luteal data were grouped and are presented in Fig 2 as a function of the relative exercise intensity. Plasma epinephrine levels at rest did not differ at sea level versus after acclimatization to altitude. The values during exercise were significantly greater at 65% versus 50% $\dot{V}O_2$ peak at sea level. After acclimatization to high altitude, the response to exercise was dependent on the relative exercise intensity, as plasma epinephrine levels at altitude were similar to those found at 65% intensity at sea level.

Plasma norepinephrine levels did not differ as a function of cycle phase for any condition studies (rest and exercise at sea level and altitude; Fig 3A and B). Unlike the epinephrine response, plasma norepinephrine measured at rest was significantly higher after acclimatization to altitude as compared with sea level (Fig 4). During submaximal exercise at sea level, plasma norepinephrine was dependent on the exercise intensity, with values significantly higher at 65% versus 50% $\dot{V}O_2$ peak. However, unlike plasma epinephrine, altitude appeared to have an additive effect on the plasma norepinephrine response, as values at altitude were significantly greater than those found for the same relative exercise intensity at sea level (Fig 4). Thus, the norepinephrine response was altered after acclimatization to altitude such that plasma norepinephrine levels were higher

**Table 1. Absolute and Relative $\dot{V}O_2$peak During 45 Minutes of Submaximal Exercise at Sea Level and After Acclimatization to 4,300 Meters**

| Parameter | Sea Level | | Altitude |
|---|---|---|---|
| Absolute $\dot{V}O_2$peak (mL/kg/min) | 21.9 ± 0.6 | 27.2 ± 0.7 | 21.4 ± 0.7 |
| % $\dot{V}O_2$peak | 52.1 ± 0.8 | 64.8 ± 1.1 | 66.0 ± 1.2 |

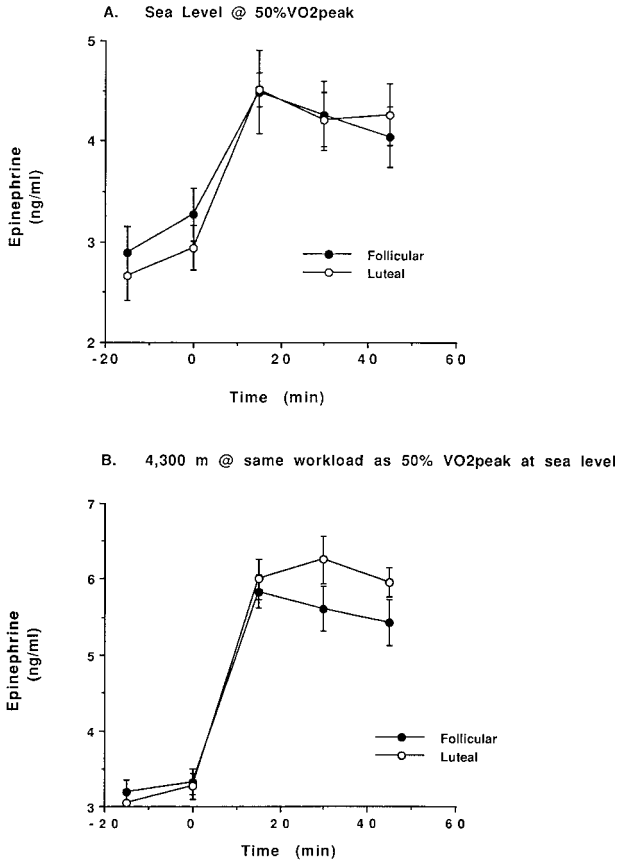


**Fig 1. Plasma epinephrine response for both the follicular and luteal phases during 45 minutes of submaximal exercise at (A) 50% $\dot{V}O_2$ peak at sea level and (B) the same absolute workload after 10 days of acclimatization at 4,300 m.**

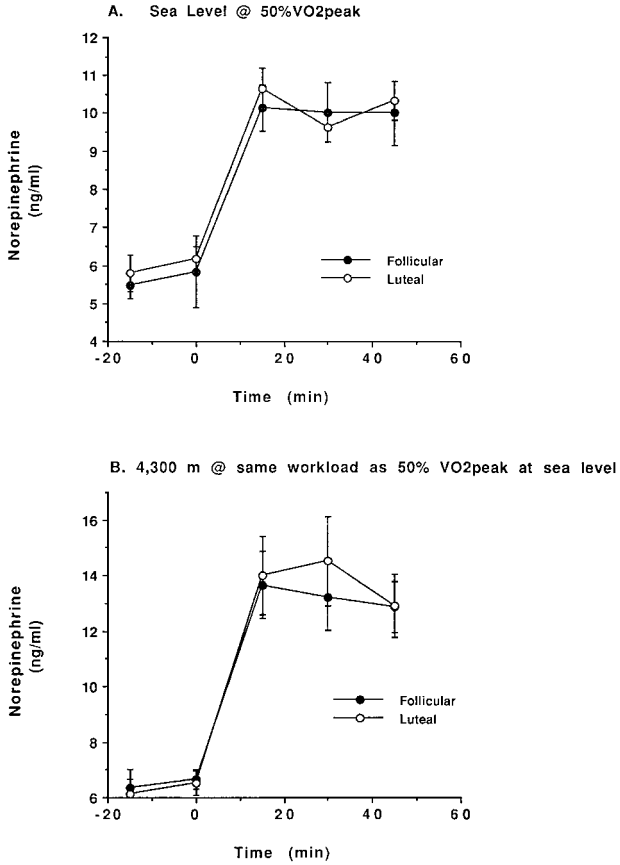


**Fig 3. Plasma norepinephrine response for both the follicular and luteal phases during 45 minutes of submaximal exercise at (A) 50% $\dot{V}O_2$ peak at sea level and (B) the same absolute workload after 10 days of acclimatization at 4,300 m.**

both at rest and during exercise at similar absolute and relative intensities when compared with sea-level values.

*Blood Lactate*

Under resting conditions, no differences in blood lactate were observed between sea level and altitude (Table 2). At sea level, it increased during exercise, with the highest values found at 65% $\dot{V}O_2$ peak exercise intensity. During exercise at altitude, blood lactate levels were significantly higher than those measured for the 50% $\dot{V}O_2$ peak, and similar when compared with the 65% $\dot{V}O_2$ peak, at sea level. This response was similar to that

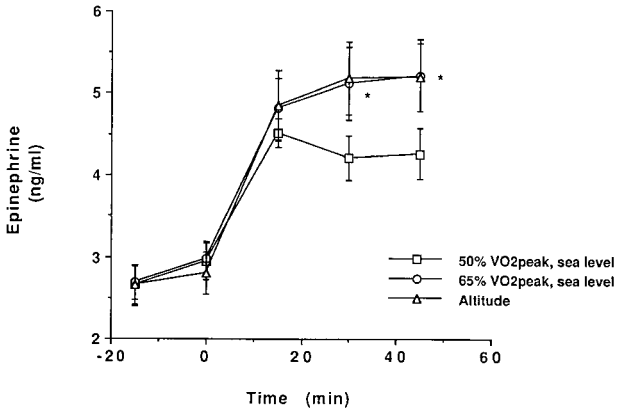


**Fig 2. Plasma epinephrine response as a function of the relative exercise intensity at sea level and at 4,300 m. Data were combined for follicular and luteal values. *Significantly different *v* 50% $\dot{V}O_2$ peak at sea level ($P < .05$).**

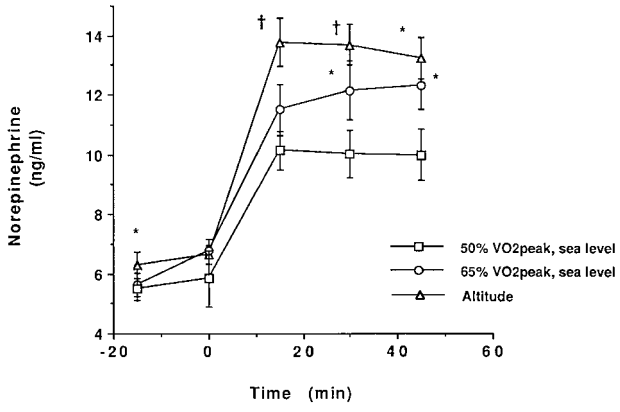


**Fig 4. Plasma norepinephrine response as a function of the relative exercise intensity at sea level and at 4,300 m. Data were combined for follicular and luteal values. *Significantly different *v* 50% $\dot{V}O_2$ peak at sea level ($P < .05$). †Significantly different *v* 50% and 65% $\dot{V}O_2$ peak at sea level ($P < .05$).**

**Table 2. RER and Blood Lactate During 45 Minutes of Submaximal Exercise at Sea Level and After Acclimatization to 4,300 Meters**

| Parameter | Time (min) 0 | 15 | 30 | 45 |
|---|---|---|---|---|
| RER | | | | |
| 50% $\dot{V}O_2$peak | 0.85 ± 0.02 | 0.96 ± 0.01 | 0.95 ± 0.01 | 0.93 ± 0.01 |
| 65% $\dot{V}O_2$peak | 0.89 ± 0.01 | 1.00 ± 0.01 | 0.97 ± 0.01 | 0.95 ± 0.01 |
| Altitude | 0.84 ± 0.02 | 0.96 ± 0.01* | 0.93 ± 0.01* | 0.91 ± 0.01* |
| Blood lactate (mmol/L) | | | | |
| 50% $\dot{V}O_2$peak | 0.52 ± 0.05 | 1.94 ± 0.23† | 1.54 ± 0.29† | 1.27 ± 0.27† |
| 65% $\dot{V}O_2$peak | 0.51 ± 0.05 | 4.73 ± 0.49 | 3.93 ± 0.48 | 2.92 ± 0.32 |
| Altitude | 0.60 ± 0.04 | 3.87 ± 0.50 | 3.80 ± 0.54 | 3.27 ± 0.47 |

*Significantly different *v* 65% $\dot{V}O_2$peak ($P < .05$).
†Significantly different *v* 65% $\dot{V}O_2$peak and altitude ($P < .05$).

demonstrated for plasma epinephrine, and consequently, blood lactate during exercise was highly correlated with plasma epinephrine (Fig 5).

*RER*

The RER did not differ at rest across any condition. During submaximal exercise at sea level, the RER increased as a function of exercise intensity and was significantly greater during 65% versus 50% $\dot{V}O_2$ peak exercise (Table 2). However, during exercise at altitude, the RER was significantly lower when compared with both the same relative and absolute exercise intensity at sea level. Further, this decrease in RER associated with acclimatization was negatively correlated with the increase in plasma norepinephrine ($r = -.88$).

*Heart Rate*

The heart rate response to all exercise bouts is shown in Fig 6. The resting heart rate was significantly elevated at altitude compared with sea-level conditions. Compared with rest, the heart rate increased significantly for all exercise bouts. At sea level, the heart rate was significantly higher during exercise at 65% versus 50% $\dot{V}O_2$ peak. Heart rates during exercise at altitude were similar to those found for 65% $\dot{V}O_2$ peak exercise at sea level. Thus, the relative rather than absolute exercise intensity was the major factor influencing the heart rate at altitude.

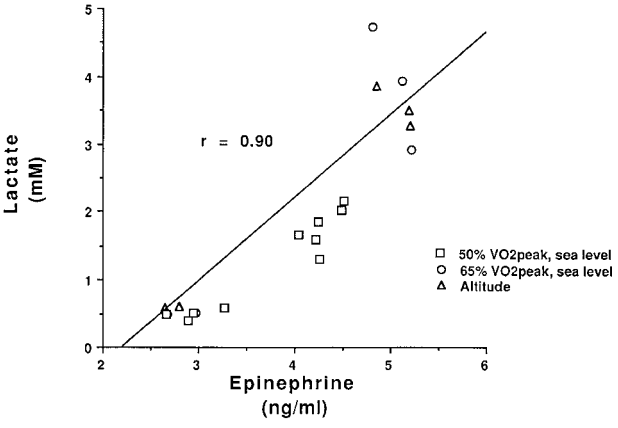


**Fig 5. Relationship between plasma epinephrine and blood lactate during 45 minutes of submaximal exercise at 50% and 65% $\dot{V}O_2$ peak at sea level and 65% $\dot{V}O_2$ peak at altitude.**

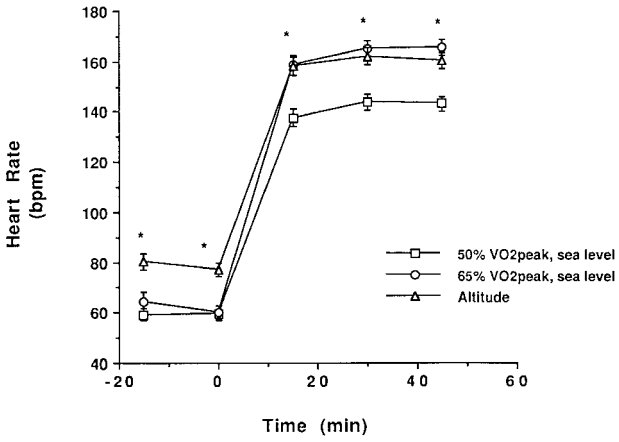


**Fig 6. Heart rate response as a function of the relative exercise intensity at sea level and at 4,300 m. Data were combined for follicular and luteal values. *Significantly different *v* 50% $\dot{V}O_2$ peak at sea level ($P < .05$).**

## DISCUSSION

The major findings of the present investigation are as follows: (1) the epinephrine response to exercise in women after 10 days of acclimatization to 4,300 m is solely dependent on the relative exercise intensity, and (2) the norepinephrine response to exercise is a function of the relative exercise intensity but is potentiated by high-altitude exposure. Further, it was determined that the sympathoadrenal system in these women responded to exercise after high-altitude exposure similarly to that previously documented in men. The cycle phase appeared to have little effect on these responses.

The observation that the epinephrine response after acclimatization to altitude is dependent on the relative exercise intensity is consistent with previous studies in men.[2,20] Upon initial exposure to high altitude, the adrenomedullary response is significantly elevated both at rest and during submaximal exercise compared with values at sea level. This has been interpreted to be the direct result of the hypoxic stimulus on the adrenal gland, resulting in an increased release of epinephrine.[2,21-23] However, after acclimatization and the associated improvement in the oxygen carrying capacity of the blood (decreased plasma volume and increased red blood cell number and $CaO_2$), the hypoxic stress on the adrenals is diminished and the epinephrine response to exercise returns to that observed at sea level. Thus, given that after acclimatization the adrenal response has returned to normal, it is not surprising that epinephrine levels during submaximal exercise for women in this study were completely dependent on the relative stress/exercise intensity. To our knowledge, this is the first study to compare the epinephrine response after acclimatization to high altitude with that observed at similar absolute and relative workloads at sea level. Young et al[20] investigated men who exercised for 30 minutes at the same relative intensity (80% $\dot{V}O_2$ max) both at sea level and at 4,300 m. On day 3 at altitude, plasma epinephrine levels during exercise were significantly greater as compared with sea level; but by day 8, values during

exercise had returned to those found at sea level. Our findings are consistent with the results of Young et al[20] since, after acclimatization, submaximal exercise at an identical relative workload elicited similar plasma epinephrine responses.

The plasma norepinephrine response to exercise after acclimatization was different from that found for epinephrine. In addition to the relative exercise intensity, it appears that acclimatization to high altitude had an additive effect on the plasma norepinephrine response. The combination of both 65% $\dot{V}O_2$ peak exercise and altitude elicited a greater increase in norepinephrine content versus the same relative exercise bout at sea level (Fig 4). We have previously demonstrated that in both men and women, there is a steady increase in resting sympathetic nerve activity during the first week at altitude.[4,5,22] This increase has been documented by the measurement of 24-hour urinary norepinephrine excretion, resting arterial levels, and the net release of norepinephrine from resting legs. At 4,300 m, the increase in sympathetic nerve activity appears to plateau at these elevated rates by days 5 to 7. As the subjects of the present investigation were tested on day 10 at altitude, an additive effect of this sympathetic adaptation was observed on the relative exercise intensity. In the only other comparable study, Young et al[20] reported that the plasma norepinephrine response to 80% $\dot{V}O_2$ max exercise was significantly greater by day 8 at altitude versus a similar relative exercise intensity at sea level. Our results agree with those findings and suggest that the sympathetic response to a given relative exercise intensity is exacerbated after acclimatization to altitude.

The potential significance of these sympathoadrenal adaptations is evident when addressed in relation to key physiologic and metabolic adjustments made in response to exercise at altitude. As with epinephrine, the heart rate response to exercise was dependent on the relative exercise intensity imposed. The heart rates during exercise at altitude were similar to those observed at the same relative intensity performed at sea level. Submaximal exercise during acute exposure to altitude has been consistently demonstrated to elicit significantly higher heart rates compared with sea level.[24-26] This adaptation assists in improving cardiac output and, consequently, oxygen delivery during acute exposure. Increased heart sympathetic nerve activity, as well as elevated epinephrine levels, contribute to this heart rate response.[27] However, after acclimatization, the heart rate for a given work intensity is known to decline toward sea-level values. Whether this adaptation is due to a downregulation of β-adrenergic receptors in the heart,[28-31] a return of sympathetic nerve activity in the heart toward sea-level values,[27,32] and increase in parasympathetic nerve activity,[27,32] or a combination of these factors is still under investigation. Regardless of the mechanism(s), the heart rate response to submaximal exercise after acclimatization is similar to that found at sea level and is dependent on the relative exercise intensity.

The association between blood lactate and plasma epinephrine (Fig 5) found in the present investigation is consistent with previous studies demonstrating a relationship between these variables.[2,33] Epinephrine is well documented to increase muscle glycogenolysis via activation of phosphorylase *a*, leading to an increase in lactate production.[34] As already described, the epinephrine response to exercise after acclimatization to high altitude was dependent on the relative exercise intensity. Blood lactate responded in an identical manner, as values during exercise at altitude were similar to those found with 65% $\dot{V}O_2$ peak exercise at sea level. Thus, both the epinephrine and lactate responses to exercise after acclimatization to altitude are dependent on the relative intensity. While other factors can contribute to the lactate response to exercise at altitude,[22] epinephrine appears to play a role in this response. This is consistent with other studies demonstrating a tight coupling between increases in plasma epinephrine and lactate during exercise in hypoxia.[2,33]

An interesting relationship ($r = -.88$) was observed between the increase in plasma norepinephrine and the decrease in the RER associated with exercise after acclimatization to altitude. The RER was significantly lower during exercise after acclimatization to altitude compared with the same relative exercise intensity at sea level. This would suggest that for the women in the present study, a greater utilization of lipid energy sources during exercise was associated with acclimatization to altitude.[35] Such a shift in substrate selection with chronic altitude exposure has been suggested previously.[20,25,36] However, recent studies with isotopic tracers indicate that in men, acclimatization to altitude results in a greater reliance on blood glucose as a fuel during exercise.[37,38] Thus, a gender effect may explain the differences between these studies and the results of the present investigation, as women are known to utilize fat to a greater extent than men both at rest and during submaximal exercise.[39,40] While a strong correlation between the increase in plasma norepinephrine and the decrease in the RER does not necessarily imply cause and effect, there is reason to suspect that alterations in sympathetic nerve activity can influence substrate selection. It is well documented that mobilization of adipose fat stores is regulated, in part, by sympathetic activation of hormone-sensitive lipase.[41-43] Thus, the elevation in sympathetic nerve activity found at altitude in the present study likely contributed to the lower RER observed and the greater reliance on fat during exercise.

The finding that there were no differences in the catecholamine response between menstrual cycle phases during exercise both at sea level and at altitude is not surprising. Studies examining possible phase differences in catecholamine levels measured under resting conditions have produced equivocal results.[15-17] Of the studies that suggest a phase difference, it is generally reported that norepinephrine (but not epinephrine) levels are slightly elevated during the luteal phase compared with the follicular phase.[15,16] When an exercise stimulus is imposed on top of such a small cycle phase difference, it is likely masked by the large increase in plasma catecholamines (3- to 4-fold) associated with the exercise stress. Data from this investigation would also suggest that whether at rest or during exercise, the sympathoadrenal response to acclimatization at altitude is unaffected by the menstrual cycle phase.

A limitation of the present study concerns the lack of exercise testing on the first day of exposure to altitude. This negates the ability to make comparisons between acute exposure and day 10 at altitude (which we consider a chronic or acclimatized condition). However, there are several lines of evidence to indicate clearly that day 10 at altitude for our subjects represents an acclimatized state. This includes repeated measurements over time of such variables as $Sa_{O_2}$, $\dot{V}_E$, heart rate, and, most

importantly for the purposes of this study, urinary catecholamine excretion rates. It should be noted that we have previously reported the urinary catecholamine excretion rates in these same women over each of 12 days at altitude.[5] These data indicate that the women in the present study responded to altitude in a similar manner as previously determined by our group for men who were exercise-tested on day 1 of altitude exposure,[2-4] and furthermore, evidence for acclimatization with regard to the catecholamine response was present.

In summary, the results from this investigation suggest that the sympathetic response to exercise at the same relative intensity is potentiated by 10 days of acclimatization to 4,300 m. However, the epinephrine response to exercise does not demonstrate such an affect and is dependent on the relative intensity only. These sympathoadrenal responses to high-altitude exposure can influence a number of metabolic and physiologic variables. Finally, the menstrual cycle phase appears to have little effect on the sympathoadrenal response to exercise at altitude.

## ACKNOWLEDGMENT

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