Catecholamine responses to α-adrenergic blockade during exercise in women acutely exposed to altitude

ROBERT S. MAZZEBO,1 JOY D. CARROLL,1 GAIL. E. BUTTERFIELD,2 PAUL B. ROCK,3 EUGENE. E. WOLFEL,4 STACY ZAMUDIO,4 AND LORNA G. MOORE4

1Department of Kinesiology and Applied Physiology, University of Colorado, Boulder, Colorado 80309; 2Palo Alto Veterans Affairs Health Care System, Palo Alto, California 94304–1290; 3US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760–5007; and 4University of Colorado, Health Sciences Center, Denver, Colorado 80220

Received 27 January 2000; accepted in final form 24 July 2000

Mazzeo, Robert S., Joy D. Carroll, Gail. E. Butterfield, Barry Braun, Paul B. Rock, Eugene E. Wolfel, Stacy Zamudio, and Lorna G. Moore. Catecholamine responses to α-adrenergic blockade during exercise in women acutely exposed to altitude. J Appl Physiol 90: 121–126, 2001.—We have previously documented the importance of the sympathetic nervous system in acclimatizing to high altitude in men. The purpose of this investigation was to determine the extent to which α-adrenergic blockade affects the sympathoadrenal responses to exercise during acute high-altitude exposure in women. Twelve eumenorrheic women (24.7 ± 1.3 yr, 70.6 ± 2.6 kg) were studied at sea level and on day 2 of high-altitude exposure (4,300-m hypobaric chamber) in either their follicular or luteal phase. Subjects performed two graded-exercise tests at sea level (on separate days) on a bicycle ergometer after 3 days of taking either a placebo or an α-blocker (3 mg/day prazosin). Subjects also performed two similar exercise tests while at altitude. Effectiveness of blockade was determined by phenylephrine challenge. At sea level, plasma norepinephrine levels during exercise were 48% greater when subjects were α-blocked compared with their placebo trial. This difference was only 25% when subjects were studied at altitude. Plasma norepinephrine values were significantly elevated at altitude compared with sea level but to a greater extent for the placebo (↑59%) vs. blocked (↑35%) trial. A more dramatic effect of both altitude (↑104% placebo vs. 95% blocked) and blockade (↑50% sea level vs. 44% altitude) was observed for plasma epinephrine levels during exercise. No phase differences were observed across any condition studied. It was concluded that α-adrenergic blockade 1) resulted in a compensatory sympathoadrenal response during exercise at sea level and altitude, and 2) this effect was more pronounced for plasma epinephrine.

epinephrine; norepinephrine; sympathetics; hypoxia

SYMPATHOADRENAL ACTIVITY IS enhanced on exposure to high altitude and plays an integral role in helping to adapt to hypobaric hypoxia. Our laboratory has previously documented the importance of both the sympathetic and adrenal medullary responses during acute, as well as more prolonged, exposure to high altitude in men (12–17). Furthermore, our laboratory has also documented these sympathoadrenal responses with the added stress of exercise while at altitude (12–15). These studies have demonstrated that, during initial exposure to 4,300 m (0–3 days), the adrenal secretion of epinephrine is significantly elevated in an attempt to compensate for the reduction in arterial O2 saturation (12, 13). However, as indicated by both plasma and urinary excretion content, the epinephrine levels returned to sea-level values by days 4 and 5 of altitude exposure. Unlike epinephrine, the norepinephrine response (as measured by plasma content, urinary excretion rates, and norepinephrine release across muscle) indicated a progressive increase in sympathetic nerve activity over time at altitude, peaking on days 5–7 and remaining elevated throughout the duration of altitude residence.

As these sympathoadrenal responses have been shown to regulate a number of metabolic and physiological adaptations to altitude (substrate selection, cardiovascular and respiratory adjustments), the potential mechanisms whereby α-adrenergic activation contributes to these adaptations is of interest. Previous studies examining the role of β-adrenergic function at altitude suggest that, while playing an important role, these receptors only account for part of the overall sympathoadrenal contribution to altitude adaptations (13, 20, 25, 27). As the α-adrenergic receptors are known to regulate a number of key functions (cardiac activity, blood flow, substrate metabolism), a purpose of this study was to examine the extent to which α-blockade affects the ability to adjust to hypoxic stress. It was hypothesized that the presence of α-adrenergic blockade would alter the ability to adjust to exercise during acute hypoxia. Furthermore, as little is known with regard to the mechanisms and magnitude to which women adapt to high-altitude exposure, a
second purpose of this study was to examine how female subjects adapt to acute altitude exposure both at rest and during the added stress of exercise in the absence and presence of α-blockade.

METHODS

Subjects. Twelve healthy, recreationally active, nonsmoking, eumenorrheic, sea-level residents (age 24.7 ± 1.2 yr; weight 70.6 ± 4.3 kg) volunteered to participate in the study. All subjects read and signed an informed consent approved by the Human Subjects Committees from the University of Colorado Health Sciences Center, Stanford University, and the US Army Surgeon General’s Human Use Review Committee.

Protocol. Sea-level and simulated altitude experiments were conducted in the environmental chamber at US Army Research Institute of Environmental Medicine in Natick, MA. Subjects were tested on two different occasions: once while receiving a placebo and once while receiving the α-blocker prazosin (3 mg/day). All trials were conducted in a randomized and double-blind manner. A phenylephrine challenge was conducted on all subjects on day 3 of sea-level conditions to confirm the extent of blockade. On each testing session, subjects resided in the environmental chamber for 68 h under sea-level conditions, after which they were brought to a simulated 4,300 m (445 mmHg) within a 10-min adjustment period. Subjects were tested twice under these conditions, both with and without prazosin. Experiments were conducted 28 days apart in an attempt to have tests occurring during the same phase of the menstrual cycle to control for possible cycle variations on catecholamine levels. Each subject, on admission to the study, kept a menstrual cycle diary, noting the date and duration of menses, the date of a luteinizing hormone (LH) surge, and duration of the cycle. On the basis of a 3-mo history documented by diary or by information provided from the subject on cycle length, each subject began testing for her LH surge using an ovulation predictor kit (OvuQuick, Becton-Dickson, Rutherford, NJ) at least 4 days before the estimated time of the LH surge. Ovarian steroid hormones were measured to document cycle phase. Women were considered to be in the follicular phase when concentrations of estradiol were present and progesterone levels had to achieve 0.41 ng/ml for placebo and prazosin trials compared with sea-level values (10.7 ± 2.0 μg·kg\(^{-1}\)·min\(^{-1}\)) compared with the placebo trial (2.0 ± 0.3 μg·kg\(^{-1}\)·min\(^{-1}\)). Thus the presence of α-adrenergic blockade was confirmed.

Plasma catecholamines. At sea level, significant differences were found in norepinephrine levels between placebo and prazosin groups at rest (0.70 ± 0.12 and 0.32 ± 0.19 μg/ml plasma, respectively; P < 0.02). During the progressive exercise test at sea level, a similar pattern was observed such that, when subjects were blocked, significantly higher norepinephrine levels (P < 0.03) were found compared with those for placebo trials (mean for all workloads combined, 2.82 ± 0.32 and 4.16 ± 0.41 μg/ml for placebo and prazosin groups, respectively; Fig. 1). In response to altitude exposure, resting norepinephrine levels were significantly elevated (↑) (P < 0.03) for both placebo and prazosin trials compared with sea-level values (↑63 and 50%, respectively). Mean exercise values also indicated that norepinephrine levels while at altitude were significantly greater (P < 0.04) than those found at sea level (↑59 and 35% for placebo and prazosin trials, respectively). While at altitude, resting norepi-
nephrine levels continued to be greater for prazosin trials ($P < 0.03$) compared with placebo; however, during exercise at altitude, no significant differences existed between placebo and prazosin trials.

Epinephrine response to both $\alpha$-blockade and altitude was even more dramatic than that found for norepinephrine (Fig. 2). At sea level, significant differences were found between placebo and prazosin groups at rest ($0.28 \pm 0.04$ and $0.42 \pm 0.07$ ng/ml plasma, respectively; $P < 0.02$). During the progressive exercise test at sea level, a similar pattern was observed such that, when subjects were blocked, significantly higher epinephrine levels were found compared with placebo trials (mean for all workloads combined, $0.8 \pm 0.06$ and $1.51 \pm 0.13$ ng/ml for placebo and prazosin groups, respectively; $P < 0.01$). In response to altitude exposure, resting epinephrine levels were significantly elevated for both placebo and prazosin trials compared with sea-level values ($\uparrow 104$ and $95\%$, respectively; $P < 0.01$). Mean exercise values also indicated that epinephrine levels while at altitude were significantly greater than those found at sea level ($\uparrow 110$ and $66\%$ for placebo and prazosin trials, respectively; $P < 0.02$). Additionally, epinephrine levels during exercise at altitude were significantly greater ($P < 0.03$) for the prazosin compared with the placebo trial, unlike results found for norepinephrine.

Twenty-four-hour urinary catecholamines. Norepinephrine and epinephrine 24-h excretion concentrations are shown in Figs. 3 and 4, respectively. There were no significant differences in urinary norepinephrine excretion rates between drug and placebo groups during the 3 days at sea level or the 2 days at high altitude. Additionally, while urinary norepinephrine excretion rates tended to be higher after 2 days at altitude, values were not different from the combined 3 days at sea level. However, in both groups, urinary epinephrine excretion rates increased significantly after 24 h at high altitude compared with sea level ($1.3 \pm 0.4$ to $29.5 \pm 7.1$ and $2.8 \pm 1.3$ to $34.9 \pm 12.1$ μg epinephrine/24 h for placebo and prazosin trials, respectively; $P < 0.01$). Urinary epinephrine excretion rates continued to rise on day 2 at altitude, with the prazosin trial rates being significantly greater than those found for placebo ($74.7 \pm 17.5$ vs. $42.9 \pm 12.3$ μg epinephrine/24 h, respectively; $P < 0.02$).

Fig. 1. Plasma norepinephrine levels at rest and during a progressive exercise test in subjects at sea level as well as after 2 days at simulated 4,300 m. All subjects were tested after administration of a placebo and $\alpha$-blockade on separate occasions, both at sea level and altitude. Values are means ± SE; $n = 12$. Exh, exhaustion.

Fig. 2. Plasma epinephrine levels at rest and during a progressive exercise test in subjects at sea level as well as after 2 days at simulated 4,300 m. All subjects were tested after administration of a placebo and $\alpha$-blockade on separate occasions, both at sea level and altitude. Values are means ± SE; $n = 12$.

Fig. 3. Twenty-four-hour urinary norepinephrine excretion rates for all subjects at sea level and at 4,300 m after administration of a placebo and $\alpha$-blockade. Values are means ± SE; $n = 12$. Fig. 4. Twenty-four-hour urinary epinephrine excretion rates for all subjects at sea level and at 4,300 m after administration of a placebo and $\alpha$-blockade. Values are means ± SE; $n = 12$.
DISCUSSION

The principal findings of the present study suggest that 1) compared with sea level, a strong sympathoadrenal response occurs in women both at rest and during progressive exercise when they are acutely exposed to high altitude, and 2) α-adrenergic blockade elicits a compensatory sympathoadrenal response (both at sea level and altitude), which results in enhanced catecholamine levels compared with placebo trials.

To our knowledge, this is the first study to examine the combined effects of acute hypoxia and exercise on the sympathoadrenal responses in women. Furthermore, no prior studies, in either men or women, have been conducted to assess the influence of α-adrenergic blockade under these conditions. Based on previous studies indicating that women respond to the stress of both acute (7, 24) and chronic (5) exercise with significantly lower catecholamine responses compared with men, we originally hypothesized that the responses may be different between the genders with the combined stress of acute hypoxia and exercise. Additionally, these gender-based catecholamine differences are thought to contribute, in part, to some of the metabolic and physiological differences observed between men and women during exercise. In support of this, using both β- and α-adrenergic blockade, Hellstrom et al. (7) concluded that there are gender differences in the adrenergic regulation of substrate metabolism during exercise that are specific to the α-adrenergic receptors. The observation in the present study that plasma epinephrine levels were elevated both at rest (104%) and during exercise (110%) in women acutely exposed to high altitude is consistent with previous investigations performed on men at a similar altitude (12–14). After 4 h at 4,300 m, men exercising for 45 min at 67% of altitude maximum VO₂ (VO₂ max) had increased plasma epinephrine levels of 126% compared with sea-level values (12), indicating a similar response to that found for the women in the present investigation. An early rise in plasma epinephrine levels with high-altitude exposure has been associated with the decrease in arterial oxygen content. Hypoxia acts as a direct stimulus on the adrenal medulla, resulting in increased epinephrine release and elevated arterial concentrations (1, 4, 8, 9, 19, 21). In support of this, the extent of this response is dependent on the duration and severity of the hypoxic stimulus. During acute hypoxia, when arterial O₂ saturation levels are the lowest, arterial epinephrine concentration is significantly elevated. Increased circulating epinephrine serves as a homeostatic mechanism to maintain oxygenation to tissues via increasing heart rate, stroke volume, vasodilation, and ventilation. In previous studies in men, arterial oxygenation improved with acclimatization, and, consequently, epinephrine levels declined toward sea-level values. This adrenal medullary response to acute hypoxia in the women of the present study is further documented by the 24-h urinary epinephrine excretion rates (Fig. 4). Urinary epinephrine excretion rates after 24 h at altitude increased dramatically over the averaged rates at sea level for the placebo trial (1.3 ± 0.4 vs. 29.5 ± 7.1 μg/day for sea level and altitude, respectively). After day 2 at altitude, urinary epinephrine excretion rates continued to increase even further (42.9 ± 12.3 μg/day), providing evidence of sustained adrenal medullary activation during the initial days of exposure. Whereas this pattern of increased urinary epinephrine excretion rates during acute hypoxia is similar to that previously reported from our laboratory in men (17), the magnitude of this response appears to be much greater in women.

Whereas the degree was not as great as that seen for epinephrine, a similar pattern was observed for the plasma norepinephrine response to acute altitude exposure both at rest and during exercise. Under these conditions (altitude and exercise), measurement of plasma norepinephrine levels has been shown to be a good indicator of whole body sympathetic nerve activ-

![Fig. 4. Twenty-four-hour urinary epinephrine excretion rates for all subjects at sea level and at 4,300 m after administration of a placebo and α-blockade. Values are means ± SE; n = 12. *Significantly different from sea level; †significantly different from placebo (P < 0.05).](http://jap.physiology.org/)

| Table 1. Resting and peak exercise blood pressures and heart rates |
|-----------------------|---------------------|---------------------|
|                       | Sea Level           | Altitude            |
|                       | Placebo Prazosin    | Placebo Prazosin    |
| **Systolic pressure, mmHg** |
| Rest                  | 111 ± 2             | 110 ± 4             |
| Peak exercise         | 159 ± 6             | 151 ± 7             |
| **Diastolic pressure, mmHg** |
| Rest                  | 65 ± 1              | 65 ± 2              |
| Peak exercise         | 70 ± 3              | 61 ± 5†             |
| **Mean arterial pressure, mmHg** |
| Rest                  | 81 ± 1              | 81 ± 2              |
| Peak exercise         | 100 ± 3             | 90 ± 5†             |
| **Heart rate, beats/min** |
| Rest                  | 77 ± 3              | 78 ± 3              |
| Peak exercise         | 172 ± 4             | 179 ± 2             |

Values are means ± SE; n = 12 subjects. *Significantly different from normoxia; †significantly different from placebo trial, P < 0.05.
ity (14). An increase in whole body sympathetic nerve activity during acute hypoxia has been shown in previous investigations in men (10, 12, 14). With the use of microneurography, an increase specifically in muscle sympathetic nerve activity under resting conditions has been demonstrated in men acutely exposed to hypoxia (22, 23). Furthermore, an increase in net norepinephrine release from the resting leg in men after 4 h at 4,300 m adds additional support for an elevation of sympathetic nerve activity in response to acute hypoxia. This augmented sympathetic response to hypoxia is also observed when the added stress of exercise is imposed on the women tested in this investigation (Fig. 1). For any given submaximal workload, plasma norepinephrine levels were significantly greater compared with sea-level values (†63 and 59% for rest and exercise, respectively). It has been suggested that this elevation in norepinephrine content is a function of the relative exercise intensity as \( V_{\text{O}_2 \text{max}} \) is reduced at altitude (4, 9). The relative exercise intensity is clearly a primary factor in determining the extent to which plasma norepinephrine levels and sympathetic nerve activity are influenced at altitude. However, it is also clear from the resting responses mentioned above that hypoxia can act independently from its effect on \( V_{\text{O}_2 \text{max}} \).

In the presence of \( \alpha \)-blockade, a striking sympathoadrenal secondary effect was observed at sea level as well as with acute altitude exposure. Prazosin is considered to be a selective \( \alpha_1 \)-adrenergic blocker with a relatively low affinity for \( \alpha_2 \)-receptors. Thus its primary effect is to reduce peripheral vascular resistance by inhibiting the vasoconstriction produced by norepinephrine released at smooth-muscle nerve endings (3). As cited above, altitude exposure elicits an elevation in muscle sympathetic nerve activity, which is associated with an increase in mean arterial pressure (26). This adaptation will shunt blood flow from skeletal muscle (tissue in which the sympathetic response is the greatest during altitude exposure), allowing a greater percentage of cardiac output to be directed toward more essential tissues to assist in maintaining oxygen homeostasis (23). However, in the presence of \( \alpha \)-blockade, vasoconstriction is inhibited and mean arterial pressure is reduced. The results of the present investigation suggest that this results in a strong adrenal medullary response releasing epinephrine in a likely attempt to increase cardiac output and maintain arterial pressure (see Table 1). In support of this, selective \( \alpha_1 \)-blockade (prazosin) has been shown to significantly augment both heart rate and ventricular contractility during exercise in dogs (6).

Other investigations, performed at sea level, have also demonstrated a compensatory catecholamine response in humans (18) and animals (2, 6) during exercise after \( \alpha_1 \)-blockade. The present study found an additive effect such that both hypoxia and \( \alpha_1 \)-blockade resulted in a greater catecholamine response than either variable alone. This potentiated response in circulating catecholamines is likely to have a number of metabolic and physiological consequences. In humans and animals, \( \alpha \)-blockade producing an elevation in plasma catecholamines results in increased plasma lactate and glucose levels during acute exercise (2, 11, 18). Alterations in cardiac output as well as mean arterial pressure are also affected by an elevation in circulating catecholamines. The extent to which the augmented catecholamine response found for the women in the present study during \( \alpha \)-blockade contributed to metabolic and physiological adjustments to exercise at altitude remains to be determined.

Finally, there appears to be no direct effects of hypoxia on enhancing the prejunctional release of neuronal norepinephrine or on intraneural metabolism and uptake of the neurotransmitter in muscle (8, 21), suggesting that the enhanced spillover observed in the present study is directly related to an increase in sympathetic activity. Both no change and an increase in clearance of plasma norepinephrine have been reported (10, 22). An increase in clearance would actually tend to lower plasma levels and, therefore, would not explain the increases associated with altitude. We are confident from our previous studies directly measuring net norepinephrine release from both resting and exercising skeletal muscle that the increase in plasma levels of norepinephrine associated with altitude exposure reflect elevations in sympathetic nerve activity and subsequent spillover of the neurotransmitter into the circulation (14).

In summary, the results of the present investigation confirmed that, as previously demonstrated in men, acute exposure to altitude elicits a significant sympathoadrenal response in women both at rest and during a progressive exercise test. Furthermore, \( \alpha \)-adrenergic blockade elicits a compensatory sympathoadrenal response (both at sea level and altitude), which results in enhanced catecholamine levels compared with placebo trials.

REFERENCES


