# Influence of $\alpha$-Adrenergic Blockade on the Catecholamine Response to Exercise at 4,300 Meters

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**This investigation examined the influence of $\alpha$-adrenergic blockade on plasma and urinary catecholamine responses to both exercise and high-altitude exposure. Sixteen nonsmoking, eumenorrheic women (age 23.2 ± 1.4 years, 68.7 ± 1.0 kg) were studied at sea level and during 12 days of high-altitude exposure (4,300 m). Subjects received either $\alpha$-blockade (prazosin 3 mg/d) or a placebo in a double-blinded, randomized fashion. Resting plasma and 24-hour urine samples were collected periodically throughout the duration of the study. Further, subjects participated in submaximal exercise tests (50 minutes at 50% sea level maximum oxygen consumption [$V_{O_2}$max]) at Sea level and on days 1 and 12 at altitude. Urinary norepinephrine (NE) excretion rates increased significantly over time at altitude, with blocked subjects having greater values compared to controls. Plasma NE levels increased significantly with chronic altitude exposure compared to sea level and acute hypoxia both at rest and during exercise. NE levels at rest were greater for blocked compared to control subjects during all conditions. Urinary and plasma epinephrine (EPI) levels increased dramatically, with acute altitude exposure returning to sea level values by day 12 of altitude exposure. EPI levels were greater for blocked compared to placebo both at rest and during exercise for all conditions studied. Changes in $\alpha$-adrenergic activity over time at altitude were associated with select metabolic and physiologic adjustments. The presence of $\alpha$-blockade significantly affected these responses during chronic altitude exposure. It was concluded that: (1) $\alpha$- adrenergic blockade elicited a potentiated sympathoadrenal response to the stress of both exercise as well as high-altitude exposure, and (2) the sympathetics, via $\alpha$-adrenergic stimulation, contribute to a number of key adaptations associated with acclimatization to high altitude.**


WE HAVE PREVIOUSLY documented the sympathoadrenal responses during acclimatization to 4,300 meters. Specifically, results have clearly demonstrated a dissociation of the epinephrine (EPI) and norepinephrine (NE) responses during continued residence (12 to 21 days) at 4,300 meters both at rest and during submaximal exercise.[1-3] Arterial EPI levels in resting and exercising subjects were significantly elevated upon acute exposure to high altitude when compared to sea level values. After acclimatization, EPI values were significantly reduced when compared to those of acute exposure, approaching but not reaching sea level values. In contrast, NE levels increased progressively during the initial days at altitude reaching a plateau by day 5 to 7.[1-3] These responses were found to be consistent for both men and women.[4,5]

As the sympathetics are well documented to play a major role in the adjustments to disruptions in homeostasis (eg, hypoxia), the increase in sympathetic nervous system (SNS) activity observed during chronic altitude exposure likely makes a significant contribution during the acclimatization process. NE, the major neurotransmitter of the SNS, when interacting with $\alpha$- adrenergic receptors can regulate a number of key physiologic and metabolic processes, including blood flow, vascular resistance, blood pressure, substrate selection, immune function, and metabolic rate.[6-9] Our purpose was to determine the extent to which $\alpha$- adrenergic blockade influenced the ability to adapt to 12 days exposure to 4,300 meters. Given the consistent finding of increased SNS activity during acclimatization, we hypothesized that $\alpha$-adrenergic blockade with prazosin would affect key metabolic and physiologic adjustments made in response to chronic exposure to 4,300 meters in healthy women.

## MATERIALS AND METHODS

### *Subjects*

Sixteen healthy, eumenorrheic women (age 23.2 ± 1.4 years, 68.7 ± 4.5 kg) volunteered to participate in the study. Subjects were recreationally active, nonsmoking, sea-level residents not taking oral contraceptives at the time of the testing. Testing procedures received approval from the University of Colorado Health Sciences Center Institutional Review Board. Sea level tests were performed at the Veterans Affairs Medical Center in Palo Alto, CA. Altitude tests were performed at the summit of Pikes Peak, CO (4,300 meters) where subjects resided for 12 consecutive days. Subjects' diet and physical activity habits were closely monitored to avoid any weight fluctuations.

### *Study Design*

Subjects randomly received either $\alpha$-adrenergic blockade (prazosin 3 mg/d; n = 8), or a placebo (n = 8) in a double-blinded design. Drug administration began 3 days prior to initial testing at the Veterans Affairs Medical Center in Palo Alto, CA (15 meters, 752 mm Hg) and subjects remained on the drugs for the duration of the 12 days of sea level testing. Alpha-adrenergic blockade was confirmed by the dose response of systolic blood pressure to incremental increases in phenylephrine (phenylephrine challenge test), on the third and ninth day of the testing protocol at sea level and on day 9 at Pikes Peak.

An initial maximal oxygen consumption ($V_{O_2}$max) test was performed at sea level. Subjects participated in 2 submaximal exercise tests at sea level for 50 minutes at 50% of $V_{O_2}$max. The first test was

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conducted three days after administration of prazosin (SL day 1), and the second test was 11 days later (SL day 12) to control for any potential effect of prazosin over time (similar to the duration on prazosin at Pikes Peak). All exercise tests were performed on an electronically braked bicycle ergometer.

Altitude studies were conducted at the Maher Memorial Research Facility on the summit of Pikes Peak (4,300 meters, 462 mm Hg) approximately 8 weeks after sea level testing. Administration of prazosin or placebo began 3 days prior to arrival at altitude. Within 4 hours of arrival (day 1) and again on day 12, subjects performed a 50-minute submaximal exercise bout at the same absolute intensity that elicited 50% of sea level $V_{O_2}$max. A $V_{O_2}$max test was performed on day 8 at altitude.

### *Blood and Urine Collection*

Blood samples were collected at rest and during exercise from an antecubital vein via an indwelling catheter at −15, 0, 25, 40, and 50 minutes. Twenty-four–hour urine samples were collected continuously during the 12 days at altitude for catecholamine determination. Blood and urine samples were treated with 5 mmol/L reduced glutathione to control for catechol oxidation.

### *Catecholamine Measurements*

Blood and urinary catecholamine levels were determined by means of high-performance liquid chromatography (HPLC; BioRad Model 1330 pump, Model 1340 electrochemical detector, Hercules, CA) with electrochemical detection as previously described.[1] Dihydroxybenzylamine (DHBA; Sigma, St Louis, MO) was used as the internal standard. Catecholamines were absorbed onto acid-washed alumina with 1.5 mo/L tris (hydroxymethyl) aminomethane (Tris) buffer at pH 8.6 in 2% EDTA. The alumina was then washed 2 times with 3 mL of distilled water. The catecholamines were extracted with 100 $\mu$L of 0.1N perchloric acid with 10 minutes of shaking and final centrifugation at 12,000 × *g*. One hundred milliliters of eluant was then injected into the HPLC column (Reverse phase, Bio-Sil ODS-5S, BioRad), and eluted with mobile phase (6.8 g sodium acetate-anhydrous, 1.0 g sodium heptane sulfonate, 60 mL acetonitrile, 1.0 g $Na_2EDTA$ in 1 L pH adjusted to 4.8). The flow rate was set at 1.1 mL/min at 2,000 psi at 0.65 volts. The chromatogram was integrated on a Shimadzu Integration System, Model C-R3A (Tokyo, Japan).

### *Basal Metabolic Rate and Plasma Volume*

Basal metabolic rate (BMR) was determined by use of indirect calorimetry as previously reported.[7,10] Measurements were made at sea level as well as on days 2, 3, 4, 5, 6, 9, and 12 at 4,300 meters. BMR was measured the morning after 6 to 8 hours of bed rest (before rising) and 8 to 10 hours postprandial.

Plasma volume, measured at sea level and on days 3 and 10 at altitude, was determined by the carbon monoxide method as previously described.[11] Briefly, subjects were allowed to rest semirecumbent for at least 10 minutes, and then to rebreathe into a system approximately 5 L in volume containing 100% $O_2$ and a $CO_2$ absorber. After the subject rebreathed for 5 minutes, a 3-mL blood sample was drawn from a venous catheter placed in an arm vein to provide the baseline value. One hundred percent CO in volumes of 50 mL at sea level and 80 mL at 4,300 meters (STPD) were then injected into the rebreathing system. With the subject continuing to rebreathe, adding 100% $O_2$ as necessary, blood samples were drawn at 5, 10, and 15 minutes. Hematocrit (microhematocrit technique) and hemoglobin concentrations (Radiometer OSM3, Copenhagen, Denmark) were measured in duplicate for each blood sample, and the remainder of the sample was stored at 4°C for measurement in triplicate of carboxyhemoglobin concentration by gas chromatography. Total hemoglobin was then calculated by the volume of CO administered divided by the delta CO in milliliters per gram. Blood volume was calculated as total hemoglobin divided by the hemoglobin concentration of the subject, and red blood cell mass was calculated as blood volume multiplied by the on-site hematocrit. Plasma volume was then calculated as total blood volume less the red blood cell mass. The values reported here are the mean of the 10- and 15-minute samples.

### *Ovarian Hormones*

Cycle phase was monitored by recording basal body temperature daily upon awakening, ovulation predictor kits (OvuQuick, Becton-Dickinson, Rutherford, NJ), and by noting the dates of ovulation and date of and duration of menses for 3 months before and continuing until 1 cycle after completion of the high-altitude phase of the study. Serum ovarian hormones were measured on study days 1, 3, 6, 9, 10, and 12 at sea level and high altitude in order to verify cycle phase and document hormone concentrations. Women were considered to be in the follicular phase when cycle data in conjunction with measured hormone concentrations showed estradiol to be present (10 to 375 pg/mL) and progesterone absent (<2.5 ng/mL) and in the luteal phase when both estradiol (50 to 115 pg/mL) and progesterone were present (2.5 to 28 ng/mL). Estradiol and progesterone were measured after the study was completed, in duplicate, using a chemiluminescence enzyme immunoassay (Diagnostic Products Corp, Immunolite kits, Los Angeles, CA). The interassay variation was 11% ± 5%, while the intra-assay variation was 9% ± 3%.

### *Statistics*

All values reported are means ± SE. Differences across all testing conditions were determined by a repeated measures 2-way analysis of variance (ANOVA) with significance set at $P < .05$. Tukey posthoc comparisons were used to identify significant differences among means. Pearson product correlations were used to assess the relationship between urinary NE excretion rates and BMR.

## RESULTS

### *Oxygen Consumption*

$V_{O_2}$peak was 35.8 ± 2.1 and 34.5 ± 1.5 mL/kg/min for placebo and blocked groups, respectively, while at sea level. This decreased to 26.4 ± 1.1 and 27.7 ± 1.5 mL/kg/min when tested at 4,300 meters. The intensity of 50-minute submaximal bout of exercise performed at sea level was 51.6% ± 1.0% of $V_{O_2}$max. The same absolute workload performed on days 1 and 12 at altitude corresponded to a 67.4% ± 2.4% relative intensity.

### *Phenylephrine Challenge*

A high degree of $\alpha$-adrenergic blockade was maintained throughout the study both at sea level and high altitude as indicated by the results of the phenylephrine challenge as previously reported.[8] Briefly, the dose of phenylephrine required to raise systolic blood pressure 20 mm Hg above baseline was designated as the $PD_{20}$, which was the end point used to document the degree of $\alpha$-adrenergic blockade. At sea level, the $PD_{20}$ was 1.47 ± 0.73 $\mu$g/kg/min prior to administration of prazosin and increased to 9.45 ± 2.22 $\mu$g/kg/min at day 3 ($P < .05$), indicating a significant degree of $\alpha$- adrenergic blockade. The $PD_{20}$ on day 9 at sea level was 6.87 ± 2.99 $\mu$g/kg/min and 15.05 $\mu$g/kg/min on day 9 at 4,300 meters, indicating no decrement in the degree of blockade due to drug tolerance or altitude exposure.

**Table 1. Estradiol and Progesterone Levels during the Follicular and Luteal Phase Determined at Sea Level and on Days 3 and 10 at Altitude**

| | Sea Level | | 4,300 m Day 3 | | 4,300 m Day 10 | |
|---|---|---|---|---|---|---|
| | Prazosin | Placebo | Prazosin | Placebo | Prazosin | Placebo |
| Follicular estradiol (pg/mL) | 63 ± 43 | 86 ± 67 | 99 ± 51 | 72 ± 42 | 42 ± 36 | 36 ± 16 |
| Follicular progesterone (ng/mL) | 0.9 ± 0.4 | 1.0 ± 0.1 | 1.6 ± 0.9 | 1.6 ± 0.4 | 1.1 ± 0.2 | 0.9 ± 0.3 |
| Luteal estradiol (pg/mL) | 81 ± 41 | 101 ± 54 | 38 ± 18 | 98 ± 46 | 103 ± 20 | 83 ± 10 |
| Luteal progesterone (ng/mL) | 7.3 ± 1.6 | 6.4 ± 3.6 | 4.2 ± 2.6 | 12.6 ± 4.7 | 10.9 ± 1.0 | 10.6 ± 2.1 |

*Menstrual Cycle Phase*

Ovarian hormones are reported in Table 1. No differences were found between the luteal and follicular phase for both plasma and urinary catecholamines levels; consequently, values have been grouped.

*Plasma and Urinary Catecholamines*

At rest, plasma NE levels were significantly elevated with chronic altitude exposure in placebo subjects when compared to other conditions (Fig 1). Further, despite exercising at the same absolute and relative workloads, NE levels for the placebo group were significantly greater after acclimatization when compared with acute altitude exposure. The same pattern was found for blocked subjects. However, plasma NE levels were greater for blocked compared to placebo subjects during exercise at sea level. There was no difference in plasma NE levels between groups during exercise with acute altitude exposure or after acclimatization. For both placebo and blocked subjects, plasma EPI levels increased dramatically during exercise with acute altitude exposure returning to sea level values by day 12 (Fig 2). Plasma EPI levels were greater for blocked compared to placebo in all conditions studied.

Twenty-four–hour urinary NE excretion rates did not differ over time while at sea level for both groups. However, urinary excretion rates were significantly greater for blocked versus placebo subjects while at sea level (Fig 3). Urinary NE excretion rates increased upon exposure to altitude and continued to increase steadily during subsequent days at altitude for both groups reaching a plateau at day 4 to 6. Excretion rates remained elevated thereafter for the duration of the altitude residence. Similar to sea level findings, NE excretion rates at altitude were significantly greater for blocked versus placebo subjects.

Urinary EPI excretion rates did not differ between groups or over time when measured at sea level (Fig 3). Urinary EPI excretion rates increased immediately with altitude exposure for both groups peaking by day 3 and then declining steadily thereafter. No differences in EPI excretion rates were observed between groups while at altitude.

*Plasma Volume*

Plasma volume decreased over time at altitude for control subjects only and was inversely associated with increase in 24-hour urinary NE excretion ($r = -0.61$, $P = .002$; Fig 4).

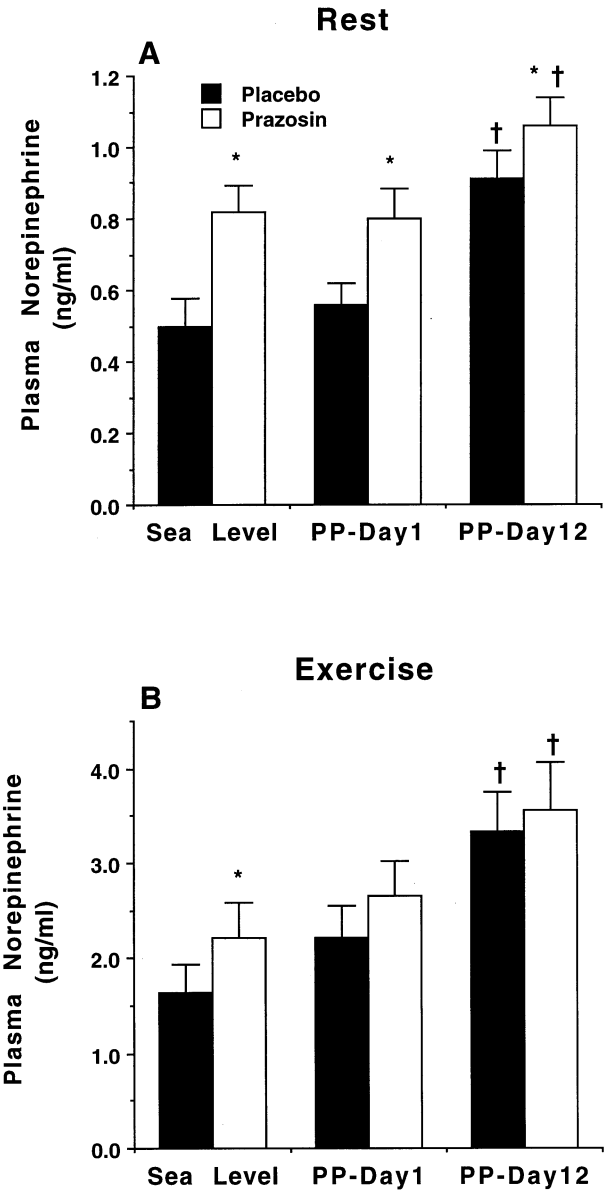


**Fig 1. Plasma NE response during 50 minutes of submaximal exercise (50% of $Vo_2max$) across all 3 conditions studied for placebo (A) and α-blocked (B) subjects. *Significantly different from placebo group. †Significantly different from sea level and Pikes Peak day 1 ($P < .05$).**

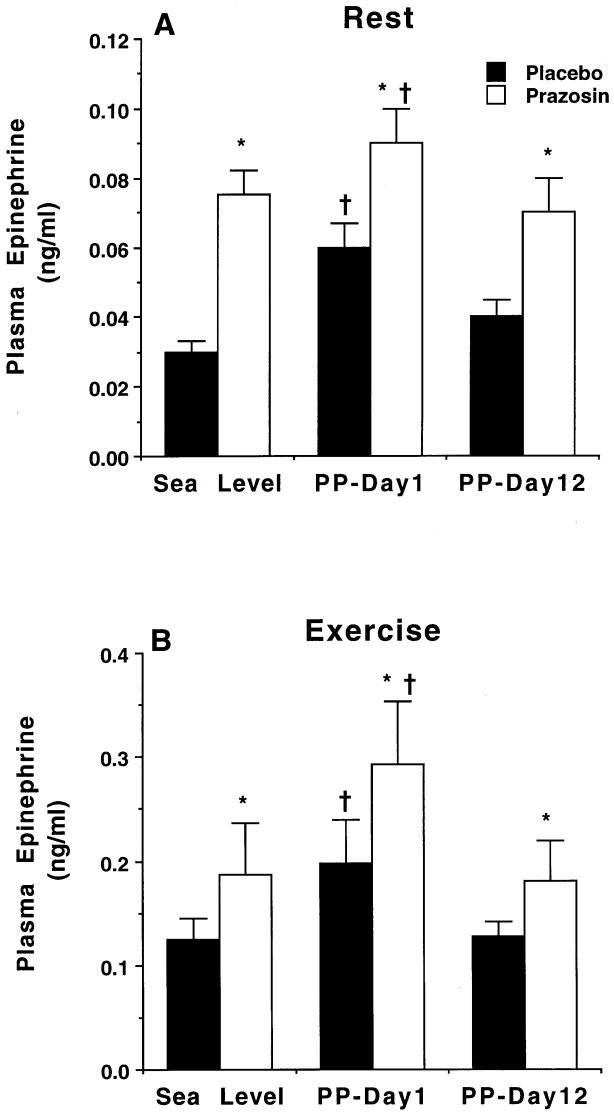


**Fig 2. Plasma EPI response during 50 minutes of submaximal exercise across all 3 conditions studied for placebo (A) and $\alpha$-blocked (B) subjects. *Significantly different from placebo group. †Significantly different from sea level and Pikes Peak day 12 ($P < .05$).**

Plasma volume remained unchanged for the prazosin-treated subjects over time at altitude.

*BMR*

Compared to sea level values, BMR increased upon initial exposure to altitude in both placebo and blocked subjects (Fig 5A). This increase in BMR peaked on day 3 to 4 and remained elevated for the remaining days at 4,300 meters. The presence of $\alpha$-adrenergic blockade significantly lowered the BMR compared to placebo subjects. Nonetheless, the blocked group still demonstrated a significant increase in BMR at altitude when compared to sea-level values.

## DISCUSSION

The major findings of the present study were that: (1) $\alpha$-adrenergic blockade elicited a potentiated sympathoadrenal response to the stress of both exercise as well as high-altitude exposure, and: (2) the sympathetics, via $\alpha$-adrenergic stimulation, contribute to a number of key adaptations associated with acclimatization to high altitude.

To our knowledge, this is the first investigation to examine the influence of $\alpha$-adrenergic blockade during chronic exposure to hypoxia. As we have previously documented a significant SNS response to 4,300 meters,[1-5] we sought to determine the

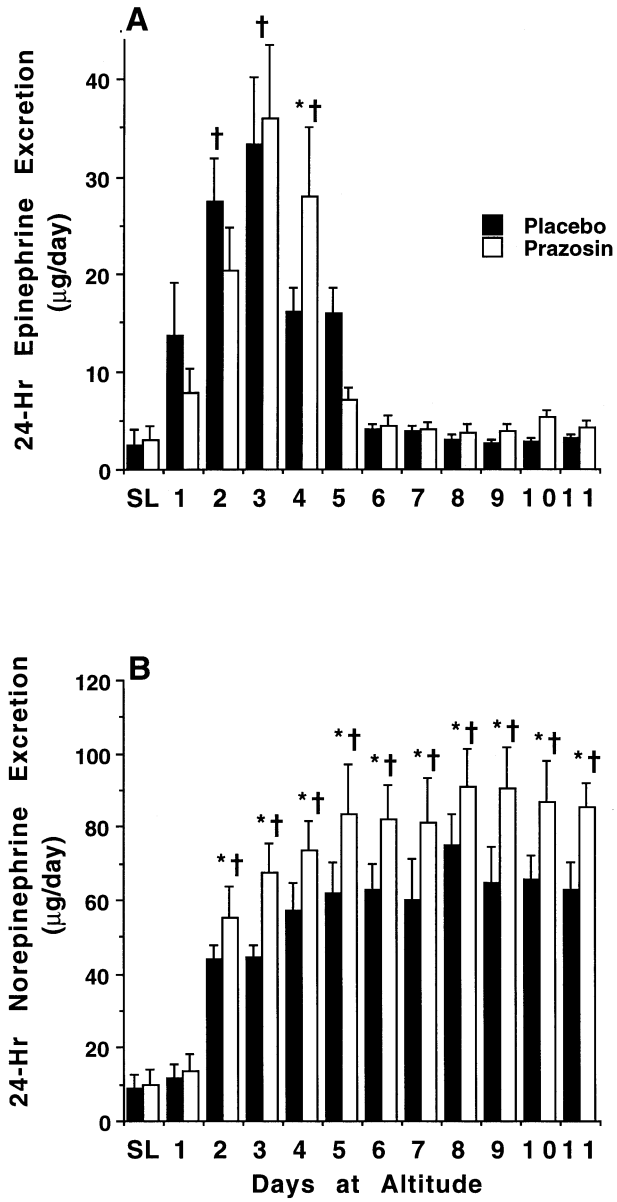


**Fig 3. Mean 24-hour urinary EPI (A) and NE (B) excretion rates both placebo and $\alpha$-blocked subjects over time at altitude. *Significantly different from placebo group. †Significantly different from sea level ($P < .05$).**

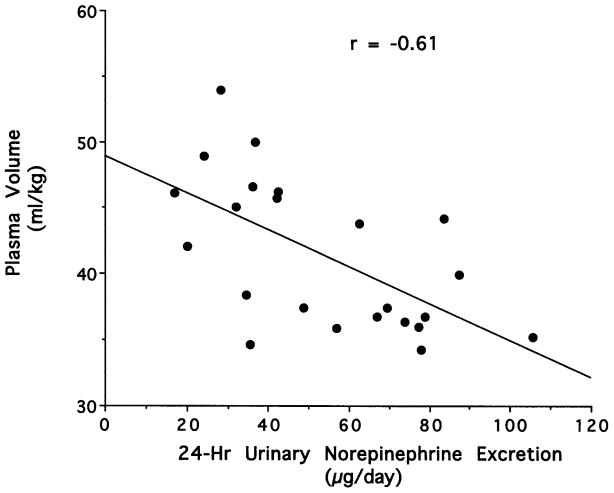


**Fig 4. Relationship between 24-hour urinary norepinephrine excretion rates and plasma volume across all days studied for control subjects only.**

role of the α-adrenergic pathway during acclimatization. Our preliminary investigation at a simulated altitude of 4,300 meters examined the effect of α-adrenergic blockade during acute exposure (68 hours).[12] It was demonstrated that when compared to placebo subjects, α-adrenergic blockade resulted in a compensatory sympathoadrenal response both at rest as well as during a graded exercise test. This was particularly evident for the EPI response. Furthermore, it was determined that hypoxic exposure potentiated this response. The results of the present investigation extend those findings to include chronic hypoxia. Specifically, plasma EPI increased significantly with acute exposure to altitude both at rest and during exercise (Fig 2). This response has been observed previously[1,2,4,5] and is most likely related to the direct stimulatory effect of hypoxia on adrenal medullary release of epinephrine. During acclimatization, as arterial oxygen saturation improves, this stimulus is lessened and plasma epinephrine levels return toward sea-level values. The presence of α-adrenergic blockade elicits a compensatory response such that plasma EPI levels are significantly increased across all conditions studied (sea level, acute and chronic altitude exposure). A primary effect of prazosin, a selective $\alpha_1$-adrenergic blocker, is to reduce peripheral vascular resistance by inhibiting the vasoconstriction produced by NE released at smooth muscle nerve endings.[13] Consequently, the strong adrenal response observed in blocked subjects likely reflects a compensatory response in attempt to increase cardiac output and maintain arterial pressure. 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]

Plasma NE levels measured under resting conditions during acute altitude exposure are similar to those found for sea level (Fig 1). During exercise, acute hypoxia resulted in elevated levels of plasma NE compared to sea level; however, it appears that this response is primarily dependent upon the relative work intensity. When subjects work at a similar percentage of $V_{O_2}$max at sea level and acute altitude exposure, the NE response is not found to be significantly different.[5] With acclimatization, plasma NE levels, both at rest and during exercise, were significantly elevated compared to sea level as well as acute exposure. Thus, despite working at the same absolute and relative exercise intensity as acute altitude exposure, chronic exposure elicited greater plasma NE levels. Furthermore, urinary NE excretion rates, a marker of whole-body sympathetic nerve activity, increased steadily over time at altitude, reaching a plateau on days 4 to 6 and staying elevated throughout the remaining days at 4,300 meters (Fig 3). The increase in sympathetic activity during acclimatization is supported by measurements of net NE release across resting muscle. A reversal from

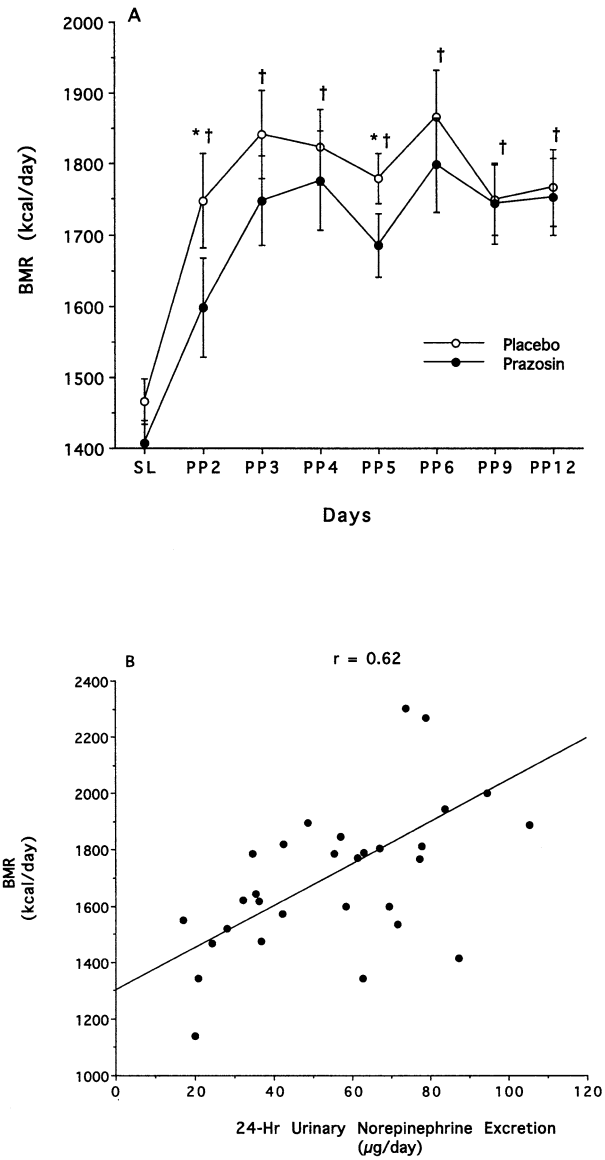


**Fig 5. (A) BMR measured at sea level and on days 2 to 12 for placebo and α-blocked subjects. (B) Correlation between 24-hour urinary NE excretion rates and BMR across all days studied. *Significantly different from placebo group. †Significantly different from sea level ($P < .05$).**

net NE uptake by resting leg at sea level to that of net release after chronic exposure to 4,300 meters clearly demonstrates enhanced sympathetic nerve activity.[3] As shown in Fig 3, subjects receiving prazosin had significantly greater urinary NE excretion rates compared with controls over time at altitude. This would suggest a compensatory increase in overall (whole-body) sympathetic nerve activity in $\alpha$-blocked subjects while at altitude.

NE levels in plasma are a function of the rate of spillover into the circulation.[14] Under resting conditions this represents approximately 10% to 20% of the NE released by sympathetic nerve terminal, with a small amount being secreted by the adrenal medulla. Hypoxia does not appear to influence the prejunctional release of neuronal NE or the intraneuronal metabolism and uptake of the neurotransmitter in muscle,[15,16] suggesting that the elevated levels of NE observed in our study are directly related to an increase in sympathetic nerve activity. No change or an increase in clearance of plasma NE has been reported during acute hypoxia.[17,18] An increase in clearance would actually tend to lower plasma levels and therefore would not explain the increase associated with altitude. No studies exist examining the effect of chronic high-altitude exposure on plasma NE clearance. Other investigations, performed at sea level, have also demonstrated a compensatory catecholamine response in humans[19] and animals [6,20] 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 when measured under resting conditions.

### *Physiological Significance*

The physiological contribution of the $\alpha$-adrenergic receptors during the acclimatization to 4,300 meters can be determined, in part, via $\alpha$-adrenergic blockade. Stimulation of $\alpha$-adrenergic receptors, primarily by norepinephrine, results in vasoconstriction of vascular smooth muscle.[13] As a consequence, an increase in vascular resistance and blood pressure ensue. We have shown that the increase in sympathetic nerve activity correlated with the increases in both vascular resistance and arterial pressure known to occur over time at altitude.[1,9] As we have previously reported, the women in the present study on prazosin demonstrated an attenuation in the rise in peripheral vascular resistance.[21] While forearm vascular resistance increased over time at 4,300 meters for control subjects, no difference was found for the prazosin-treated group, indicating that the $\alpha$-adrenergic stimulation plays a significant role in this adaptation to high altitude. These alterations in vascular resistance associated with $\alpha$-adrenergic blockade translate into similar responses in mean arterial blood pressure (MABP). The prazosin-treated subjects had lower resting MABP both at sea level and at 4,300 meters, as has been reported.[22] Increases in MABP during acclimatization to high altitude are well documented and are thought to be related to the increase in sympathetic nerve activity.[9] Results from the present study suggest that the $\alpha$-adrenergic pathway contribute to the blood pressure response during acclimatization to 4,300 meters.

A decrease in plasma volume is a consistent adaptation found in response to high-altitude exposure, resulting in an increased concentration of existing red blood cells and thereby improving oxygen-carrying capacity of blood. In the present study, a significant correlation was observed between changes in 24-hour urinary NE excretion rates, a marker of whole-body daily sympathetic nerve activity, with that of plasma volume ($r = -0.61$, $P = .002$; Fig 4) for control subjects only. As plasma volume did not change over time at altitude for the prazosin-treated subjects (or correlate with urinary NE, $r = -0.29$, $P = .210$), this suggests that the sympathetic, via $\alpha$-adrenergic stimulation, contributes to the regulation of plasma volume associated with high-altitude exposure (manuscript in preparation). Since the majority of the blood volume is contained within veins, it would appear that venoconstriction leading to plasma volume reduction, may be mediated by the $\alpha$-adrenergic system. Alpha-1 receptors are present in both arteries and veins and contribute to vasoreactivity.[23]

Another consistent observation associated with high altitude exposure is an elevation in BMR in both men and women.[7,10] While the exact cause(s) for this phenomenon remained unknown, several studies have suggested a relationship with the increase in catecholamines associated with high altitude.[7,10,24] The BMR for our subjects was significantly elevated over time at altitude (Fig 5A). For control subjects, a significant correlation existed between BMR and urinary NE excretion rates (Fig 5B; $r = 0.62$, $P = .003$). The presence of $\alpha$-adrenergic blockade significantly lowered the BMR compared to placebo subjects. However, while reduced, an elevation in BMR still occurred with altitude exposure in the prazosin-treated subjects when compared to sea-level values, suggesting that mechanisms other than $\alpha$-adrenergic pathways also contribute to this response. Other potential mechanisms may still involve the catecholamines via $\beta$-adrenergic mediated pathways as treatment with a $\beta$-blocker (propranolol) significantly lowered resting $V_{O_2}$ and metabolic rate while at 4,300 meters.[24]

Recently, we have reported that both acute and chronic high altitude exposure induced marked elevations in plasma interleukin-6 (IL-6) levels in the subjects from the present investigation.[8] IL-6 is an important cytokine involved in a number of biological processes, including the regulation of the immune/inflammatory reaction to various stressors,[25,26] as well as the synthesis of acute-phase proteins.[27,28] Importantly, during the 12 days of acclimatization to 4,300 meters, resting IL-6 levels remained elevated for placebo subjects. However, they returned to sea-level values in the prazosin-treated group. Thus, the attenuated IL-6 levels induced by prazosin demonstrated a significant $\alpha$-adrenergic contribution to the IL-6 response under these types of stressful conditions (chronic hypoxia).

In summary, data from the present investigation suggests that $\alpha$-adrenergic blockade results in a compensatory sympathoadrenal response to the stress of both exercise as well as high-altitude exposure. Furthermore, the $\alpha$-adrenergic limb of the SNS contributes to a number of key physiologic and metabolic adaptations associated with acclimatization to high altitude. It is likely that the contribution of the $\alpha$-adrenergic pathway goes beyond those mentioned here possibly playing a role in the regulation of other critical systems (substrate selection, cardiac output, ventilation, etc). Future research will be necessary to determine the full extent of the $\alpha$-adrenergic contribution during both acute and chronic high-altitude exposure.

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