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WOMEN AT ALTITUDE: VOLUNTARY MUSCLE EXERCISE  
PERFORMANCE WITH AND WITHOUT  $\alpha$ -ADRENERGIC  
RECEPTOR BLOCKADE

U.S. ARMY RESEARCH INSTITUTE  
OF  
ENVIRONMENTAL MEDICINE  
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**WOMEN AT ALTITUDE: VOLUNTARY MUSCLE EXERCISE  
PERFORMANCE WITH AND WITHOUT  $\alpha$ -ADRENERGIC  
RECEPTOR BLOCKADE**

Prepared by

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## BACKGROUND

The current study was performed during the third year of a three year collaborative project within the Defense Women's Health Research Program (DWHRP) titled "*Women at Altitude: Effects of Menstrual Cycle Phase and Alpha-Adrenergic Blockade on High-Altitude Acclimatization*" involving investigators from USARIEM, the Palo Alto Veteran's Affairs Health Care System, Palo Alto, CA, and the University of Colorado Health Sciences Center, Denver, CO.

The major purpose of the current year's project was to study the  $\alpha$ -adrenergic contribution to altitude acclimatization in women during the first 12 days of residence at 4300 m. The approach used was to block some of the  $\alpha$ -adrenergic receptors using prazosin (a selective  $\alpha_1$ -adrenergic receptor antagonist) to assess the physiological role and importance of the  $\alpha_1$ -adrenergic system in the regulation of circulation and metabolism, at rest and during exercise, at altitude.

## **ACKNOWLEDGMENTS**

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The authors wish to thank each of the volunteers who had to endure an incredibly arduous and time-consuming study.



## EXECUTIVE SUMMARY

It is not clear if women, like men, have impaired muscle endurance performance during initial altitude exposure or if increased sympathetic activation is essential to mediate the many physiological responses and adjustments that characterize longer altitude exposures. To study these issues, 14 healthy women ( $22 \pm 2$  yr) were randomly assigned to receive either 2 mg prazosin ( $n=7$ ) or placebo ( $n=7$ ) *t.i.d.* (double-blind design) for 12d at sea level (SL) and during the first 12d of HA residence (4300 m). Using an adductor pollicis muscle exercise model, subjects performed repeated voluntary static contractions at 50% of maximal voluntary contraction (MVC) force for 5 sec followed by 5 sec rest until exhaustion, defined as a MVC force decline to 50%. MVC force was measured before and at the end of each min of exercise. Exercise tests were performed at SL, and on days 1 and 11 of HA. Heart rate (HR, ECG), arterial oxygen saturation ( $S_aO_2$ , pulse oximetry), and mean arterial blood pressure (MAP, auscultation) were determined each min during exercise. For both groups, at HA compared to SL, there were: 1) no changes in MVC force and endurance time to exhaustion, 2) increases in resting and exercise HR ( $P<0.05$ ), 3) decreases in resting and exercise  $S_aO_2$  ( $P<0.05$ ), 4) no changes in resting and exercise MBP. Moreover, no statistically significant differences were detected between groups for any measure on any test day. These findings indicate that: 1. small muscle endurance exercise performance of women, unlike that of men, is not impaired during initial altitude exposure, and 2. pharmacological blocking of  $\alpha_1$ -adrenergic receptors during altitude acclimatization does not result in a meaningful change in either muscle exercise performance or in cardiopulmonary function during isolated muscle exercise.

## INTRODUCTION

Endurance performance during large muscle group exercise is impaired in men and women during initial exposure to altitude (9). The impairment is considered to relate closely to the reduction in maximal aerobic power due to arterial hypoxemia (3). Also in response to the hypoxia of altitude, many well-documented ventilatory, cardiocirculatory, and hematological adjustments begin almost immediately and continue to undergo modification for the entire sojourn (12,33,36,40,42). As a result, hypoxemia is nearly compensated for and exercise performance gradually improves. Such widespread and integrated physiological changes suggest concomitant neural activity coordination (13,14,19).

The precise mechanisms of the hypoxia-induced initial acceleration and eventual improvement in progressive fatigue of the active muscles are, however, poorly understood. The lack of understanding derives, in part, from the considerable variation in work performed by a given muscle within a group of active muscles and an inability to quantitate muscle fatigue during conventional exercise modes, e.g., treadmill and cycle ergometry. To circumvent such limitations, our group uses an isolated small-muscle intermittent static contraction exercise model (4). By measuring maximal voluntary contractile force before, during, and after intermittent static contractions at a given submaximal target force using the adductor pollicis muscle, multiple objective indices of muscle performance within a single testing session can be obtained: 1. an initial strength level, 2. a precisely defined exhaustion point used to quantitate muscle endurance time, and 3. a rate of force recovery.

Using this approach in men, we determined that muscle strength was not altered during initial exposure to altitude (4,300 m) compared to the pre-exposure, sea level value (4). Endurance time to exhaustion during initial altitude exposure was, however, accelerated by approximately 25%. After two weeks of continued exposure, the decrement in muscle endurance performance was fully restored. These findings firmly establish --- in men --- that the initial decrement and subsequent improvement in endurance performance characteristic of large muscle dynamic exercise (e.g., running) are due at least partly to intramuscular factors. It is unclear whether women respond similarly during altitude exposure (7,8).

Therefore, isolated muscle exercise performance in women was studied as part of a larger

investigation that focused on the relationship between physiological adjustments and changes in sympathetic nerve activity during altitude acclimatization. We hypothesized that muscle endurance performance would be impaired during initial altitude exposure and would subsequently improve with continued exposure. In addition, because a selective  $\alpha_1$ -adrenergic receptor antagonist (prazosin) was to be administered to some women while at altitude, we could assess the role of  $\alpha_1$ -adrenergic receptor stimulation in affecting the time course and/or magnitude of local muscle exercise performance changes during altitude acclimatization.

## METHODS

### SUBJECTS

Fourteen healthy women who were sea-level residents and who had normal menstrual cycles and no history of oral contraceptive use or pregnancy in the preceding year gave informed written consent to participate. Each women underwent a medical history and a physical examination, and no one had any contraindications to altitude exposure. Prior to random assignment to a placebo ( $n = 7$ ) or prazosin ( $n = 7$ ) group, each subject underwent a phenylephrine challenge test (2) to determine the degree and possible adverse effects to the dose of prazosin to be used in the study. The ages, heights, and weights of the subjects in each group are presented in **Table 1**.

### STUDY DESIGN

A double-blind, placebo-controlled experimental study design was used. All testing occurred at the Geriatric Research Education and Clinical Center of the Palo Alto Veterans Administration Medical Center, Palo Alto, CA (sea level, 30 m) and while the women resided at the United States Army Pikes Peak Laboratory on the summit of Pikes Peak, CO (4300 m). A one month interval separated the sea level and altitude phases. Diet, fluid intake, and physical activity were strictly controlled at sea level and altitude to assure maintenance of nitrogen, energy, fluid balances and body weight.

At least one adductor pollicis muscle fatigue practice test session and a definitive test session were performed at sea level while definitive test sessions were performed on the first (within 24 hr of arrival) and 11th days of altitude residence. Total travel time by airplane and

automobile from California to the summit of Pikes Peak was approximately 4 hours. Data from the practice test session(s) were not used in any of the analyses. For all muscle fatigue test sessions, subjects were treated with either placebo or prazosin.

### **MEDICATION ADMINISTRATION**

Each subject received orally either prazosin (Minipress, 2 mg *t.i.d.* or 6 mg•day<sup>-1</sup>) or an identically-appearing placebo at 0600, 1400, and 2200 h at sea level and altitude. At sea level, medication was administered for 14 consecutive days. Medication was also administered for an additional two days at sea level prior to traveling to Pikes Peak, and then for the next 12 consecutive days while at altitude. At sea level, the definitive adductor pollicis test session was conducted after the subjects had been provided placebo or prazosin for 10 days; at altitude, fatigue tests were conducted on days 1 and 11 after the subjects had been provided placebo or prazosin for 3 and 13 days, respectively. Degree of alpha-adrenergic blockade was determined using a phenylephrine challenge test on day 9 at sea level and altitude.

### **ADDUCTOR POLLICIS MUSCLE TESTING PROCEDURES**

At both locations, the identical muscle testing apparatus, testing and calibration procedures, force transducer, force feedback display, and data recorder were used by the same investigators responsible for conducting the tests. Ambient temperature was comfortably maintained (range: 20° to 23° C) at both locations.

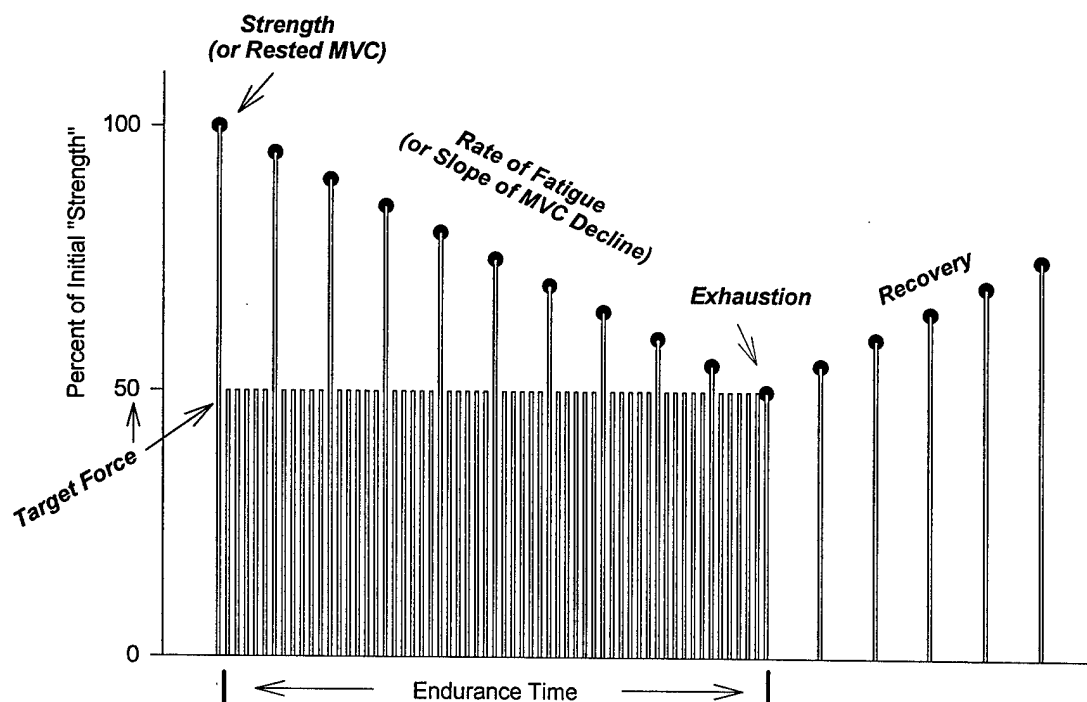
Definitive muscle fatigue experiments were performed using a device which permitted voluntary static contractions isolated to the adductor pollicis muscle (4,24). The right hand and arm of the subject were secured in supination with the fingers flexed and thumb abducted. A force transducer (model SSM-250, Interface, Scottsdale, AZ; sensitivity 1.5 mV•kg<sup>-1</sup>) was attached by an inextensible link to a strap looped around the interphalangeal joint of the right thumb. The force transducer was interfaced with an amplifier (model 13-421202, Gould, Cleveland OH; 90% response time in 2 ms), chart recorder (model 2200, Gould), and oscilloscope. Subjects had visual contact with an oscilloscope tracings at all times to provide them with feedback for maintaining the correct force during submaximal contractions.

After the subject was seated and the hand and thumb properly oriented and secured, three, 5-sec baseline maximal voluntary contractions (MVCs) were performed. There was a one-min

rest between each MVC. For each subject, the highest MVC force attained ("rested" MVC force or strength) was used to set the target force of submaximal contractions.

Submaximal exercise consisted of intermittent, 5-sec voluntary static muscle contractions at a target force of 50% of rested MVC force followed by 5-sec rest (i.e., duty cycle = 0.5). At the end of every min (i.e., every sixth contraction), a MVC was performed for 5 full sec instead of the 50% MVC force contraction. An investigator timing the events verbally instructed the subjects to start and stop each submaximal and maximal contraction. During each maximal and submaximal contraction, subjects were required to increase muscle force as rapidly as possible to the maximal or target level, respectively. When the target force could not be maintained for 5 sec or MVC force fell to or below target, the subjects were considered exhausted and were instructed to stop the submaximal contractions. A MVC was performed immediately upon reaching exhaustion and at the end of each min for 3 min of recovery. **Figure 1** is a schematic of adductor pollicis muscle fatigue exercise model illustrating the study protocol and specific measurements obtained.

**FIGURE 1**  
**Adductor Pollicis Muscle Fatigue Exercise Model**



During submaximal exercise and recovery, blood pressure, heart rate and arterial oxygen saturation were recorded forty-five seconds after each MVC force determination. Systemic blood pressure and heart rate were determined by noninvasive auscultation of the left arm and by 3-lead electrocardiograph, respectively (model 4240, Suntech, Raleigh, NC). Mean arterial blood pressure was calculated as one third pulse pressure plus diastolic blood pressure. Blood oxygen saturation was determined by pulse oximetry of an ear (Nellcor N-200 Pulse Oximeter, Pleasanton, CA).

## DATA ANALYSES

Independent t-tests were used to determine differences between groups for age, height and weight. Two factor (group X days) analyses of variance (ANOVA) with repeated measures on one factor (days) were used to identify differences in elapsed time (hours) between exercise test and medication administration, and rested MVC force and endurance time to exhaustion. Three-factor (group X days X time) ANOVA with repeated measures on two factors (days and time) were used to identify differences in mean arterial blood pressure, heart rate, and blood oxygen saturation during exercise and recovery. If ANOVA identified a significant *F* value, Tukey's multiple comparison procedure was used to detect statistical significance of specific differences. For all analyses, a difference of  $P < 0.05$  was accepted as statistically significant. Data are presented as means  $\pm$  SE or as otherwise indicated.

## RESULTS

### PHYSICAL CHARACTERISTICS OF SUBJECTS

There were no differences ( $P > 0.05$ ) between groups for age, height, or body weight.

*Table 1*  
*Test Subject Physical Characteristics*

Characteristic:	Placebo	Prazosin
Age (yr)	22 (21 to 33)	22 (20 to 25)
Height (cm)	163 (154 to 176)	171 (158 to 185)
Weight (kg)	68 (52 to 94)	69 (55 to 88)

Values are means (range)

## ALPHA RECEPTOR BLOCKADE

At sea level and altitude, the dose of phenylephrine required to raise systolic blood pressure by 20 mmHg or more was higher ( $P < 0.01$ ) in the prazosin group compared to the placebo group. The data in **Table 2**, collected during phenylephrine challenge tests, indicate significant  $\alpha_1$ -adrenergic receptor blockade at sea level and altitude.

**Table 2**  
*Amount of Phenylephrine Needed to Increase Systolic Blood Pressure by 20 mmHg ( $PD_{20}$ )*

Test Day:	Placebo	Prazosin
Sea Level, Day 9	$1.12 \pm 0.3$	$6.42 \pm 0.9^*$
Altitude, Day 9	$3.91 \pm 0.7$	$15.05 \pm 2.78^*$

\*  $P < 0.01$  Placebo vs Prazosin;  $PD_{20}$  units are  $\mu\text{g} \cdot \text{kg} \cdot \text{min}^{-1}$ ; Values are means  $\pm$  SE.

Each of the three definitive muscle fatigue tests were conducted approximately 2.5 to 3.5 hours after the most recent medication administration. Among testing days, there were no intra- or intergroup differences in elapsed time between medication administration and the exercise session that followed (**Table 3**).

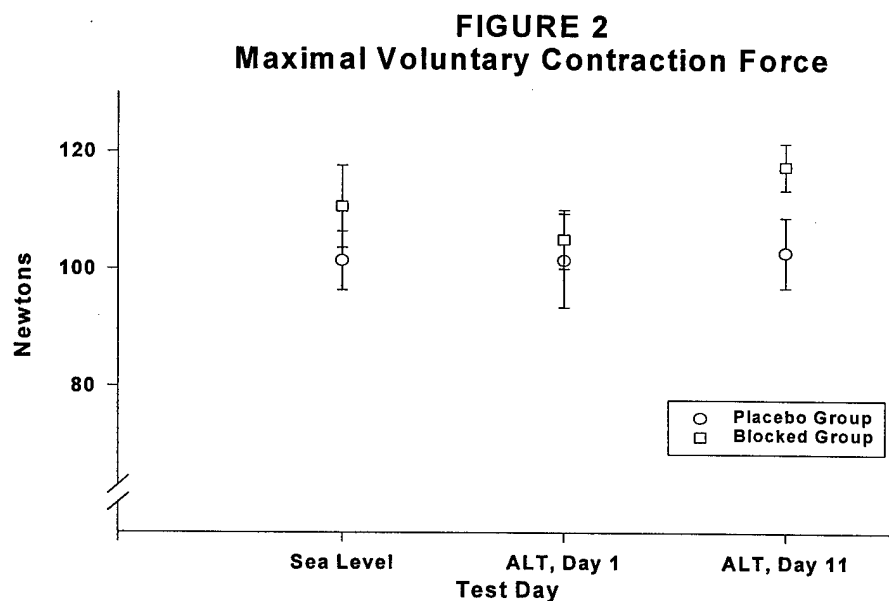
**Table 3**  
*Elapsed Time (hours) Between Exercise Test and Medication Administration*

Test Day:	Placebo	Prazosin
Sea Level	$3.2 \pm 0.5$	$3.4 \pm 0.4$
Altitude, Day 1	$3.8 \pm 1.0$	$3.0 \pm 0.7$
Altitude, Day 11	$2.9 \pm 0.5$	$2.6 \pm 0.6$

Values are means  $\pm$  SE

## MUSCLE STRENGTH

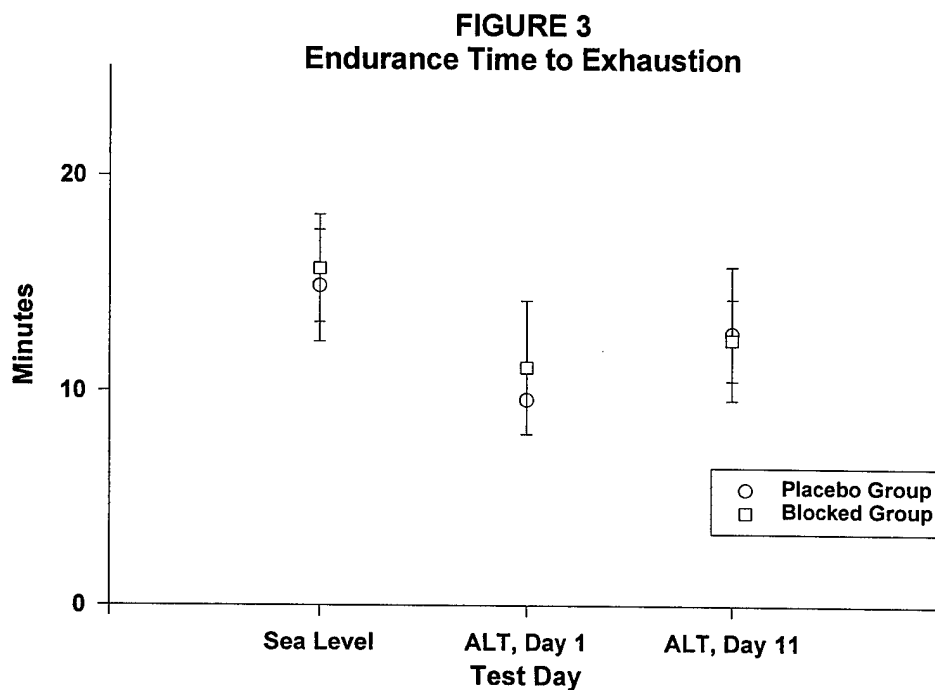
Adductor pollicis muscle strength at sea level was  $101 \pm 5$  Newtons (range: 75 to 127 N) versus  $111 \pm 7$  N (range: 77 to 120 N) for the placebo and prazosin groups, respectively ( $P>0.05$ ). For both groups, adductor pollicis muscle strength did not change significantly ( $P>0.05$ ) for either day at altitude compared to sea level. There was also no difference between groups on either day at altitude (**Figure 2**).





## ENDURANCE TIME TO EXHAUSTION

Both groups were able to continue exercising for approximately 15 minutes at sea level, and for approximately 10 and 12 minutes on day 2 and 11 of the altitude exposure, respectively. For each group, endurance time to exhaustion did not change for either day at altitude compared to sea level ( $P>0.05$ ). There were no significant differences between groups on any test day (Figure 3).



## POINT OF EXHAUSTION AND RECOVERY OF MVC FORCE

For both groups at sea level and for each of the two days at altitude, exhaustion occurred at approximately 53% of rested MVC force (**Table 4**). The point of exhaustion did not differ between groups ( $P>0.05$ ) and was not affected by altitude exposure ( $P>0.05$ ).

During recovery, restoration of MVC force was rapid in the first minute for both groups at sea level and for each day at altitude (all  $P<0.01$ ); MVC force increased by an average of 19 percentage points (range: 13 to 23%) to an overall average of approximately 72% of rested MVC force. For minutes 2 to 5 for each group at sea level and on each of the two days at altitude, there tended ( $P > 0.05$ ) to be a slight and gradual MVC force improvement to an overall mean of approximately 80% of rested MVC force by min 5. There were no differences between groups at sea level or altitude for any min of recovery.

**Table 4**  
*Adductor Pollicis Muscle MVC Force at Exhaustion and During 5' of Recovery*

Test Day	Group	Exhaustion	Min 1	Min 2	Min 3	Min 4	Min 5
Sea Level	Placebo	50 $\pm$ 2	69 $\pm$ 3*	76 $\pm$ 4*	79 $\pm$ 5*	79 $\pm$ 5*	82 $\pm$ 6*
	Prazosin	54 $\pm$ 3	76 $\pm$ 6*	81 $\pm$ 4*	79 $\pm$ 5*	82 $\pm$ 5*	86 $\pm$ 6*
HA1	Placebo	54 $\pm$ 2	67 $\pm$ 5*	66 $\pm$ 4*	71 $\pm$ 5*	73 $\pm$ 6*	70 $\pm$ 4*
	Prazosin	52 $\pm$ 2	74 $\pm$ 3*	77 $\pm$ 4*	81 $\pm$ 1*	81 $\pm$ 3*	82 $\pm$ 2*
HA11	Placebo	54 $\pm$ 1	71 $\pm$ 3*	75 $\pm$ 3*	77 $\pm$ 4*	77 $\pm$ 5*	79 $\pm$ 5*
	Prazosin	54 $\pm$ 1	76 $\pm$ 2*	78 $\pm$ 2*	81 $\pm$ 2*	81 $\pm$ 3*	83 $\pm$ 4*

Values are percentages (means  $\pm$  SE) of MVC force of rested muscle.

\* $P < 0.01$  from the point of exhaustion

## HEART RATE, ARTERIAL OXYGEN SATURATION, AND MEAN ARTERIAL BLOOD PRESSURE

Because of intersubject and intrasubject variations in dropout times due to muscular exhaustion (individual exercise times ranged from 4 min to 30 min; median: 12 min) in both groups at sea level and altitude, comparisons to assess between and within group potential differences in heart rate, arterial oxygen saturation, and blood pressure were made at rest, after 1 min of exercise, after a 25% drop from rested MVC force, and at the point of exhaustion.

Heart rates (**Table 5**) during exercise were not statistically significantly higher than during rest at sea level or altitude (the only exception was at exhaustion at sea level for the placebo group). Resting and exercise heart rates increased at altitude compared to sea level for both groups. At altitude, heart rates on day 1 tended ( $P > 0.05$ ) to be higher than on day 11. There were no differences between groups at sea level or altitude at any of the times or force decline levels.

**Table 5**  
*Heart Rate (beats / min) before, during (after the first minute of exercise and after a 25% loss of MVC force), and at exhaustion*

	Pre-exercise resting		After 1st min of exercise		25% loss of MVC force		Exhaustion	
Day:	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin
SL	70 $\pm$ 6	74 $\pm$ 7	72 $\pm$ 5	77 $\pm$ 8	78 $\pm$ 5	82 $\pm$ 7	90 $\pm$ 8 <sup>#</sup>	84 $\pm$ 5
HA1	100 $\pm$ 7*	96 $\pm$ 6*	107 $\pm$ 7*	99 $\pm$ 6*	104 $\pm$ 9*	101 $\pm$ 5*	105 $\pm$ 7*	104 $\pm$ 6*
HA11	90 $\pm$ 4*	84 $\pm$ 4	94 $\pm$ 4*	86 $\pm$ 3	93 $\pm$ 6*	91 $\pm$ 3	95 $\pm$ 6	98 $\pm$ 6*

n = 7 in each group; Values are means  $\pm$  SE; \*P < 0.05 from SL; <sup>#</sup>P < 0.05 from resting.

Arterial oxygen saturation (**Table 6**) during exercise was not statistically significantly different than during rest at sea level or altitude. Resting and exercise saturations decreased at altitude compared to sea level for both groups. At altitude, saturations on day 11 tended ( $P > 0.05$ ) to be higher than on day 1. There were no differences between groups in saturation at sea level or altitude at any of the times or force decline levels.

**Table 6**  
*Arterial Blood Saturation (%) before, during (after the first minute of exercise and after a 25% loss of MVC force), and at exhaustion*

	Pre-exercise resting		After 1st min of exercise		25% loss of MVC force		Exhaustion	
Day:	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin
SL	98 $\pm$ 1	97 $\pm$ 1	99 $\pm$ 1	98 $\pm$ 1	97 $\pm$ 1	98 $\pm$ 1	96 $\pm$ 1	98 $\pm$ 1
HA1	85 $\pm$ 1*	86 $\pm$ 1*	86 $\pm$ 2*	87 $\pm$ 2*	89 $\pm$ 2*	88 $\pm$ 2*	89 $\pm$ 1*	87 $\pm$ 2*
HA11	89 $\pm$ 1*	88 $\pm$ 1*	91 $\pm$ 1*	89 $\pm$ 1*	91 $\pm$ 1*	89 $\pm$ 1*	92 $\pm$ 1	88 $\pm$ 2*

Values are means  $\pm$  SE; \*P < 0.05 from SL.

Mean arterial blood pressure during exercise for both groups at sea level and altitude became progressively higher with extended duration of exercise (**Table 7**). At sea level, blood pressure at any of the compared times or force decline levels tended ( $P > 0.05$ ) to be lower by an average of about 7 mmHg for the prazosin group compared to the placebo group; for both altitude days, the absolute blood pressure differences were lessened. Blood pressure during day 1 at altitude compared to sea level, tended to increase at each of the times or force decline levels for the prazosin group compared to the placebo group. Blood pressures for both groups were very similar on day 11 as on day 1 at altitude. There were no significant differences in blood pressure between groups at sea level or altitude at any of the times or force decline levels.

**Table 7**

***Mean Arterial Blood Pressure (mmHg) before, during (after the first minute of exercise and after a 25% loss of MVC force), and at exhaustion***

	Pre-exercise resting		After 1st min of exercise		25% loss of MVC force		Exhaustion	
	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin	Placebo	Prazosin
<b>SL</b>	90 ± 3	85 ± 3	95 ± 4	87 ± 3	106 ± 5 <sup>#</sup>	96 ± 2	104 ± 3 <sup>#</sup>	98 ± 2 <sup>#</sup>
<b>HA1</b>	87 ± 2	90 ± 2	89 ± 4	89 ± 5	102 ± 7 <sup>#</sup>	102 ± 3	104 ± 5 <sup>#</sup>	106 ± 5 <sup>#</sup>
<b>HA11</b>	91 ± 3	94 ± 2	94 ± 3	92 ± 3	103 ± 4	100 ± 4	107 ± 5 <sup>#</sup>	105 ± 4

Values are means ± SE; <sup>#</sup>P < 0.05 from rest

## DISCUSSION

Results of this study indicate that: 1. small muscle endurance exercise performance of women, unlike that of men (4) is not impaired during initial altitude exposure, and 2. pharmacological blocking of  $\alpha_1$ -adrenergic receptors did not result in a meaningful change in either muscle exercise performance *per se* or in cardiopulmonary function during exercise throughout the altitude exposure. The finding of no impairment in small muscle endurance performance at altitude in women corroborates our previous work (7).

### EXERCISE PERFORMANCE

At sea level, muscle endurance performance is greater for women than men (17,20, 25,28,39) despite women and men being matched on muscle strength (17), muscle cross-sectional area (22), daily activity or training level (20,25,27), relative percentage of maximal force used during exercise (20,25,39), total body mass (20,25), composition of dietary intake (37), and age (28). The greater endurance performance of women compared to men at sea level has been proposed to involve a lower glycolytic to  $\beta$ -oxidation in skeletal muscle in women than in men (11,27), a decreased rate of leg muscle glycogen depletion and a lower blood lactate concentration during dynamic leg exercise at similar relative work rates (37), and a larger proportion of active muscle volume occupied by slow-twitch fibers (a consequence of women having a smaller, fast-twitch fiber cross-sectional area (11,27)).

Explaining the greater adductor pollicis muscle endurance of women than men in terms of possible gender differences in glycolytic relative to oxidative metabolism and in the ratio of slow-to-fast twitch fiber area must be considered with caution, however, since the proportion of slow fatiguing type I muscle fibers for both genders is much greater for the adductor pollicis (mean: 80% (34)) than for the leg extensor muscles (mean: 50% (11,27)). A predominance of type I fibers in the adductor pollicis muscle for both women and men would tend to minimize potential gender differences in muscle endurance due to differences in fiber type. Thus, it is unclear as to why muscle endurance exercise performance during initial altitude exposure was unaffected in women while being greatly impaired in men.

### $\alpha$ -ADRENERGIC BLOCKADE

The level of sympathetic activity, as reflected by plasma and urinary catecholamine levels (10), becomes significantly elevated at rest and during exercise within 24 to 48 hours of initial altitude exposure and continues to rise over the next 1 to 3 weeks to levels that are 2 to 3 times

higher than at sea level (19,23,31). Augmented sympathetic activity at altitude has been linked with increases in heart rate, arteriolar and venous tones, blood pressure, and adipose tissue lipolysis and with reductions in plasma volume, stroke volume, and cardiac output (5,6,14,30,33,35,43). Some of these changes --- along with other associated changes that include increases in ventilation, 2,3 DPG concentration, oxidative enzymes, myoglobin, and decreases in lactate and ammonia accumulation (12,18,26,32,41,40,38) --- at least partly compensate for the hypoxia, and gradually improve oxygen transport and exercise performance. Collectively, these findings suggested that increased sympathetic activation “orchestrated” the closely-integrated changes that characterize altitude acclimatization. If so, then interfering with this relationship should have altered the time course and/or magnitude of the compensatory physiological changes, and because of these alterations, exercise performance would be affected.

Our approach was to administer prazosin for two weeks at altitude. Clinical use indicated that prazosin inhibited vasoconstriction induced by endogenous catecholamines and caused vasodilation in both arteriolar resistance vessels and veins (13). The magnitude of the resulting fall in blood pressure was directly dependent on the levels of sympathetic nerve activity and hypohydration at the time of drug administration (13,15,29). The implication for the current study was that if the effects of higher and progressively rising  $\alpha_1$ -adrenergic activation during altitude exposure were blocked, and if progressively rising  $\alpha_1$ -adrenergic activation was essential for normal altitude acclimatization to occur, then the cardiopulmonary responses during exercise, and perhaps exercise performance *per se*, would differ greatly between the placebo and prazosin groups. Moreover, the differences between groups would be expected to become more pronounced with extended altitude duration.

To adequately examine this premise, it was necessary to assure maximal  $\alpha_1$ -adrenergic blockade by prazosin for the dosage provided during exercise. To that end, most adductor pollicis exercise sessions were conducted an average of 2.5 to 3.5 hours after medication administration, a period of time that was well within the 4 to 6 hour duration of action (1,15). Since time to peak concentration of prazosin is 1 to 3 hours (15), it is also likely that the exercise tests were performed when the plasma concentrations were highest and there was maximal  $\alpha_1$ -adrenergic receptor blockade. In addition, the amount of phenylephrine needed to raise systolic blood pressure 20 mmHg in the blocked group compared to the placebo group was on average 5.7 times higher at sea level and 3.9 times higher at altitude. Taken together, these data clearly

support the notion that significant  $\alpha_1$ -adrenergic receptor blockade was present during the conduct of the adductor pollicis exercise tests.

Because no consistent differences could be detected in cardiopulmonary function or in small muscle exercise performance between groups at altitude, and that muscle performance was maintained throughout the exposure as had previously been reported for women (7) it is concluded that pharmacological blocking of  $\alpha_1$ -adrenergic receptors does not result in a meaningful change in either cardiopulmonary function or in small muscle exercise performance during a two-week period of altitude acclimatization. The absence of cardiopulmonary or performance changes may be due to slight compensatory adjustments either in sympathetic and parasympathetic neural discharge or in  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$  receptor activities (16). It could also be that  $\alpha_1$ -adrenergic receptor stimulation *per se* simply is of no consequence for successful altitude acclimatization to occur.

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