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13. ABSTRACT (Maximum 200) <p>Background. Prior to this 3-year effort, little was known concerning the effects of high altitude exposure in women. In year 1, we evaluated the effects of menstrual cycle phase on high altitude acclimatization. Results indicated that the effects of the menstrual cycle were modest. In year 2, we evaluated the safety and efficacy of administering an α-adrenergic blocker and made selected observations during a brief exposure to an altitude of 4300 m. The drug proved to be both safe and effective. The purpose of the studies conducted in year 3 (the present annual report) was to determine the role of α-1 adrenergic activity and its interaction with menstrual cycle phase across 12 days of altitude acclimatization. Sixteen young women were studied at sea level and on Pikes Peak, Colorado at 4300 m altitude. Results and significance: Definite α-adrenergic blockade was achieved as shown by a rightward shift in the blood pressure response to an α-adrenergic agonist. Preliminary results are presented for basal metabolic rate, ventilation, cardiac output both at rest and during exercise, venous tone and forearm blood flow, static muscle contraction, various measures of sympathetic activation and assessment of acute mountain sickness. Various effects of both altitude and α-adrenergic blockade were observed. Analyses are continuing on other variables. Menstrual cycle correlations await hormone analysis.</p>				
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FOREWORD

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James P. Brown 10/2/98
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INTRODUCTION

Project purpose and scope. The purpose of the study covered in this annual report (year 3 of our 3-year contract) is to determine the role of α_1 -adrenergic activity and its interaction with menstrual cycle phase during altitude acclimatization. This follows a study conducted in year one concerning the effects of menstrual cycle phase on altitude acclimatization, and in year two which addressed the safety and efficacy of α_1 -adrenergic blockade at sea level and high altitude.

In year three, sixteen healthy young women with normal menstrual cycles were divided into two groups. Half the subjects were treated with an α_1 -blocker (n=8, prazosin, 2 mg every eight hours or 6 mg in a 24-hr period) and remaining half were given placebo tablets (n=8). One additional α_1 -blocked subject completed the sea-level studies, but did not go to high altitude. The study was randomized, double-blind in design. Sea level studies were performed between April 20 and May 30, 1998 at the Aging Study Unit at the Palo Alto, California Veterans Affairs Health Care System. High-altitude studies were performed between July 6 and August 7, 1998 at the US Army Research Institute of Environmental Medicine's Maher Memorial Laboratory on the summit of Pikes Peak, Colorado (4300 m).

Studies were conducted to test the hypotheses that 1) α_1 -adrenergic blockade will limit the characteristic increase in systemic vascular resistance and blood pressure associated with altitude exposure and, thereby, facilitate an increase in cardiac output during rest and exercise; 2) α_1 -adrenergic blockade will limit or delay the increase in hypoxic ventilatory responsiveness mediated by peripheral chemoreceptors, which will result in lower alveolar ventilation and arterial saturation during rest and exercise; and 3) α_1 -adrenergic blockade will limit or delay the altitude-induced increase in basal metabolic rate and decrease glucose tolerance, and alter energy substrate metabolism during exercise. Due to alterations in the cardiovascular, respiratory, metabolic and other physiologic responses to altitude exposure induced by α_1 -adrenergic blockade, it is further hypothesized that 4) exercise performance will be decreased with α_1 -adrenergic blockade, 5) the occurrence of acute mountain sickness (AMS) will increase with α_1 -adrenergic blockade relative to placebo, and 6) the effects will be more pronounced during the follicular phase of the menstrual cycle. Similar studies were performed in year two during the first days of simulated high-altitude exposure, a period not as able to be well-characterized under the conditions of actual high-altitude exposure.

Project significance: This research was designed to fill major gaps in the understanding of effects of high altitude on the well-being and physical performance specifically of women. Results of this study will provide a rational basis for planning military operations in high mountain terrain that include female service members. Results will assist in identification of effective prophylaxis and/or treatment of altitude illness, and in devising strategies to minimize performance decrements in military personnel deployed to strategic high-altitude locations.

Project background: This 3-year project is the first to systematically evaluate the influence of ovarian hormones on acclimatization to high altitude. Sex differences attributable to ovarian hormone fluctuations were addressed in detail in the year one report of this contract. Previously-collected data supporting the involvement of the α_1 -adrenergic limb of the sympathetic nervous system were reported there as well.

BODY

1). Preparation: September, 1997-March, 1998. Protocols and consent forms were prepared, supplies purchased, equipment organized, and volunteers recruited. The recruiting process was carried out by personnel at the Aging Study Unit at the Palo Alto Veterans Affairs Health Care System. The total number of volunteers screened was in excess of 75. Sixteen (16) women were selected and eventually completed both the sea level and high altitude phases of the study, all of whom were residents of sea level and lived in the vicinity of Palo Alto, CA. Supplies and equipment were shipped from the research groups in Denver, CO, Natick, MA and Dallas, TX to Palo Alto immediately prior to the beginning of the study in April, 1998.

The general characteristics of the volunteers as measured at sea level are shown in the table below (mean \pm SEM):

Age (yr)	23.3 \pm 1.03
Height (cm)	166.6 \pm 2.12
Weight (kg)	68.7 \pm 3.17
VO2 max (ml/kg/min)	35.1 \pm 5.0

2). Conduct of study (April - August, 1998). Formal testing of volunteers began following final approval of the third-year study protocol by the institutional review committees from the University of Colorado Health Sciences Center, Stanford University, USARIEM, and the US Army Surgeon General's Human Use Review of Research and Development (HURRAD).

The study testing schedule included three phases, each lasting approximately one month. The initial phase was the screening process which consisted of an initial interview and a bicycle exercise trial. Formal documentation of menstrual cycles began after admission to the study and an isoproterenol challenge was administered, once while on prazosin and once on placebo. Subjects were assigned to either the prazosin (α_1 -adrenergic blocked) or placebo (unblocked) groups for further testing. The second phase consisted of a period of experimental testing at sea level, during which the volunteers continued to document their menstrual cycles. The third phase was the high-altitude study phase. During phases two or three, each subject was treated with prazosin or placebo, according to the assignment done following phase one. To the extent possible, each subject was studied in the same menstrual cycle phase during study phases two and three. A controlled diet was begun three days before study phases two and three and was maintained throughout each phase in order to assure that the women were receiving the same proportions of calories from carbohydrates, fats and proteins during each test phase.

A complicated schedule of tests was constructed. Considerations were to group studies requiring catheters onto as few days as possible to limit the number of venipunctures, to properly interleave rest and exercise studies and to allow for scattered days with a light schedule for the sake of test volunteer sanity. All tests were performed both at sea level and at altitude on the same study day. The methods, briefly, were as follows (for a fuller description of each test, please see the protocol description for year three).

a). Menstrual cycle documentation included testing for nonpregnancy status by blood test for human chorionic gonadotrophin (HCG), record of cycle length, and assessment of ovulatory status by urine test for the presence of luteinizing hormone

(LH). Blood samples were collected on multiple days at sea level and altitude for evaluation of serum estradiol and progesterone levels.

b). Documentation of α_1 -adrenergic blockade was employed to demonstrate the extent of α_1 -adrenergic blockade induced by prazosin by evaluating the blood pressure response to increasing dosages of phenylephrine administered as an intravenous infusion (Elliott 82, Elliot 88). This test lasted approximately one hour and was done three times at sea level (once while taking prazosin, once while taking placebo, and a third time after 10 days of either prazosin or placebo treatment), and once after 10 days at high altitude while on the assigned medication.

c). Assessment of fluid status and body fluid volume distribution (total body water, blood volume, extracellular fluid volume). Body fluid status was assessed by measurements of fluid intake and output (urinary volume) per 24 hr; daily body weight; and urinary and plasma sodium, potassium, chloride, and osmolality. Blood volume was measured on two occasions at sea level and at high altitude using a carbon monoxide rebreathing technique. Total body water was measured by ingestion of a stable isotope (^2H , deuterated water), with moisture from expired air collected before and 2 and 3 hours afterwards (Schoeller-86). Extracellular fluid volume was determined using sodium bromide dissolved in the deuterated water. This salt limits its distribution to the extracellular space. Blood samples for analysis of these substances were drawn before and 2 and 3 hours after ingestion of the salt. On the same days, volume regulatory (atrial natriuretic peptide, vasopressin, plasma renin activity, aldosterone) were measured.

d). Basal metabolic rate was measured before rising by indirect calorimetry on those days when the test volunteer was resident in the study unit at sea level and daily while at high altitude. Measured values were used to adjust daily food intake in order to maintain sufficient energy intake under the various study conditions. Venous blood samples were obtained for measurement of thyroid hormone, important in the regulation of metabolic rate, on several occasions while at sea level and at altitude.

e). Ventilation. Single breath flow-volume loop tests were performed to measure maximal lung capacities and flows at sea level and at altitude. Resting ventilation, ventilatory control and peripheral circulatory responses were performed with the volunteers resting in a seated position, breathing through a low resistance mouthpiece, valve and breathing circuit using a computer-controlled gas analyzer and data acquisition system (SensorMedics Corp, model Vmax229). Measured during all ventilatory tests were: minute ventilation, oxygen uptake, carbon dioxide elimination, and end-tidal oxygen and carbon dioxide by the Vmax229, heart rate by 3-lead ECG (Nellcor-200), arterial blood oxygen saturation by finger pulse oximetry (Nellcor-200), and systemic blood pressure by automated non-invasive finger photoplethysmography (Ohmeda model 2300 Finapres Blood Pressure Monitor). The resting ventilation and ventilatory control tests were performed twice at sea level (days 2 and 8) and nine times at altitude (days 1-7, 9, 12). Ventilatory control testing included the progressive isocapnic hypoxic ventilatory response (HVR) and the progressive hypercapnic ventilatory response (HCVR) tests.

f). Cardiac output during rest and exercise. Cardiac output was measured at quasi-steady state at the end of 3 min of a given exercise level by an acetylene rebreathing method. From end-expiration, the subject inspired (up to total lung capacity) a breath of gas containing 0.3% CH_4 , 0.8% C_2H_2 , 0.3% CO , 40% O_2 in balance N_2 . The subject rebreathed this mixture for 16 sec while expired gas concentrations were

measured continuously at the mouth by a rapid response infrared gas analyzer. Cardiac output was calculated from the exponential uptake of acetylene. Measurements were obtained at rest on days 1, 2, 5, 9, and 12 at high altitude and during exercise on days 2, 5, and 9 at high altitude at successive, pre-selected workloads up to the highest workload that could be sustained for 3 minutes.

g). Resting venous tone and forearm blood flow was measured noninvasively using forearm plethysmography.

h). Whole body exercise testing was performed to provide an integrated measure of the physiologic components of altitude acclimatization. An incremental, progressive exercise bout to volitional exhaustion on a bicycle ergometer was used to measure each test volunteer's peak oxygen consumption. A metabolic cart was used for measurement of O₂ uptake, CO₂ production and respiratory volume. Measurements of fuel utilization were also carried out at rest and while the subject exercised at 50% of their previously measured peak O₂ consumption for 50 min.

i). Fuel (carbohydrate) utilization. To determine fuel utilization with α_1 -adrenergic blockade, a catheter was placed in a hand vein, solutions containing stable isotopes were infused, and blood was sampled multiple times during rest and exercise for analysis of free fatty acids, catecholamine, insulin, glucagon, lactate, glucose, pyruvate, and glycerol.

j). Static muscle contraction (thumb exercise endurance) was evaluated using the adductor pollicis muscle of the hand (Fulco 94). Each volunteer was tested with her hand and forearm secured and with the thumb coupled to a force transducer by means of a strap looped around the thumb. Maximal voluntary contraction (MVC) was determined and submaximal exercise then consisted of intermittent static contractions at 50% of the initial MVC followed by five sec of rest. The cycle of MVC measurements and submaximal contractions was continued until maintenance criteria could not be met. Rate of fatigue was quantified as decline in MVC force and endurance time was defined as time to target contraction failure.

k). Tests of sympathetic reactivity ("tilt", SNS reactivity, acute hypoxia/hypercapnia, heart rate variability). Blood pressure and heart rate were recorded using an ambulatory blood pressure monitor and Holter monitor during two, 24-hour periods while at sea level and altitude as well as during the various tests described below.

"Tilt" (orthostatic response) tests involved measuring blood pressure and heart rate while the test volunteer lay supine for 20 min and after the subject was rotated to a 60-degree "head-up" position over a period of 12 min.

SNS reactivity was evaluated during cold pressor and isometric hand grip challenges. Each test raises blood pressure transiently but does so by a different mechanism. For the isometric hand grip test, maximum strength of the preferred hand was determined using a calibrated handgrip dynamometer. Then the subject was asked to squeeze the dynamometer at 30% of her maximal ability for 3 min. The cold pressor test required the subject to immerse her non-preferred hand in cold (4°C) water for 3 min.

During acute hypoxia or hypercapnia, forearm and hand blood flow, peripheral blood flow responses of the left forearm and hand were assessed by thermographic, impedance, and laser Doppler procedures performed in

conjunction with the HVR and HCVR tests. The outputs of the thermographic, impedance, and laser Doppler devices were digitized, displayed and recorded (AT-Codas, Dataq Inc) on a PC. Thermographic images were made using a AGEMA TIC-8000 Infrared System consisting of a AGEMA ThermovisionR camera, a PC and a CATS E 1.00 software package. Forearm electrical impedance data were collected using a Minnesota (model 304B) impedance cardiograph. Finger tip blood perfusion was measured from the ventral surface of the left middle finger using a laser blood perfusion monitor (TSI, Model 403A).

Heart rate variability analyses were performed to assess the balance of sympathetic vs. parasympathetic autonomic tone on two occasions at sea level and at altitude (Kleiger 92, Ori 92). ECG data were recorded while the subject lay supine as well as after rising to upright posture, under controlled and spontaneous breathing conditions.

1). Assessment of acute mountain sickness (AMS) was performed using the Environmental Symptoms Questionnaire (ESQ) and the Lake Louise AMS Scoring System (LLS) on multiple occasions at sea level and at high altitude. In addition, the Environmental Background Survey, consisting of a 57-item questionnaire, was completed to elicit information on the volunteer's previous experience in stressful climatic conditions.

3). **Preliminary analyses of study results (August - September, 1998).** Laboratory analyses and tabulation of study data have not yet been completed. The status of study analyses and results available to date are summarized below.

a). Menstrual cycle documentation awaits completion of the ovarian hormone measurements since, for example, even women demonstrating an LH surge may not ovulate and hence enter the luteal phase of the menstrual cycle. A manuscript is anticipated addressing the effect of altitude exposure on menstrual cycles using data from all three years' study.

b). α_1 -adrenergic blockade. Definite α_1 -adrenergic blockade was achieved with prazosin. The drug was well tolerated and there were no complications during the phenylephrine challenge tests. The dose of prazosin, 6.0 mg per day, was shown to produce a significant degree of α_1 -adrenergic blockade in our test volunteers as demonstrated by the response to the infusion of an α_1 -adrenergic agonist, phenylephrine. There was a definite rightward shift in the dose response curve to phenylephrine with respect to systolic blood pressure, the change from baseline in systolic pressure, diastolic blood pressure, or mean arterial pressure. The PD₂₀ (the dose of phenylephrine required to increase systolic blood pressure >20 mm Hg over baseline) increased more than 6-fold in the prazosin- compared with the placebo-treated subjects (see table below). This indicated a high degree of α_1 -adrenergic blockade.

Specifically, the PD₂₀ values were 1.69 ± 0.31 $\mu\text{g}/\text{kg}/\text{min}$ for placebo and 11.30 ± 2.14 for prazosin ($p < 0.05$). The peak phenylephrine dose being administered when the cessation criteria were met were 2.5 ± 0.3 vs 11.2 ± 1.0 $\mu\text{g}/\text{kg}/\text{min}$, placebo and prazosin respectively.

During the initial blocked agonist challenges, the individual PD₂₀ values for our test volunteers at sea level varied from 6.05 to 27.2 $\mu\text{g}/\text{kg}/\text{min}$. This variation in PD₂₀ was not attributable to dose of prazosin standardized for body weight, the PD₂₀ on placebo, the time of the agonist challenge after the last prazosin dose, or the peak

exercise VO_2 . Yet to be determined is the influence of menstrual cycle phase. Despite the variation, there was no overlap in the range of values in the unblocked and blocked states.

c). Assessment of fluid status and body fluid volume distribution (total body water, blood volume, extracellular fluid volume). Results are anticipated in approximately one month from the analyses of carbon monoxide concentration in blood samples for assessment of blood volume and of the volume regulatory hormones. After considerable effort identifying the best procedure and laboratory for the analysis of the total body water data from the 1996 and 1998 studies, the samples are currently being processed. Dietary information from the 1998 study subjects is being tabulated to document the Kcal, protein, CHO, fat, fiber, Vit E, Vit C, and trace metals (Fe, Ca, Na, K, and Zn) consumed.

d). Basal metabolic rate data have been analyzed, at least in preliminary fashion, and indicate that there appears to be an increase in BMR by day 2 of altitude exposure with values remaining elevated thereafter. No apparent difference in metabolic rate response to altitude existed between the subjects with and without α_1 -adrenergic blockade (see table below). The rise in metabolic rate was similar between those subjects who were better able to maintain dietary intake and those who were not (as a result of symptoms of altitude sickness or other factors). The metabolic rates (ml O_2 STPD/min) data are summarized in the table below:

	Sea level	Hi alt dy 2	Hi alt dy 3	Hi alt dy 4	Hi alt dy 5	Hi alt dy 6	Hi alt dy 9	Hi alt dy 12
DRUG								
Mean	1407	1537	1675	1700	1642	1746	1664	1599
SD	125.0	202.2	177.6	182.3	203.3	190.8	207.7	100.9
PLACEBO								
Mean	1466	1662	1685	1685	1708	1793	1665	1711
SD	128.7	244.8	219.1	219.1	202.6	280.0	179.7	241.3
ALL								
Mean	1434	1599	1679	1679	1673	1768	1664	1655
SD	133.5	223.5	193.3	193.3	204.7	232.7	194.6	184.5

e). Ventilation. Ventilatory data are currently undergoing final analysis. Preliminary analyses of resting ventilatory data suggest that α_1 -adrenergic blockade had no effect on the rate and/or magnitude of ventilatory acclimatization to 4300 m.

f). Cardiac output during rest and exercise. Preliminary analysis of study results in combination with those obtained in 1996 indicate that acute exposure to altitude (days 1-2) raises cardiac index at rest by 22%. Cardiac index at maximal workload was similar to sea level (within 5%). During acclimatization (day 5), cardiac index was lower than at sea level by 10% at rest and 11% during exercise. By days 9-12, cardiac index had returned to sea-level baseline values at rest and exercise. In contrast, previous studies in men (Wolfel 91) showed that cardiac index remain persistently below sea level up to days 21 at high altitude. These data show that there are sex differences in the cardiac response to high altitude, possibly due to differences in the activation of the autonomic nervous system or the regulation of intravascular fluid volume. It is known that in women, a higher progesterone level may facilitate fluid

retention and hasten the restoration of intravascular volume during acclimatization. Measurements of autonomic regulation, fluid and hormonal status have been obtained in these female subjects and are currently being analyzed at collaborating institutions to address these mechanisms.

g). Resting venous tone and forearm blood flow data have recently been reduced from 33 studies of resting vascular tone at sea level, and 32 studies of resting vascular tone at high altitude. The data have not been fully analyzed, but preliminary data analysis suggests that 1) forearm arterial blood flow is increased and vascular resistance to flow decreased by day 3 of altitude exposure. While values tend to return toward those observed at sea level, forearm arterial blood flow remains higher, and vascular resistance lower on day 10 of altitude exposure. 2) Venous compliance is reduced by day 3 at high altitude and returns towards, but does not fully attain sea-level values by day 10 of altitude exposure. 3) α_1 -adrenergic blockade increases forearm blood flow and venous compliance, but does not interact with altitude to produce effects different from those observed in unblocked women. In other words, α_1 -adrenergic blockade alters forearm blood flow and venous compliance at sea level but does not alter the effect of altitude exposure (increasing forearm arterial blood flow and reducing venous compliance). These preliminary data suggests two possible interpretations: 1) α_1 receptors are not important contributors to the peripheral vascular response to altitude exposure; or 2) other receptors can, within 5 days of the initiation of drug treatment, assume functions normally mediated by the α_1 -adrenergic receptors.

h). Whole body exercise testing. Women, like men, undergo a decrement in maximal exercise performance upon acute or 2 week's exposure to 4300 m. The decrement in women averaged 23%, very similar to the ~25% decrement reported previously in men.

i). Fuel (carbohydrate) utilization. No results of the concentrations of the various substrates are currently available as tests are still being conducted. Inspection of the respiratory exchange ratios (RER) suggests that there is an increased reliance on glucose, particularly in the drug-group (see table below):

	Sea level	Hi alt dy 2	Hi alt dy 3	Hi alt dy 4	Hi alt dy 5	Hi alt dy 6	Hi alt dy 9	Hi alt dy 12
DRUG								
Mean	0.92	0.90	0.95	0.94	0.93	0.95	0.91	0.96
SD	0.041	0.049	0.034	0.046	0.040	0.051	0.031	0.048
PLACEBO								
Mean	0.89	0.89	0.90	0.93	0.92	0.93	0.90	0.89
SD	0.041	0.035	0.029	0.051	0.035	0.053	0.025	0.069
ALL								
Mean	0.91	0.89	0.93	0.93	0.92	0.94	0.91	0.93
SD	0.041	0.041	0.036	0.049	0.038	0.054	0.028	0.056

j). Static muscle contraction (thumb exercise endurance) Analyses conducted to date indicate that α_1 -adrenergic blocked and placebo subjects have similar thumb strength and endurance at all study times. No consistent differences between groups were detected at rest, after 1 min of submaximal exercise, after 25% reduction in strength, or at exhaustion, for arterial saturation or heart rate. α_1 -adrenergic

blockade appears to have had little, if any, effect on small muscle altitude performance at sea level or at altitude.

k). Indices of sympathetic activation: catecholamine levels, blood pressure and heart rate, SNS reactivity tests ("tilt", acute hypoxia/hypercapnia, heart rate variability tests).

Catecholamines (norepinephrine, epinephrine and dopamine) have been analyzed by means of HPLC in approximately 90% of the samples collected at sea level and at high altitude. Additionally, approximately 50% of the plasma samples have been analyzed. It is anticipated that all samples will have been analyzed by mid-November 1998 and statistical analyses completed by the end of November. The extent to which α_1 -adrenergic blockade influences both sympathetic nerve activity and adrenal medullary function at sea level as well as during acute and chronic altitude exposure will be determined.

"Tilt" (orthostatic response) tests. Preliminary inspection of blood pressure and heart rate data in the placebo vs. alpha blocked group indicate that the blocked group had lower blood pressures at each study time. Even though there were large differences in blood pressure in the supine and upright positions between groups and the blocked group had lower blood pressures than the placebo group, the blood pressure response to tilt did not differ meaningfully. Additional analyses are ongoing.

SNS reactivity. Methodological details for the analysis of heart rate and blood pressure data from a total of 33 studies at sea level and 32 studies at high altitude have been worked out. It is anticipated that the data from these studies will not be fully reduced and analyzed in relation to catecholamines, resting vascular tone, ovarian and fluid volume regulatory hormones, and other measures of body fluid volumes until after January 1999.

Heart rate variability analyses. Preliminary calculations of sympathetic (SNS) and parasympathetic (PNS) indices indicate that the SNS index appears to be significantly lower on prazosin relative to placebo while supine at sea level (SL) and at high altitude on days 4 (HA4) and 11 (HA11). While upright, the SNS index is higher at HA4 relative to SL on placebo. The PNS index appears to be significantly higher on prazosin relative to placebo while supine at SL and at HA4 and HA11. While upright, the PNS index is suggestively ($0.05 < p < 0.10$) lower at HA4 relative to SL on placebo.

l). Assessment of acute mountain sickness (AMS). Individual scores for the ESQ and LLS have been calculated and statistical analysis is in progress. Results available to date suggest that the time course and severity of AMS symptoms as measured by ESQ and LLS scores appears not to have been altered by α_1 -adrenergic blockade at the level used in this study.

4. Submission/publication of manuscripts from 1996 and 1997 study data.

A paper documenting the effects of altitude exposure on resting serum and urinary catecholamine levels was published in 1998 (Mazzeo 98).

A paper concerning the effect of the menstrual cycle and altitude exposure on glucose tolerance has been accepted for publication (Braun, In press).

A paper concerning gender differences in the effect of altitude exposure on thumb endurance is under review (Fulco, submitted).

A paper addressing the effects of altitude exposure and menstrual cycle phase on utilization of glucose during rest and exercise is nearing completion and is being submitted for review October, 1998.

An abstract for the Am College of Sports Medicine is being prepared, concerning ovarian hormone levels and glucose turnover data.

A manuscript concerning the effects of altitude and menstrual cycle phase on basal metabolic rate is being submitted for publication this month.

A paper is being submitted this month concerning the effect of altitude and cycle phase on heart rate variability-based indices of SNS and PNS activity.

5. Plans for 1998-1999: completion of data analyses and submission of remaining papers. A working meeting will be held for project investigators in conjunction with the "Hypoxia '99" meeting in Jasper, BC Canada from February 27-March 3, 1999. In attendance are expected to be Mazzeo, McCullough, McCullough, Moore, Reeves, Wolfel, Zamudio from Colorado; Butterfield, Braun, DeLee and Bradford from Palo Alto; Cymerman and Muza from Natick; and Hsia and Tamhane from Dallas. Dr. Kambis who is presently at Natick (while on sabbatical) also plans to attend. Manuscripts or results sections from all data collected during the 1996-1998 years projects will be submitted before or at this working meeting.

CONCLUSIONS

A third, successful year of this project has been completed. These studies entailed the use of the α_1 -adrenergic blocker, prazosin, at sea level and during a 12-day exposure to an altitude of 4300 m. The success of this year's (and previous year's) project is attributable to the cooperation exhibited by the researchers from the four primary institutions participating in this study. Each group provided essential services. The University of Colorado team was primarily responsible for catheter insertion and blood collections, the catecholamine measurements and the overall logistical organization of the project. The Veteran's Affairs Health Care System and Stanford University team recruited the subjects, performed the metabolic testing at rest and during exercise, documented menstrual cycles, and maintained dietary control throughout the study period. The USARIEM team provided and administered the Pikes Peak facility, carried out the ventilatory studies, the orthostatic response tests, and AMS tests, and, together with the Colorado group, carried out the phenylephrine challenge studies. Finally, the Southwestern Medical Center provided the equipment and conducted, together with the Colorado group, the measurements of cardiac output. This year's success is directly attributable to the expertise of these investigators and their commitment to the project as a team.

REFERENCES

Braun B, Butterfield GE, Dominick SB, Zamudio S, McCullough RG, Rock PB, Moore LG. Women at Altitude: changes in carbohydrate metabolism at 4300 m elevation and across the menstrual cycle. *J Appl Physiol*, In press.

Elliot HL, Sumner DJ, McLean K, Reid JL. Effect of age on the responsiveness of vascular alpha-adrenoceptors in man. *J Cardiovas Pharmacol* 4:388-92, 1982.

Elliot HL, Vincent J, Meredith PA, Reid JL. Relationship between plasma prazosin concentrations and alpha-antagonism in humans: Comparison of conventional and rate-controlled (Oros) formulations. *Clin Pharmacol Ther* 43:582-7, 1988.

Fulco CS, Cymerman A, Muza SR, Rock PB, Pandolf KB, Lewis SF. Adductor pollicis muscle fatigue during acute and chronic altitude exposure and return to sea level. *J Appl Physiol* 77:179-83, 1994.

Fulco CS, Rock PB, Muza SR, Lammi E, Cymerman A, Kambis K, Lewis SF, Butterfield G, Braun B, Moore LG. Slower rate of adductor pollicis muscle fatigue and faster recovery in women than in men. *J Appl Physiol*, Submitted.

Kleiger RE, Stein PK, Bosner MS, Rottman JN. Time domain measurements of heart rate variability. *Cardiol Clin* 10:487-98, 1992.

Mazzeo RS, Child A, Butterfield GE, Mawson JT, Zamudio S, Moore LG. Catecholamine response during 12 days of high-altitude exposure (4,300 m) in women. *J Appl Physiol* 84:1151-7, 1998.

Ori Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. *Cardiol Clin* 10:499-537, 1992.

Schoeller DA, Kushner RF, Jones PJ. Validation of doubly labeled water for measuring energy expenditure during parenteral nutrition. *Am J Clin Nutr* 44:291-8, 1986.

Wolfel EE, Groves BM, Brooks GA, Butterfield GE, Mazzeo RS, Moore LG, Sutton JR, Bender PR, Dahms TE, McCullough RE, McCullough RG, Reeves JT. Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J Appl Physiol* 70:1129-36, 1991.