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CONTRACT NUMBER DAMD17-95-C-5110

TITLE: Women at Altitude: Effects of Menstrual Cycle Phase and Alpha-Adrenergic Blockade on High Altitude Acclimatization

PRINCIPAL INVESTIGATOR: Lorna G. Moore, Ph.D.

CONTRACTING ORGANIZATION: University of Colorado, Denver
Denver, Colorado 80262

REPORT DATE: October 1997

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

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19971117 023

DTIC QUALITY INSPECTED 4

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1997	Annual (22 Sep 96 - 21 Sep 97)

4. TITLE AND SUBTITLE
Women at Altitude: Effects of Menstrual Cycle Phase and Alpha-Adrenergic Blockage on High Altitude Acclimatization

5. FUNDING NUMBERS
DAMD17-95-C-5110

6. AUTHOR(S)
Lorna G. Moore, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Colorado, Denver
Denver, Colorado 80262

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

Background. Little is 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 on the ventilatory, circulatory and metabolic responses to hypoxia but that the volume regulatory adjustments were altered such that there tended to be greater fluid retention in the luteal phase subjects. The **purpose** of the studies conducted in year 2 (the present annual report) was to determine the role of α-1 adrenergic activity and its interaction with menstrual cycle phase in early altitude acclimatization. Fifteen young women were exposed to an effective altitude of 4300 m in the USARIEM hypobaric chamber for 52 hr on two occasions, once while being treated with an α-1 blocker (prazosin) in a randomized, double blind fashion. **Results and significance:** Definite α–adrenergic blockade was achieved as demonstrated by a rightward shift in the blood pressure response to an α-adrenergic agonist, phenylephrine. Prazosin blocked the altitude-associated rise in systemic blood pressure during exercise and after tilt. Hematocrit was lower in α-blocked than placebo-treated subjects, implying a relaxation of venous tone, but this effect appeared similar at low and high altitudes. Ventilation, hypoxic and hypercapnic ventilatory responses were unaffected by α-adrenergic blockade at either altitude. Analyses are continuing on other variables. Thus, the information obtained to date suggests that α-1 adrenergic activation is a key factor in orthostatic and exercise-related elevations in blood pressure at high altitude, in keeping with the study hypothesis.

14. SUBJECT TERMS
Defense Women's Health Research Program

15. NUMBER OF PAGES
17

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Lana S Moore 10-17-97

PI - Signature Date

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INTRODUCTION

Project purpose and scope. The purpose of the study covered in this annual report (year 2 of our 3-year contract) is to determine the role of α-1 adrenergic activity and its interaction with menstrual cycle phase in early altitude acclimatization. Fifteen healthy young women with normal menstrual cycles were exposed to an effective altitude of 4300 m in a hypobaric chamber for 52 hr on two occasions, once while being treated with an α-1 blocker (prazosin, 1 mg every eight hours or 3 mg in a 24-hr period) and once while taking a placebo. The study was of a randomized, double blind design. Menstrual cycle phase was constant (either follicular or luteal) during the blocked *vs.* unblocked studies for each subject. Sea level comparison studies were performed prior to the altitude exposure. The studies were performed at the US Army Research Institute of Environmental Medicine, Natick, MA.

Studies were conducted to test the hypotheses that 1) α-1 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 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 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 blockade, it is further hypothesized that: 4) exercise performance will be decreased with α-1 blockade; 5) the occurrence of acute mountain sickness (AMS) will increase with α-1 blockade relative to placebo; and 6) the effects will be more pronounced during the follicular phase of the menstrual cycle. The study planned for year three will test the effects of α-1 blockade during a chronic (12 day) exposure to altitude.

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 both female service members. Results will assist in identification of effective prophylaxsis 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 study to systematically evaluate the influence of ovarian hormones on acclimatization to high altitude. Gender differences attributable to ovarian hormone fluctuations have been explained in detail in the year 1 report of this contract.

BODY

1). Preparation: September, 1996-May, 1997. During this period, protocols and consent forms were prepared, supplies were purchased, equipment was organized, and volunteers were recruited. The recruiting process was carried out by personnel at the USARIEM, Thermal and Mountain Division. The total number of volunteers

screened was in excess of 100. Fifteen (15) women were selected for the study, all of whom were residents of sea level and lived in the vicinity of Boston, MA. Supplies and equipment were shipped from the research groups in Denver, CO and Palo Alto, CA to Natick immediately prior to the beginning of the study in June, 1997.

The general characteristics of the volunteers are shown in the table below (mean ± SEM):

Age (yr)	24.7 ± 1.18
Height (cm)	169.2 ± 1.96
Weight (kg)	70.8 ± 2.49
Resting HR (bpm)	79.1 ± 2.45
Resting MAP (mm Hg)	75.2 ± 1.84
VO2 max (ml/kg/min)	33.7 ± 1.94

2). Conduct of study (June - July, 1997). Formal testing of volunteers began following final approval of the second-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. During the first month, the volunteers documented their menstrual cycles, received required hypobaric chamber orientation and safety training and were familiarized with testing procedures. The second phase consisted of a six-week period of experimental testing, during which the volunteers continued to document their menstrual cycles. This testing consisted of studies at sea level and at 4300 m altitude performed on two occasions, once while receiving prazosin or once while being treated with a placebo. The third phase was a repetition of the second. During either phase two or three, the subject was treated with prazosin and during the other with placebo. The subject was tested in the same phase (either follicular or luteal) during two consecutive menstrual cycles on these occasions. The following table shows the study testing schedule:

Preliminary Phase (sea level, 1 mo)	Experimental Phase (sea level & altitude, 6 wks)	Follow-up Phase (sea level, 1 mo)
Pregnancy screen	Pregnancy screen	Pregnancy screen
Ovulatory & menstrual cycle assessment	Ovulatory & menstrual cycle assessment	Ovulatory & menstrual cycle assessment
Altitude chamber training	α blockade documentation	
Procedure training	Sea-level/altitude testing	
Preliminary testing		

A controlled diet was maintained for seven days during each of the experimental study periods in order to assure that the women were receiving the same proportions of calories from carbohydrates, fats and proteins during each test phase. The testing schedule which each volunteer underwent is shown in Appendix A. In this diagram an "X" designates a day on which the measurements were made. The echocardiogram studies and DEXA measurements were not done during this study due to time, cost and space constraints. All other tests were successfully carried out. The methods employed were described in the year 2 protocol description, and are briefly described as follows:

a). Menstrual cycle documentation included documentation of non-pregnant status by blood test for human chorionic gonadotrophin (HCG), a record of cycle length, and assessment of ovulatory status by urine test for the presence of luteinizing hormone (LH). Blood samples were collected on two sea level and two altitude days for evaluation of serum ovarian hormone levels.

b). Environmental Background Survey (EBS) consisted of a 57-item questionnaire completed one time during the preliminary phase to elicit information on the volunteer's previous experience in stressful climatic conditions as well as epidemiologic, medical and menstrual history data.

c). Documentation of α-adrenergic blockade (α-1 agonist challenge) was employed to demonstrate the extent of α-blockade induced by prazosin by evaluating the blood pressure response to increasing dosages of phenylephrine administered as an intravenous infusion (2, 3). This test lasted approximately a one hour and was done twice at sea level, once while taking prazosin and once while taking placebo.

d). Fluid status assessment. Since altered fluid-volume regulation is thought to play a role in altitude acclimatization, body fluid status was assessed using 24-hour fluid intake; 24-hour urinary volume; daily body weight, bio-impedance measurements for total body water and intra- and extra-cellular fluid; urinary and plasma sodium, potassium, chloride, and osmolality; and calculated percent change in plasma volume.

e). Basal metabolic rate was measured daily before rising by indirect calorimetry. Since alterations in basal metabolic rate at altitude will change total energy requirement, it was anticipated that measurements of basal metabolic rate would allow for adjustment of the daily energy intake. However, symptoms of acute mountain sickness were so severe that, although energy intake was encouraged and recorded, it could not be fully adjusted for increased need.

f). Carbohydrate regulation. Since insulin secretion and glucose production are regulated by α-1 adrenergic receptors, we measured glucose tolerance once at sea level and once at altitude during each experimental test phase (once on prazosin, once on placebo). Following a 12-hour overnight fast, an intravenous catheter was placed, a fasting blood sample was taken, then a standard 75 gm carbohydrate meal was eaten. Blood samples were taken at 30, 60, 90 and 120 minutes following meal ingestion. The blood samples were analyzed for insulin, glucose and C-peptides. These analyses are presently in progress.

g). Bio-impedance Testing. A bioelectric-impedance technique was used to estimate changes in water intra-and extra-cellular body water. Subjects were tested after 2-hour fast from food and liquid and after being supine without moving for 10 minutes. An electric current (800 uA maximum at 50 kHz) was passed through the body from electrodes on the hand to similar electrodes on the ankle. The testing required approximately 15 minutes to complete and was performed once at sea level and once at altitude during each sea-level/altitude exposure.

h). Ventilation. Standard spirometry (vital capacity) and respiratory control measurements (HVR and HCVR) were measured once each at sea level and altitude

during each test period during the experimental phase of the study. The measurement of hypoxic ventilatory response (HVR) used the progressive, isocapnic hypoxic test. Resting ventilatory measurements (minute ventilation, breathing frequency, tidal volume, end-tidal PO_2 and PCO_2) were measured daily. During these studies, blood pressure, heart rate and arterial saturation were also measured using non-invasive methods.

i). Blood pressure and heart rate. Since blood pressure is greatly influenced by α-adrenergic activity, blood pressure and heart rate were measured on multiple occasions. Blood pressure and heart rate were measured during the following tests: twice daily during the assessment of acute mountain sickness, during the ventilatory control tests, during the orthostatic response testing, during the exercise test, and during the phenylephrine challenge testing period. During some of the studies, blood pressure was measured manually, and during others using an automated blood pressure device.

j). Orthostatic response testing was done to determine how each experimental test phase (once on placebo, once on placebo) modifies the cardiovascular response to an orthostatic challenge during early acclimatization to altitude. A "tilt-test" was performed which required the volunteer to lie supine while blood pressure and heart rate were measured for 20 minutes. Then, the subject was rotated to a 60-degree "head-up" position and blood pressure and heart rate were measured every two minutes for 12 minutes. Volunteers were tested once at sea level and once at altitude during both prazosin and placebo phases.

k). Exercise testing was performed to provide an integrated measure of many of the physiologic components of altitude acclimatization. An incremental, progressive exercise bout to volitional exhaustion on a bicycle ergometer was used to assess each volunteer's peak oxygen consumption. A metabolic cart was used for measurement of O_2 uptake, CO_2 production and respiratory volume. To determine possible shifts in fuel utilization with α-1 blockade, a catheter was placed in a warmed hand vein and blood was sampled at rest, at the end of each work load, and as close to exhaustion as possible for analysis of glucose, insulin and free fatty acids. In addition, the Borg Relative Perceived Effort scale was used to quantitate each volunteer's subjective assessment of her physical effort (1).

l). Assessment of acute mountain sickness (AMS). The absence of symptoms of AMS is generally taken to be an indication of adequate acclimatization. To assess degree of AMS, we used the Environmental Symptoms Questionnaire (ESQ), the Lake Louise AMS Scoring System (LLS) and voice onset time analysis (VOT). All were administered twice daily during the experimental testing phases.

m). Intraocular pressure (IOP). IOP may provide a marker for altitude acclimatization and may be affected by adrenergic activity. Measurements were made with a hand held tonometer (TONO-PEN™XL) or the equivalent and were taken after the cornea was anesthetized with a topical solution. Measurements were made at rest once at sea level and daily at altitude during each sea-level/altitude exposure. These measurements were done to determine whether intraocular pressure is affected by altitude-induced changes in retinal blood flow, and what relation those changes might have to AMS.

3). Analysis of study results (August - September, 1997). Laboratory analyses have been initiated but not yet completed for ovarian hormones, fluid volumes, glucose, insulin, and C-peptides. Tabulation from the other tests is still underway and thus study results are not, at this time, available for all variables. Identification of menstrual cycle phase necessarily 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. Nevertheless, some preliminary data from the variables that have been analyzed to date are available. These findings are summarized below.

a). 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, 3.0 mg per day, was shown to produce a significant degree of α-1 adrenergic blockade in our 15 subjects 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 with phenylephrine with respect to systolic blood pressure, the change from baseline in systolic pressure, diastolic blood pressure, or mean arterial pressure (Appendix B). The PD 20 (*i.e.* the dose of phenylephrine required to increase systolic blood pressure greater than 20 mm Hg over baseline) increased 5-fold in the prazosin- compared with the placebo-treated subjects (Table below). This indicated a high degree of α-1 adrenergic blockade in our subjects.

Phenylephrine Challenge Mean Data.

	Placebo	Prazosin
REST:		
Systolic blood pressure (mm Hg)	106 ± 2	102 ± 2
Diastolic blood pressure (mm Hg)	63 ± 2	62 ± 1
Mean arterial pressure (mm Hg)	77 ± 2	75 ± 1
Heart rate (BPM)	70 ± 2	73 ± 3
PEAK PHENYLEPHRINE DOSE: *		
Systolic blood pressure (mm Hg)	132 ± 2	136 ± 4
Diastolic blood pressure (mm Hg)	84 ± 2	79 ± 3
Mean arterial pressure (mm Hg)	100 ± 2	98 ± 3
Heart rate (BPM)	51 ± 3	54 ± 3
PD20 (μg/kg/min) †	2.0 ± 0.3	10.7 ± 2.0 §

* Higher dose of phenylephrine required with placebo vs prazosin (2.5 ± 0.3 vs 11.2 ± 1.0 μg/kg/min).
† Phenylephrine dose required to increase systolic blood pressure 20 mm Hg above baseline pressure.
§ $p < 0.001$, paired t-test.

The individual PD20 values for our subjects varied from 3.4 to 31.0 ug/kg/min. The reasons for the variation in the degree of α-1 blockade with the same dose of

prazosin have not yet been determined. The variation was not attributable to dose of prazosin standardized for body weight, the PD20 on placebo, the time after prazosin dose of the agonist challenge, or the peak exercise VO_2 of the subject. We have yet to determine the influence of the phase of the menstrual cycle on the PD20. Despite the variation in the degree of blockade, there were definite changes seen in the blood pressure response during hypobaric hypoxia to exercise and tilt in the subjects taking prazosin.

b). Prazosin blocked the altitude-associated rise in systemic blood pressure during exercise and after tilt. Thus, this data together with the blood pressure during exercise indicated that α-1 adrenergic activation was a key factor in orthostatic and exercise-related elevations in blood pressure at high altitude, in keeping with the study hypothesis. During exercise, α–1 blockade lowers blood pressure and raises heart rate both at sea level and at altitude (Appendices C and D). While the elevation in heart rate was similar at low and high altitude, prazosin had a greater effect on decreasing blood pressure at high than at low altitude. This was due chiefly to higher blood pressures in the placebo-treated subjects at high than at low altitude. The values in prazosin treated subjects were nearly equivalent at the two elevations, implying that α-1 adrenergic activation was likely an important contributor to the altitude-associated rise in blood pressure.

Further support for a role of α-1 adrenergic activation at high altitude was provided by the "tilt" test. The tilt maneuver described above prompted a rise in blood pressure at high altitude while on placebo treatment but this rise was completely eliminated by prazosin (Appendix E).

Blood pressure was also analyzed during the brief bouts of added hypoxia or hypercapnia experienced by subjects during the ventilatory control tests (HVR and HCVR). There was less rise in blood pressure during 5 to 7 min of induced hypoxia or hypercapnia in the prazosin than placebo-treated subjects, again implying that α-1 adrenergic activation was a contributor to blood pressure elevation during these maneuvers. Thus, this data together with the blood pressure during exercise indicated that α-1 adrenergic activation was a key factor in orthostatic and exercise-related elevations in blood pressure at high altitude, in keeping with the study hypothesis.

c). Ventilation (resting end-tidal PCO_2) was unaffected by α-1 adrenergic blockade at sea level but may have had a modest effect on diminishing the fall in end-tidal PCO_2 during the first 52 hours of altitude exposure (Appendix F). However, there was no effect of prazosin on the hypoxic ventilatory response or on the hypercapnia ventilatory response during sea level or high altitude exposure.

d) Hematocrit was lower in α-1 blocked than placebo-treated subjects, implying a relaxation of venous tone. On preliminary inspection the diminution in hematocrit was similar at sea level and at high altitude, suggesting that the degree of relaxation was similar at low and high altitude.

e). Basal metabolic rate increased in all women in response to acute exposure to 4300 m (pre-altitude exposure = 1463 ± 197 kcal/da *vs* first day of exposure = 1670 ± 197 kcal /da). This parameter was not, however, affected by α-1 blockade at sea level

(blocked, pre-altitude exposure = 1446 ± 166 kcal/da *vs* unblocked pre-altitude exposure = 1449 ± 228) or at altitude (blocked, day 1 of exposure = 1717 ± 172 *vs* unblocked, da 1 of exposure = 1620 ± 219). Other analyses (*e.g.* resting metabolic rate, body fluids, carbohydrate regulation, bio-impedance testing, AMS, IOP, and exercise performance) are not yet complete.

CONCLUSIONS

A second, 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 52-hour exposure to an effective altitude of 4300 m. Preliminary findings indicate that high altitude exposure specifically activates the α-1 adrenergic system as indicated by the greater fall in blood pressure during tilt at high than at low altitude. The role of α-1 activation in other physiologic systems involved in high-altitude acclimatization awaits completion of data analysis.

The success of this year's project is attributable to the cooperation exhibited by the researchers from the three institutions participating in this study. Each group provided essential services; the University of Colorado team carried out the phenylephrine challenge studies, the catheter insertion and blood collections, the catecholamine measurements and the data organization; the Veteran's Affairs Health Care System and Stanford University team performed the metabolic testing at rest and during exercise, the bio-impedance measurements and maintained dietary control throughout the study period; the USARIEM team provided and operated the high-altitude chamber, recruited the subjects, documented their menstrual cycles and carried out the ventilatory studies, the orthostatic response tests, the IOP and AMS tests. The second year's success is directly attributable to the expertise of these investigators and their commitment to the project as a team.

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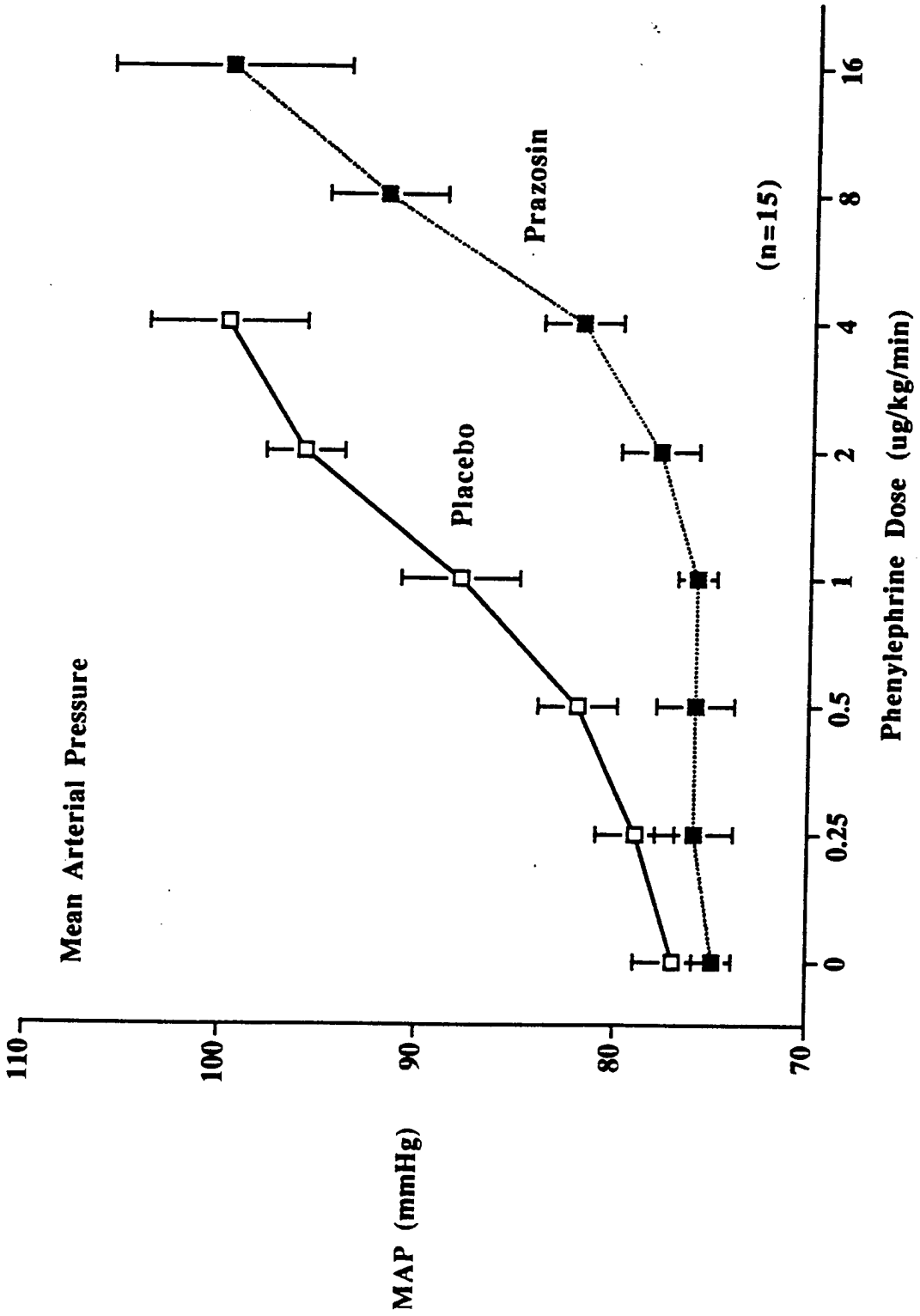
Appendix A. Study testing schedule

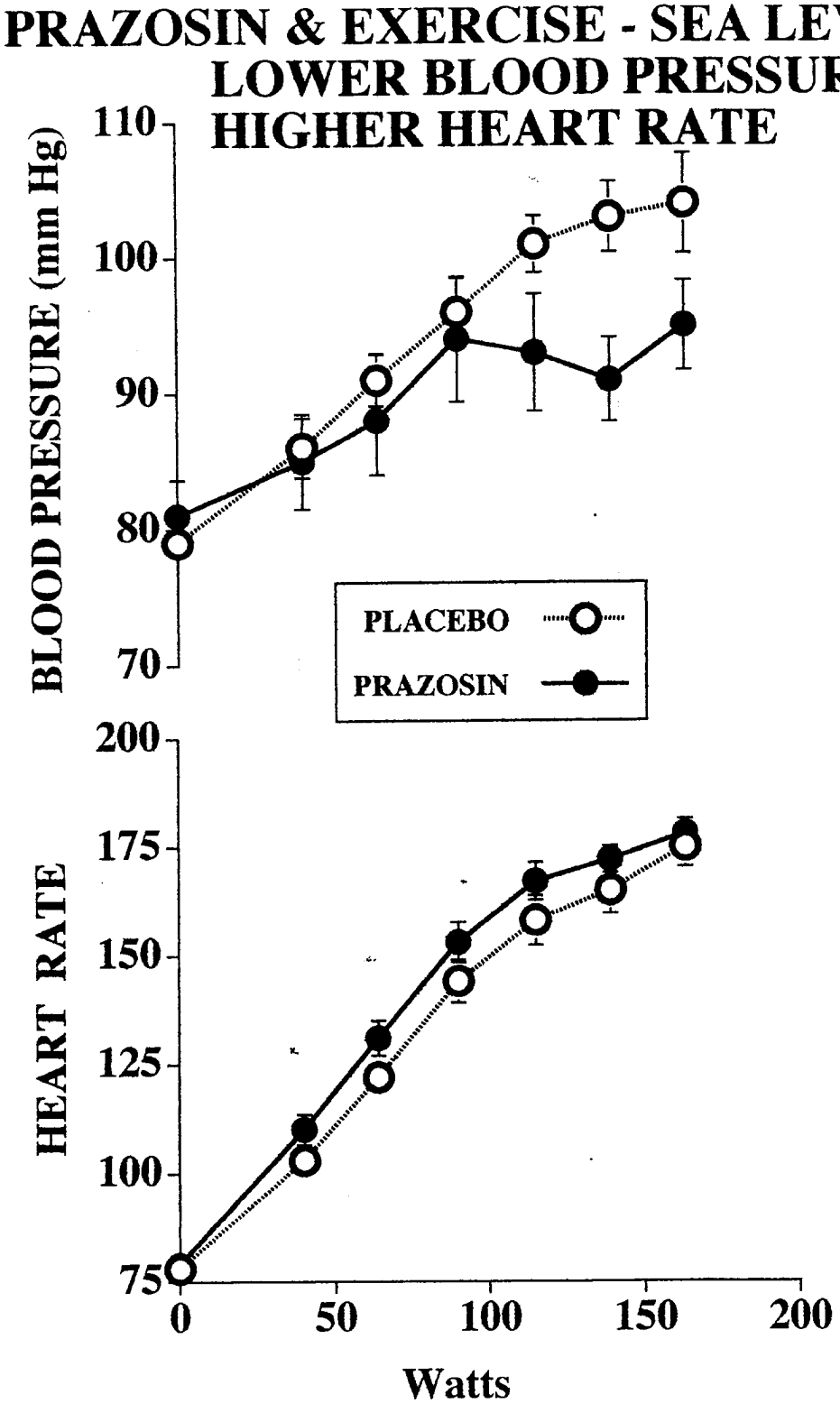
TEST PROCEDURE	TEST DAY							
	Sea Level					Altitude		
	1	2	3	4	5	6	7	8
Prazosin/placebo administration			X	X	X	X	X	X
Document α-1 blockade					X			
Control diet	X	X	X	X	X	X	X	X
Dietary intake record			X	X	X	X	X	X
24-hr urine			X	X	X	X	X	X
Basal metabolic rate				X	X	X	X	X
Meal tolerance test				X			X	
Bioelectric impedance test				X		X	X	
Resting ventilation				X	X	X	X	X
Ventilatory control tests				X			X	
Echocardiogram					X		X	
Orthostatic response test					X		X	
Exercise test					X			X
Blood pressure measurement				X	X	X	X	X
Symptom questionnaire				X	X	X	X	X
Voice recording					X	X	X	X
Intraocular pressure				X			X	X
Serum ovarian hormones					X		X	X

Tests at altitude shaded.

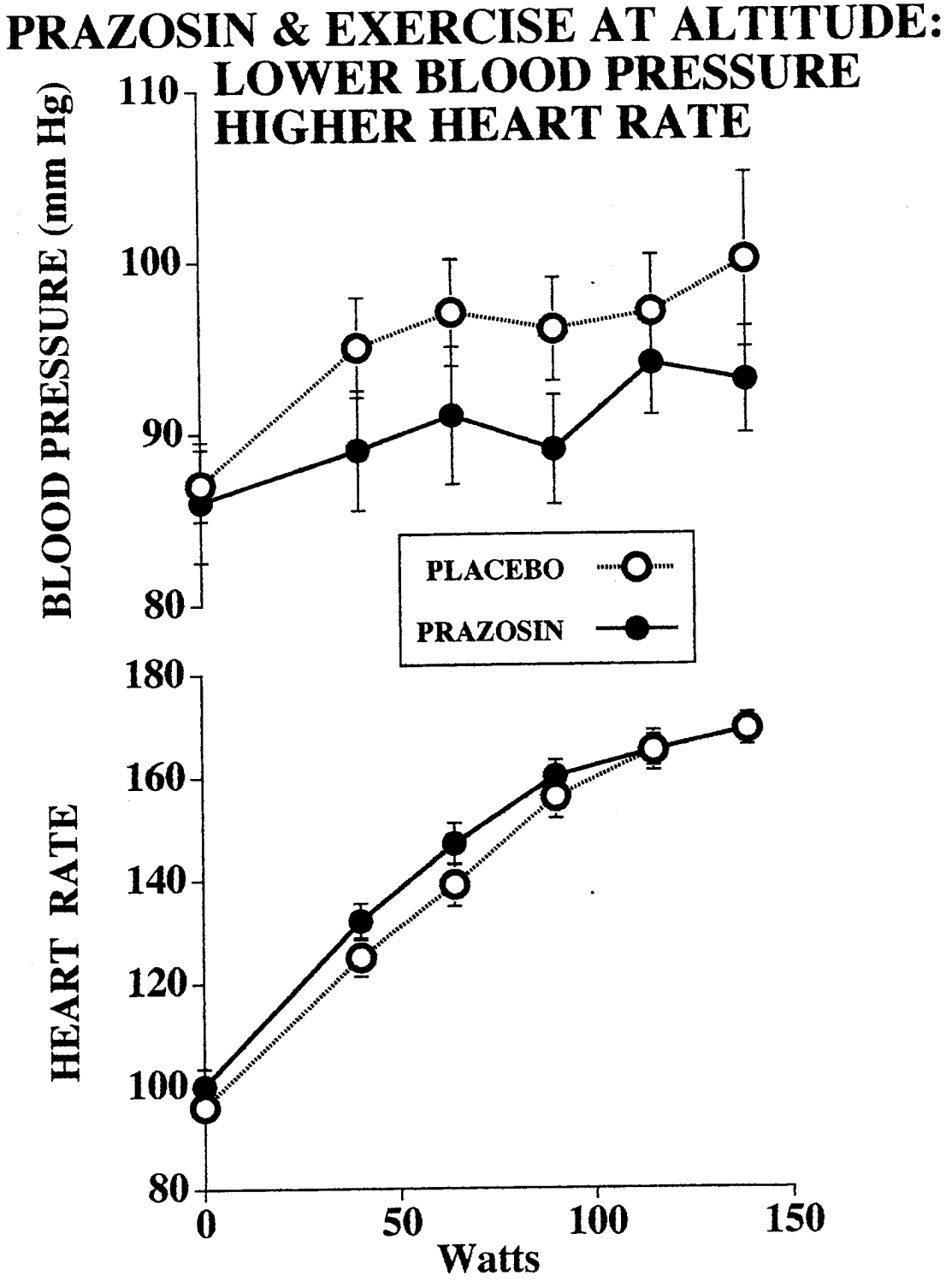
Appendix B. Mean arterial pressure response to a challenge of the a-agonist phenylephrine while on placebo or the α-1 adrenergic blocker prazosin. Demonstration of α-1 blockade.



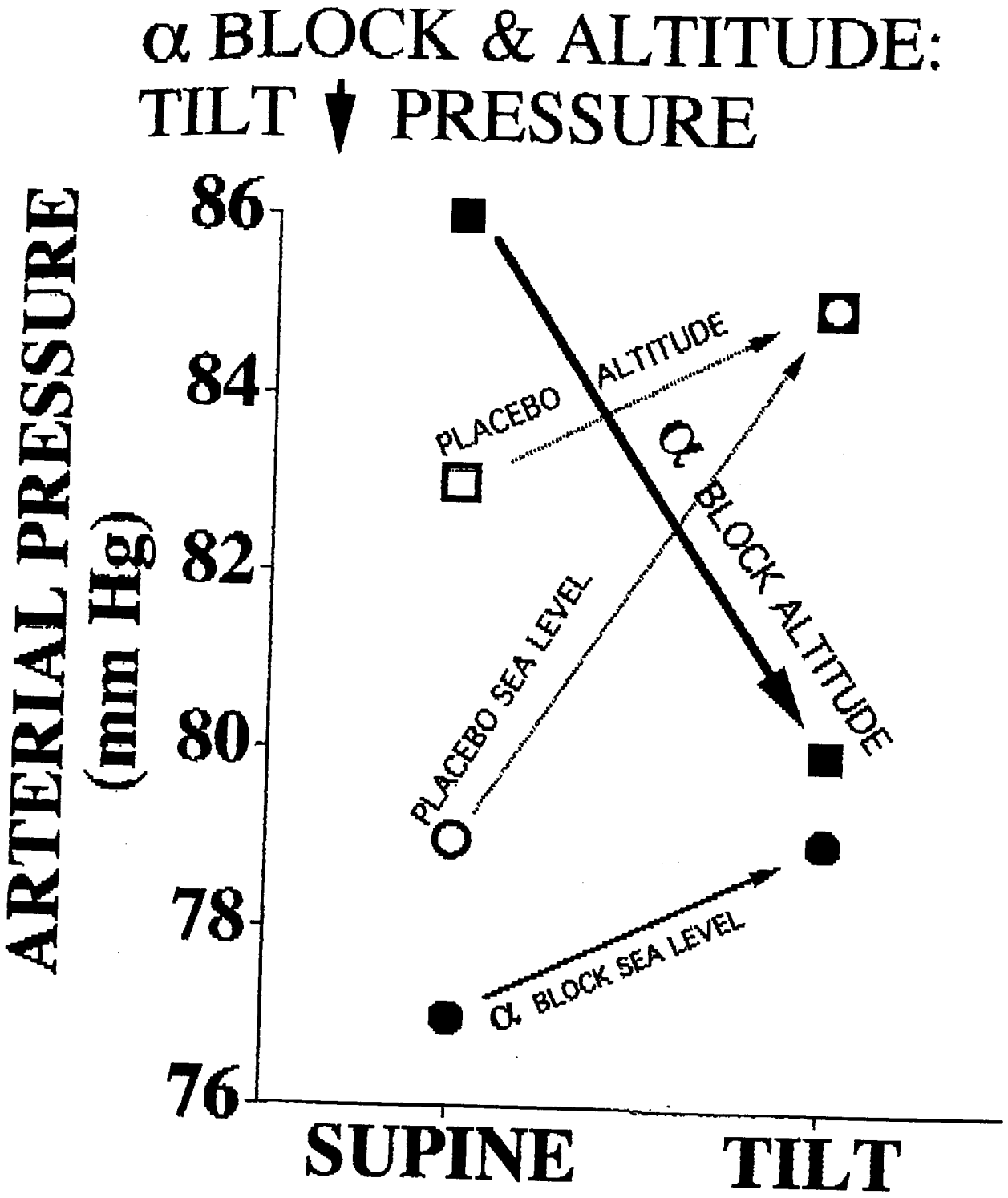
Appendix C. Mean arterial pressure and heart rate during exercise at sea level. Volunteers on placebo or prazosin.



Appendix D. Mean arterial pressure and heart rate during exercise at effective altitude of 4300 m. Volunteers on placebo or prazosin.



Appendix E. Arterial blood pressure during "tilt test" at sea level and at an effective altitude of 4300 m. Volunteers on placebo or prazosin.



Appendix F. End-tidal PCO_2 during 52 hours of altitude exposure and ventilatory (V) and blood pressure (BP) responses to hypoxia (HVR_S, $HBPR_S$) and hypercapnia ($HCVR_S$, $HCBPR_S$). Volunteers on placebo or prazosin.