CONTRACT NO: DAMD17-91-C-1112

TITLE: BETA-ADRENERGIC BLOCKADE AND LACTATE METABOLISM DURING EXERCISE AT HIGH ALTITUDE

PRINCIPAL INVESTIGATOR: John T. Reeves

CONTRACTING ORGANIZATION: University of Colorado
School of Medicine
4200 East 9th Street
Denver, Colorado 80262

REPORT DATE: August 5, 1992

TYPE OF REPORT: Midterm Report

PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	5 August 19992	Midterm Report (6/10/91-3/9/92)

4. TITLE AND SUBTITLE
Beta-Adrenergic Blockade and Lactate Metabolism During Exercise at High Altitude

5. FUNDING NUMBERS
Contract No.
DAMD17-91-C-1112

0601102A
3M161102BS15.CA.064
WUDA335893

6. AUTHOR(S)
John T. Reeves

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Colorado
School of Medicine
4200 East 9th Street
Denver, Colorado 80262

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development 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 words)*

The primary thrust of this contract was to perform high altitude research on Pikes Peak Colorado (with the sea level phase to be done in Palo Alto) in the summer of 1991. The work was to test the hypothesis that the adreno-sympathetic system mediated many of the adaptations to high altitude, particularly the metabolic changes.

14. SUBJECT TERMS
RA III; RA V; Environmental Adaptation; High Altitude; Exercise; Metabolism; Volunteers

15. NUMBER OF PAGES

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

FOREWORD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR56.

The primary thrust of this contract was to perform high altitude research on Pikes Peak Colorado (with the sea level phase to be done in Palo Alto) in the summer of 1991. The work was to test the hypothesis that the adreno-sympathetic system mediated many of the adaptations to high altitude, particularly the metabolic changes.

With regard to metabolism, the primary hypothesis was that the high beta adrenergic stimulation on arrival at altitude would stimulate lactate release which then would be fuel for the working muscles. After 3 weeks acclimatization, we expected that the subsidence of the high adrenergic tone would be associated with less lactate turnover and other metabolic fuels, such as glucose and possibly fat would be utilized to make up the difference.

To approach these hypotheses, we enlisted 12 healthy young men to go to the Peak, 6 of them having beta adrenergic blockade (propranolol 240 mg/day) and 6 being controls. (With attrition of one control subject after the sea level phase, 11 men were taken to the Peak.) The investigative team involved the cooperation of scientists from the University of California at Berkeley, Stanford University, University of Colorado (Boulder and Denver Campuses), NASA, St. Louis University, University of Waterloo, Canada, and the University of Sydney, Australia, in addition to the scientists from USARIEM.

Femoral artery and vein catheterizations were done on three study days for the purpose of measuring cardiac output, arterial pressure and obtaining blood samples for blood gases and various metabolites. The catheterizations were performed once at sea level and twice at altitude (on arrival and after three weeks at altitude). As a result of the dedication and cooperation of the investigative team and the subjects, all facets of this complicated study were accomplished with good enthusiasm and without injury or complication to the subjects, or compromise of the scientific goals. A physician was present at all times on Pikes Peak to observe the subjects.

The contract extends well beyond the data collection period because of the wealth of collected data to be organized and the mountain of samples to undergo chemical analysis. With regard to data synthesis, the following progress has been made since the last report.

variability related to the 24 hour excretion of norepinephrine. In the beta blocked subjects, the pressure rise was blunted but still present, and in them also, the magnitude of the rise was related to the norepinephrine excretion. Therefore, our tentative conclusion is that alpha adrenergic activation over time at altitude is likely to cause hypertension in recent arrivals at altitude. These findings are being prepared for publication by Dr. Wolfel of the University of Colorado Health Sciences Center in Denver. This manuscript will be submitted for publication to a major journal within the next month.

2. Catecholamine metabolism. The study allowed for a more complete description of body handling of catecholamines than has previously been reported. Thus, the 24 hour urinary excretion of norepinephrine was found to progressively rise to a stable plateau over the first 8-10 days of the altitude stay at 4300 m. There was a suggestion that the excretion began to decrease in the final days of the 21 day stay. Arterial blood levels on arrival and at the end of the stay correlated well with the urinary excretion. Epinephrine and Dopamine were not much altered by altitude exposure.

We obtained femoral arterio-venous differences for the catecholamines at rest and during exercise. The data indicated that exercise was associated by a release of norepinephrine from the exercising leg and an uptake of epinephrine. These data are unique and are being prepared for publication by Dr. Robert Mazzeo of the University of Colorado at Boulder.

3a. Lactate handling. The analyses of more than 10,000 samples of blood by mass spectroscopy is not yet complete. However, the measurement of the non labeled lactate has indicated that the beta blockade did reduce the circulating lactate levels. However, the beta adrenergic blockade did not completely prevent the decrease in lactate levels with acclimatization. Thus the "lactate paradox" cannot be entirely explained by changes in epinephrine activity. This large body of work is being conducted by Dr. George Brooks at Berkeley.

3b. Glucose kinetics. We determined on a previous study that the decrease in lactate metabolism with acclimatization was accompanied by an increase in glucose metabolism. In this study we sought to determine whether glucose kinetics would be altered by beta adrenergic blockade. Stable isotopes were administered intravenously through a plastic intracath inserted into an arm vein under aseptic conditions. Blood samples were drawn at rest and during exercise from an identical catheter in the opposite arm, as well as from the femoral artery and vein catheters. Dr. Brooks has now completed his measurements of glucose kinetics using mass spectroscopy and is now performing the data analyses.

4. Blood volume. Measurement of blood volumes by carbon monoxide method indicated that there was the expected decrease in plasma volume with acclimatization and this was not affected by the beta blockade. Over the 3 week residence on the Peak, the red cell mass increased (in most subjects) such that the decrease in plasma volume tended to be opposed by an increase in red cell mass, thus minimizing the fall in total blood volume. These measurements are to be confirmed by the plasma volume measurements utilizing Evans blue (Dr. Greenleaf, NASA) which have now been completed. The analyses of Carbon monoxide were conducted by Dr. Tom Dahms of St. Louis University. The results are being compiled and coordinated for publication by Dr. Robert F. Grover, Emeritus Professor from the University of Colorado.

5. Body Weight. Diet management for the subjects was under the direction of Dr. Gail Butterfield of Stanford University. The diet for each subject was carefully managed so as to prevent weight loss. Analysis of samples and data relating to the nitrogen balance, the

daily basal metabolic rate, the body insensible water loss, and tissue weight loss are being done by Dr. Butterfield. These sample analyses have not yet been completed.

6. Spectral analysis of the electrocardiogram for sympathetic and parasympathetic tone is being done by Dr. Rich Hughson of Waterloo University in Canada. These analyses are important because blood levels of epinephrine and urinary excretion are not very sensitive measures of beta sympathetic activity. We therefore expect to get novel and important information from detailed analysis of the basal heart rate. Dr. Hughson has looked at ventilation in conjunction with the power spectra and is processing the data. This should be completed in August or September.

7. Muscle biopsies were performed by Dr. Wolfel on the three catheterization days. During each catheterization the muscle biopsies were done at rest and following exercise using local anesthesia and aseptic technique. The muscle samples were analyzed in the laboratory of Dr. Wolfel. Beta blockade did not block lactate accumulation in the muscle on arrival at altitude. Both with and without blockade, the exercise values fell to nearly sea level values. There was little glycogen sparing effect after acclimatization. Dr. Wolfel is organizing these data for publication.

8. Echo-doppler measurements. Dr. Mark Selland performed measurements of cardiac volumes at rest and at 30 minutes of exercise using a 2-D echocardiograph instrument. The measurements were done at both sea level and at altitude. The data indicate that the ventricular volume and stroke volume decrease with time at altitude. In addition there was an increase in pulmonary artery pressure with acute exposure to altitude and a tendency to decrease with time at altitude. Dr. Selland is analyzing and preparing the data for publication.

Administration of the Contract.

While most of the awarded funds have been expended, rebudget was requested and approved to allow for continuing technical assistance for the mass of analysis yet to be done. A second but minor rebudget will be requested in the coming weeks, but the request will not be submitted until we have clarified payment of an invoice to one of the vendors.