AD_____

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 AVE.
DENVER, CO 80262

REPORT DATE: January 28, 1993

TYPE OF REPORT: FINAL REPORT

PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND. FORT DIETRICK, MD 21702-5012

DISTRIBUTION STATEMENT: APPROVED FOR PUBLIC RELEASE;
DISTRIBUTION UNLIMITED.

The findings of this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

FINAL REPORT - DAMD 17-91-C-1112

BETA ADRENERGIC BLOCKADE AND LACTATE METABOLISM DURING EXERCISE AT HIGH ALTITUDE

January 28, 1993

FOREWORD

For the protection of human subjects, the investigators have adhered to policies of applicable Federal Law 45CFR 56.

INTRODUCTION:

This contract was to perform high altitude research on Pikes Peak Colorado with the sea level phase to be done at Palo Alto in the summer of 1991. The thrust 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 the metabolic changes, the primary hypothesis was that high adrenergic stimulation on arrival at altitude would stimulate epinephrine release which in turn would stimulate the release of lactate and its metabolism by the working muscle. After 3 weeks acclimatization to 4300 m, we expected the subsidence of the adrenergic tone would be demonstrated by lower levels of epinephrine which would then cause less release and metabolism of lactate. Other metabolic fuels, particularly glucose and fat, would become relatively more important.

To approach these hypotheses we enlisted 12 healthy young men to go to the Peak, 6 of them having beta blockade (propranolol 240 mg/day) and 6 being on placebo. With the attrition of one control subject after the sea level phase, 11 men were taken to the peak. The investigative team included scientists from a number of institutions, including University of California at Berkeley, Stanford University, University of Colorado both the Denver and Boulder campuses, NASA, St. Louis University, University of Waterloo, Canada, and the University of Sydney, Australia.

Femoral artery and vein catheterizations were done on 3 days for the purpose of measuring cardiac output, arterial pressure, arterial blood gases, and various metabolites. The catheterizations were done once at sea level, on arrival at altitude, and after 3 weeks acclimatization to altitude. As a result of the dedication and cooperation of the investigative team, and the very good spirit among the subjects, all facets of this complicated study were accomplished without injury or complication to the subjects and without compromise of the scientific goals. A physician was present at all times at sea level and on the Peak which insured that the subjects were in good health throughout.

REPORT DOCUMENTATION PAGE

OMB No 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	28 JANUARY 1993	FINAL REPORT (6/10/91 - 12/9/92)

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

NSN 7540-01-280-5500

Standard Form 298 (Rev 2-89)
Prescribed by ANSI Std 239-18
298-102

The contract has extended well beyond the data collection period because of the wealth of data which was collected and which required further analysis. This analysis is currently proceeding at the expense of the participating laboratories.

RESEARCH SUMMARY TO DATE:

1. Ambulatory blood pressure monitoring.

Blood pressure by cuff was monitored for 24 hours on 2 occasions at sea level and on arrival at 4300 m, after 8 to 9 days and after 19 days at 4300 m. The results have been submitted (1) by Dr. Wolfel. In summary, the results showed that the subjects taking placebo increased their arterial pressures both during the day and at night. In two subjects the increases were substantial. The magnitude of the increase related to their urinary excretion of nor epinephrine. For the subjects taking propranolol, the ambulatory pressures were less, but these subjects also increased their pressure at 4300 m, and the increase also related to their nor epinephrine excretion. We concluded that nor epinephrine was the primary factor mediating the blood pressure rise, but we could not exclude a possible role for epinephrine. These are novel data.

2. Catecholamine metabolism.

As expected, 24 hour urinary excretion of epinephrine was little changed, but the excretion of nor epinephrine increased to a plateau of the first 10 days. The novel aspect of the research was that the blood studies suggested that at rest there was a net release of nor epinephrine across the leg. The data suggested that resting muscle was a major source of the increased blood level for nor epinephrine. Dr. Mazzeo has submitted the paper for publication (2).

We had expected that the beta blocked subjects would not show an increase in blood lactate on arrival at altitude and that they would therefore not show the usual decrease in lactate with acclimatization. However, the data indicated that propranolol lowered blood lactate both at sea level and at altitude, but it did not completely block the rise in lactate on arrival nor did it completely prevent the subsequent fall with acclimatization. That is, the beta adrenergic system could not be invoked to explain the "lactate paradox". Thus the working hypothesis could not be sustained. However, the studies did show that the beta adrenergic system could account, in part for the lactate changes at altitude, even though other factors were operating.

3. Lactate and Glucose Kinetics.

As indicated in the mid term report, there are thousands of samples to be analyzed by mass spectroscopy before the kinetics can be established. At this time, the analysis of glucose samples has been completed. Scanning of the data indicates that the glucose turnover at rest and during exercise is reasonable, indicating that the quality of the data is good. The lactate samples are now in process of analysis. Because the analysis is not yet complete, we are not in a position to offer conclusions about the results. However, the analyses are proceeding according to plan and completion is expected by the 1st of June.

4. Blood volume.

The blood volume data are of particular interest, because Dr. Grover had proposed that red cell mass increase would not compensate for the plasma volume decrease at altitude, while Dr. Dahms was of the contrary opinion. The analysis has proceeded between Dr. Grover, Dr. Dahms, and Dr. Greenleaf, requiring considerable melding of three laboratories. The data show good agreement between the Evans blue and the carbon monoxide methods. The results indicate that there is the expected drop in plasma volume. The surprise was that half of the subjects showed a compensatory increase in red cell mass, while half did not. Whether the subject was on propranolol or not was of no consequence. Thus both Dr. Grover and Dr. Dahms appear to be correct. Some subjects can increase red cell mass during 3 weeks at 4300 m and some cannot. Reticulocytes were not different between the groups, and thus a different level of blood formation seemed not to be the answer. However, preliminary examination of blood CO levels (before the administration of CO) suggested that there were higher levels in subjects with no increase in red cell mass. We are currently pursuing the possibility that there is increased destruction of red cells in some subjects at altitude, but not in other subjects.

5. Spectral analysis of the electrocardiogram.

Dr. Richard Hughson has completed the analysis and has an initial draft of a manuscript (4). In the control group, there was alteration of both sympathetic and parasympathetic input on arrival at altitude. The data indicated that propranolol significantly reduced the sympathetic input to the heart rate, but did not change the parasympathetic input.

6. Echo Doppler analysis has indicated that pulmonary arterial pressure and resistance increased at altitude in both control and blocked subjects. The resistance however at 3 weeks was higher in the blocked subjects indicating that Beta adrenergic tone probably offset some of the hypoxic pulmonary vasoconstriction. The manuscript is in preparation.

BUDGET

Total budget for the project was $153,376. With the completion of the grant period, all funds were expended as proposed in the letter of 21 August, 1992.

CONCLUSION

The project has been completed, the data analysis continues at the expense of the various laboratories involved, and manuscripts are being prepared for publication. I feel that we are on schedule for a project of this rather enormous magnitude. Please inform me if more detail is needed.

Sincerely,

H. T. Leavenworth

Howard Leavenworth
Sponsored Programs
Ph: (303) 270-5866

John T. Reeves MD

John T. Reeves MD, Professor
Medicine & Pediatrics, E-133
Ph: (303) 270-8298 Fax: 270-8353

REFERENCES:

1. Wolfel EE, M Selland, RS Mazzeo, JT Reeves. Systemic hypertension at 4300 m is related to sympatho-adrenal activity. Submitted J. Appl. Physiol.

2. Mazzeo RS, EE Wolfel, JT Reeves. Sympathetic response during 21 days at altitude (4300 m) as determined by urinary and arterial catecholamines. Submitted Am. J. Physiol.

3. Mazzeo RS, GA Brooks, G Butterfield, A Cymerman, M Selland, EE Wolfel, JT Reeves. B adrenergic blockade does not alter the lactate response to exercise after acclimatization to high altitude. Manuscript in preparation.

4. Hughson RL, Y Yamamoto, RE McCullough, JR Sutton, JT Reeves. Sympathetic and parasympathetic control of heart rate at altitude studied by spectral analysis. Manuscript in preparation.