AWARD NUMBER: W81XWH-15-2-0075

TITLE: Evaluation of the Physiological Challenges in Extreme Environments: Implications for Enhanced Training, Operational Performance and Sex-Specific Responses

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE	*Form Approved OMB No. 0704-0188*

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	30 Sep 2015 - 29 Sep 2016

4. TITLE AND SUBTITLE

Evaluation of the Physiological Challenges in Extreme Environments: Implications for Enhanced Training, Operational Performance and Sex-Specific Responses

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-2-0075

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Montana, WPEM,
Missoula, MT, 59812

University of Nebraska at Omaha,
Omaha, NB, 68182

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The specific aim of the first segment of this project series was to determine the potentially deleterious effects of extreme environments on physiological health and protection. Recreationally active males (n=8) and females (n=8) completed three randomized and counterbalanced trials across varied recovery environmental conditions (normobaric hypoxia, 975 m; hypobaric hypoxia, 4420 m; and normobaric hypoxia, 4420 m). Exercise was identical for each of the three conditions (60 minutes of cycling at 70% VO2 peak at 975 m). Muscle samples (v. lateralis) were obtained pre-exercise and 4 hours post exercise for evaluation of gene activation response. Blood samples were obtained pre-exercise and 0, 2, and 4 hours post-exercise for markers of oxidative stress. The blood samples have yet to be fully analyzed. Muscle gene responses to exercise and recovery demonstrated minimal deleterious responses due to altitude exposure. Markers of muscle growth and breakdown were minimally altered by altitude stress. Similary, oxygen sensing/delivery genes and mitochondrial gene responses were not altered by altitude stress. Moreover, there were no differences across sex. While prior research has clearly demonstrated impairments to performance and altitude oriented losses in skeletal muscle mass and function, the present results from year 1 suggest that an impaired skeletal gene response to altitude can be offset with appropriate exercise intervention. Exercise intervention and appropriate physical training programs may act to minimize expected losses in skeletal muscle health and function during high altitude staging and operations.

15. SUBJECT TERMS

high altitude, muscle gene response, oxidative stress, sex differences.

16. SECURITY CLASSIFICATION OF: Unclassified			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	20	

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Evaluation of the physiological challenges in extreme environments: Implications for enhanced training, operational performance and sex-specific responses

1. INTRODUCTION:

The stresses of the training continuum and the operational battlefield are compounded by the potential impacts of environmental extremes and hostilities. However, it may be possible to leverage the interaction between soldier and environment to positively impact training adaptations, acclimatization, and operational performance. However, arduous environments can also act to delay and impair training success and conflict with optimizing operational readiness. The initial phase of this project series was established to determine how the gene response to exercise may be altered by normobaric and hypobaric hypoxia in recreationally active males and females. While high altitude exposure and operations can impair physical performance and skeletal muscle health (muscle loss), it is less clear how exercise countermeasures may be implemented to offset the deleterious impacts of high altitude. It is also unclear if sex differences may alter the skeletal muscle response to exercise and recovery under varied environmental stress. The objective for year one of this project series was to conduct a skeletal muscle response study using recreationally active males and females.

2. KEY WORDS:

Skeletal muscle gene response, mitochondria, oxidative stress, high altitude, sex differences, exercise,

3. ACCOMPLISHMENTS:

At this stage of year 1, our focus has been on establishing the final infrastructure for the project series. We have adhered to our many of our goal timelines from the original statement of work. Below represents an up to date sequence of accomplishments progressing through the completion of data collection and the initial analyses for the first years project.

1. The project was awarded 30 September 2015.

2. Immediately upon receiving the final paperwork regarding approval, a meeting was scheduled for the research team and co-investigators. This meeting was scheduled and completed over two days with Dustin Slivka from the University of Nebraska, Omaha and took place October 20 and 21. At this time the protocol procedures and methodology was finalized at which time the University of Montana IRB application was initiated.

3. The UM IRB application was submitted on 2 November 2015.

4. The UM investigation team attended the IRB meeting to discuss the protocol and answer committee questions regarding the protocol.

5. The UM IRB approval for study I was obtained on 8 December 2015.

6. The UM IRB approval and all additional documents was then sent directly to ARMY HRPO on 21 December 2015. A reply regarding the reception of all necessary protocol documentation for review received on 28 December 2015.

7. ARMY HRPO approval was received 29 January 2016.

8. The necessary UM approval for a sole source was developed for the purchase of the necessary hypobaric chamber systems.

9. Our new hypobaric chamber systems were delivered and set up on 22 February 2016.

10. All of the necessary laboratory arrangements, configurations and supply orders necessary to initiate data collection were completed on 22 2016

11. Study participant recruitment began immediately after receiving the ARMY HRPO approval. Initial recruitment efforts were effective and allowed us to secure all of our male study participants. However, recruitment of female participants was more challenging. It was determined that females with normal menstrual function and not on any form of hormone replacement for birth control. However, we were able to secure all necessary study participants by 15 March 2016 and have established a testing schedule for the entire data collection efforts.

12. Initial testing (preliminary descriptives) commenced on 23 February 2016.

13. Initial experimental trials testing commenced on 1 March 2016.

14. We completed 27 of our 48 trials as of the date of our previous quarterly report 14 April 2016.

15. All testing procedures and equipment has worked exceptionally well. We have found it necessary to adjust the normobaric hypoxic system to provide a more accurate inspired PO2 to equate to the barometric pressure reduction of the hypobaric hypoxia system. Simply relying on the normobaric hypoxia system and its onboard O2 sensors proved less

accurate in comparision to real-time monitoring of inspired O2 values during the trial using a reliable metabolic system.

16. Data collection was completed with the final trial on May 12, 2016.

17. Data collection (months 4-7; UM); 16 human subjects (n=8 M, n=8 F). This was revised from our original plan of 12 M and 12 F due to the inclusion of a low altitude control trial. Our previous research design accommodated a normobaric hypoxia and a hypobaric hypoxia trial (for a total of 24 planned study participants, 48 total experimental trials). However, after careful review and research team deliberations, we determined that it was imperative to include a low altitude comparison trial. Therefore, to stay within the budget associated with 48 total experimental trials, we reduced our study participants to 8 M and 8 F. We do not anticipant this to interfere with statistical power because of past similar work. Moreover, the inclusion of the low altitude comparison trial adds greatly to the overall design of the study.

18. Our UM IRB application for our year 2 study was submitted on 31 March 2016. UM IRB conditional approval was obtained in 9 May 2016. Final approval was obtained 13 May 2016.

19. We have been slightly delayed on forwarding our IRB approvals to Army HRPO due to delays from University of Nebraska Omaha. The final IRB documentation from both test locations should be completed by the end of October for immediate submission.

20. De-identified samples were shipped to the University of Nebraska, Omaha in early July 2016 as per the established materials transfer agreement. This was recognized by their IRB to facilitate sample analyses.

21. Sample analyses (skeletal muscle) and associated statistical analyses was completed on 14 September 2016 so early results could be presented at the annual review at Fort Detrick 19 September 2016.

22. Sample analyses for the oxidative stress markers is presently underway. Dr. John Quindry started the project as a co-investigator but was located at Auburn University. In August 2016, Dr. Quindry re-located and took a faculty position at Montana. Therefore a materials transfer agreement was not established with Auburn. However, the re-location has delayed sample analyses due to the need for laboratory set up requirements. Oxidative stress sample analyses are expected to be completed by December 2016.

Methodology:

The following represents the basic methodology for the data collection surrounding

Participants

15 recreationally active males and females (9 males, 6 females) were recruited from the university and local community to take part in the study. Participants were required to pass a pre-screening Physical Activity Readiness-Questionnaire and possess a peak aerobic capacity (VO_2 peak) of at least 45 $ml \bullet kg^{-1} \bullet min^{-1}$. Participants signed an informed consent form that was approved by the university Institutional Review Board.

Preliminary Testing

Hydrodensitometry

Body composition was assessed via an underwater weighing tank (Exertech, Dresbach, MN) utilizing estimated residual volume based on height and weight. Participants were required to fast for ≥ 3 hours prior to testing. Dry weight was determined using a digital scale (Befour Inc., Cedarburg, WI) and height was measured. Participants were weighed while completely submerged. Body density and percent body fat were estimated using the Siri equation.[17]

Peak Aerobic Capacity

Participants arrived at the lab fasted for ≥ 3 hours prior to VO_2 peak testing. A cycling graded exercise test, was performed on a treadmill ergometer (TMX225C, Fullvision, Inc., Newton, KS)[18] while participants' expired gas was analyzed every 15 seconds by a metabolic cart (Parvomedics, Inc., Sandy, UT). Heart rate was monitored and recorded using a heart rate watch and chest strap (Polar Electro, Kempele, FL).

Experimental Protocol

The experimental trials consisted of three visits to the laboratory, with each visit separated by approximately 14 days to minimize carryover acclimation between trials. Participants arrived at the laboratory after completing an 8-hour fast. Participants maintained a 24-hour dietary log prior to their first trial and replicated this for the subsequent trials. Additionally, participants maintained a physical activity log for 48 priors to their first trial and replicated this for the additional trials. Upon arrival to the laboratory participants' nude body mass was measured (CW-11, Ohaus, Pine Brook, NJ) and they dressed for the exercise session. Blood was then drawn via venipuncture technique while oxygen saturation was measured on the left index finger. A muscle biopsy was taken from the vastus lateralus (insert standard biopsy info here).

Following the biopsy participants exercised on a cycle ergometer for 60 minutes at approximately 70% of their peak power output achieved during the graded exercise test.

Oxygen saturation was collected after approximately 30 minutes of exercise.

Upon completion of the exercise, a second blood sample was collected while oxygen saturation was measured. Participants then showered and entered the recovery chambers within 15minutes of completion of exercise.

Participants rested for 2 hours in a fiberglass chamber. Oxygen saturation was measured after 30 minutes and 90 minutes resting in the chamber. After 2 hours of rest, participants were instructed to exit the chamber. A blood sample was collected and participants were given 10 minutes to void if necessary. Following this break participants re-entered the chamber for the second 2 hour rest period. Again oxygen saturation was measured after 30 and 90 minutes resting in the chamber.

Upon completion of 4 hours of rest in the fiberglass chamber participants were instructed to exit the chamber. A final blood sample was collected and the final biopsy was preformed.

This methodology was repeated, in a randomized order, 3 times under the following conditions for each participant

1. 3200 ft (975 m) Missoula, MT atmospheric conditions

2.14,500 ft (4420 m) via hypobaric hypoxia (pressure altered to achieve simulated altitude)

3.14,500 ft (4420 m) via normobaric hypoxia (oxygen content altered to achieve simulated altitude)

**m = meters above sea level*

Results:

The results at the time of this report are not fully completed. The descriptive data from the study participants are reported in Table 1.

Table 1. Descriptive data from study participants.

	Males	**Females**
Height (cm)	72.5±2.3	167.0±7.5*
Weight (kg)	78.0±9.8	63.9±10.1*
% BF	11.7±4.5	22.9±7.2*
VO2 peak (L/min)	4.24±0.6	2.96±0.4*
VO2 peak (ml/kg)	54.0±6.4	46.7±4.4*
VO2 peak (ml/kg FFM)	61.3±7.5	60.7±4.4
70% max power (watts)	234±22	150±268*

* $p<0.05$ vs. Males

The reproductive hormone concentrations for the female study participants are reported in Table 2. There were no significant differences across the three experimental trials for measures of estradiol and progesterone.

Table 2. Reproductive hormone concentrations for the female study participants.

	Hypoxic	Hypobaric	Control
Estradiol (pg/ml)	71.1±54.2	117.2±72	111.9±64.2
Progesterone (ng/ml)	1.3±1.3	2.3±1.7	2.2±2.2

The oxygen sensing/delivery gene response is reported in Figure 1. HIF1 and VEGF demonstrated significant changes in response to exercise and recovery. However, there were no differences across the three experimental conditions.

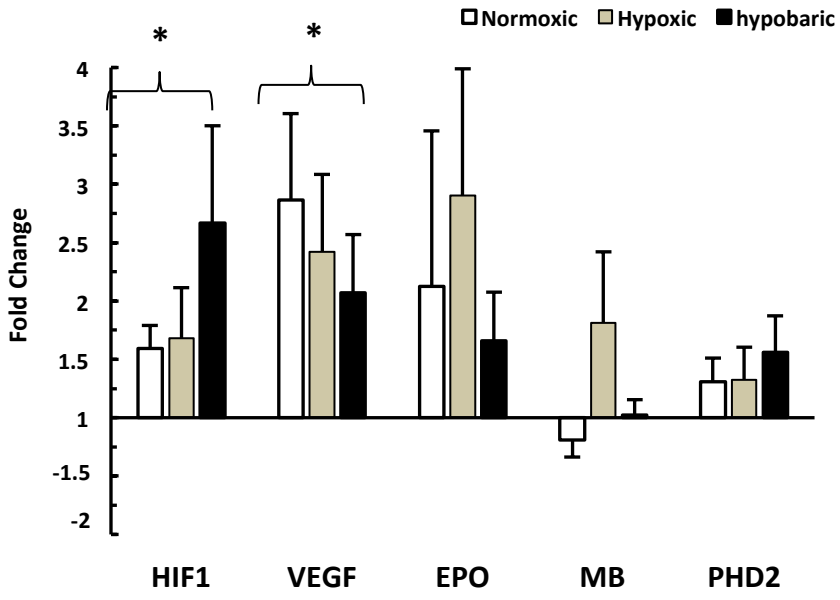

Figure 1. Oxygen sensing /delivery gene response. *p<0.05 main effect or exercise.

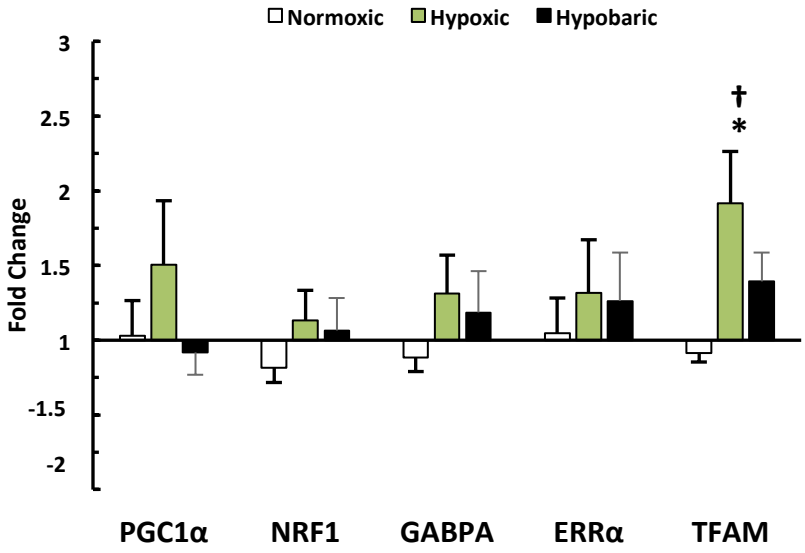

Figure 2. Mitochondrial related gene response. *p<0.05 vs. pre, †p<0.05 from normoxic and hypobaric.

These results (Figures 1 and 2) demonstrate that there were no sex differences in response to the exercise and recovery. There was also no major influence of hypoxia (hypobaric or normobaric) on these markers. These results demonstrate

that the exercise response can be preserved despite the potential influences of hypoxia.

Muscle growth and breakdown genes are shown in Figures 3 and 4. These results demonstrate expected responses to exercise and show that the myogenic response to exercise is not disrupted by hypoxia. While prior research has demonstrated compromised skeletal muscle function and mass in response to extended high altitude exposure, these results suggest that exercise intervention may assist in maintaining skeletal muscle health.

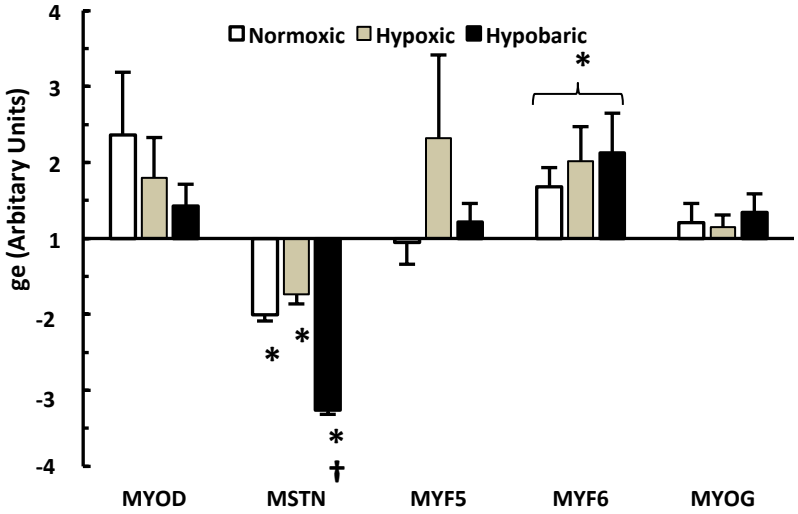

Figure 3. Muscle growth related gene response. *p<0.05 vs. pre, †p<0.05 from normoxic and hypobaric.

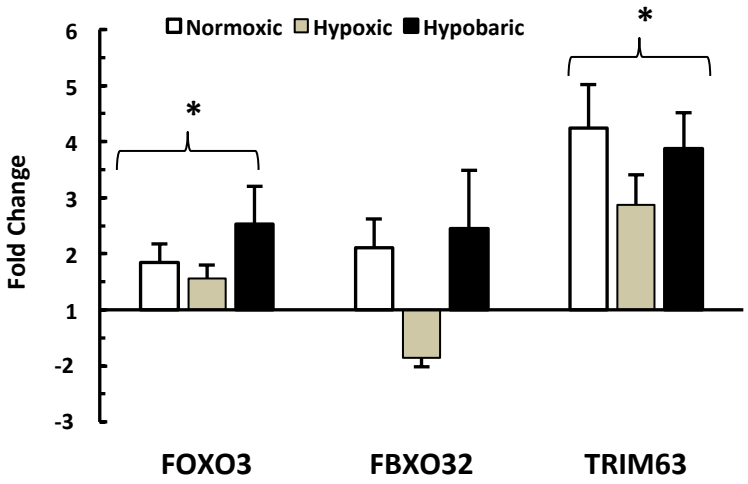

Figure 4. Muscle breakdown related gene response. *p<0.05 vs. pre.

The results from the gene responses are summarized in the abstracts that have been prepared for submission to the National ACSM meeting (see 6. below for **Products**.)

Opportunities for Training and Professional Development:

Nothing to Report

Dissemination of results:

The initial dissemination of these early results will be submitted for presentation at the National American College of Sports Medicine meeting in June 2017. The abstracts prepared for submission are provided above in the results section.

Plans for the next reporting period:

The next reporting period will include laboratory set up for the second phase of the study series. We are also awaiting final submission and subsequent approval of the protocol from ARMY HRPO. It is anticipated that data collection for the second study in the series will commence late January 2017.

4. IMPACT:

The impact of this initial project is yet to be determined based on the early, initial results. However, these data will provide foundational research describing the impacts specific exercise approaches may act to counter the deleterious impacts of high altitude. Moreover, at present, minimal sex specific responses have been

noted. This may impact programmatic procedures related to training methodologies during high altitude deployments and be uniformly applied to male and female warfighters.

Impact on the development of the principal discipline

Nothing to report at this time.

Impact on other disciplines

Nothing to report at this time.

Impact on technology transfer

Nothing to report at this time.

Impact on society beyond science and technology

Nothing to report at this time.

5. CHANGES/PROBLEMS:

There have been limited changes and problems associated with our year 1 effort. The most difficult obstacle that we have dealt with was female participant recruitment due to your requirement of no exogenous hormone use (for birth control or other). This greatly reduced our potential participant pool. Our solution was to work with our IRB to gain approval to solicit the entire campus via a series of email advertisements. At the annual meeting in October, this issue was directed to the panel and the collective thoughts were to alter future exclusion criteria for female participants.

Changes in approach

The only change in approach for year 1 was the inclusion of a control (normoxic) trial. This has been discussed above. While this required us to reduce the total number of study participants, we felt it was necessary. The total sample size was 16 (n=8 M, n=8 F) to accommodate for the budgeted 48 experimental trials.

Delays and resolutions

The only delay associated with year 1 activities was the re-location of one of our co-investigators (John Quindry). Dr. Quindry left Auburn University and accepted a position here at the University of Montana. Due to the necessary transition and lab set up, Dr. Quindry had been slightly delayed in his analyses of the samples

for markers of oxidative stress. It is anticipated that these samples will be completed by mid December.

Changes on expenditures

Nothing to report

Changes in human subjects

The only change in this area was the difficulty recruiting female study participants due to the exclusion criteria of exogenous hormones. There is nothing else to report in regards the humans subjects.

6. PRODUCTS:

At this point, the anticipated products are being initiated. We anticipate three abstracts to be submitted to the National American College of Sports Medicine (annual meeting) for 2017. The deadline for submission is November 1. We also anticipate up to 3 research manuscripts will also be prepared for submission in late 2016 or early 2017.

Below are the abstracts for submission to ACSM.

Effects of Hypobaric and Normobaric Hypoxia on Myogenic and Proteolytic Gene Expression in Humans

Caleb Ross, Robert Shute, Roksana Zak, Brent Ruby, Dustin Slivka
University of Nebraska at Omaha, Omaha, Nebraska
University of Montana, Missoula, Montana

Muscle mass is reduced during extended exposure to a hypoxic environment. Current research suggests that the physiological response to normobaric and hypobaric hypoxia may be different. It is currently unknown if these previously described differences extend to the skeletal muscle and transcriptional response regulating muscle mass. **PURPOSE:** To determine the effects of normobaric and hypobaric hypoxia on myogenenic and proteolytic gene expression. **METHODS:** Recreationally trained subjects (n = 15; age = 24 ± 4 y; VO_{2max} = 3.60 ± 0.83 L · min^{-1}) completed three trials of 60-min cycling at 70% of W_{max} followed by 4-h of recovery at ambient control conditions (975 m), normobaric hypoxia (4,420 m), and hypobaric hypoxia (4,420 m). For each trial, a muscle biopsy was taken from the *vastus lateralis* before exercise and at the end of the 4-h recovery period for analysis of gene expression (RT-qPCR). **RESULTS:** There were no differences in the myogenic gene expression of MYOD (p = 0.713), MYF-5 (0.053), or MYOG (0.832) between trials. MYF-6 was higher after exercise (p = 0.002) regardless of trial. MSTN decreased from pre- to post-exercise (p < 0.001) in all conditions and

was lower in hypobaric hypoxia compared to control condition ($p = 0.02$) and normobaric condition ($p = 0.037$). There were no differences in the proteolytic gene expression of atrogin-1 from exercise ($p = 0.811$) or by trial ($p = 0.419$). However, FOXO3 ($p = 0.009$) and MuRF-1 ($p < 0.001$) gene expression increased with exercise but were not different between conditions ($p = 0.543$, $p = 0.327$, respectively). **CONCLUSION:** These data indicate that recovery in hypoxia do not affect the expression of genes related to myogenesis and proteolysis with the exception of myostatin being attenuated in hypobaric hypoxia.
Funding provided by the Department of Defense United States Army Medical Research and Materiel Command (DOD USAMRMC: W81XWH-15-2-0075).

Effects of Hypobaric and Normobaric Hypoxia on Mitochondrial Related Gene Expression

Robert J. Shute, Roksana B. Zak, John Quindry, Brent Ruby, Dustin R. Slivka
University of Nebraska at Omaha, Omaha, Nebraska

Environmental stimuli such as temperature and hypoxia can influence cellular signaling in the skeletal muscle. Previously we have reported no changes in gene expression related to mitochondrial development with acute exposure to normobaric hypoxia. However, exposure to hypobaric hypoxia may elicit different physiological responses. **Purpose:** To determine the response of skeletal muscle mitochondrial related gene expression after 4-h exposure to normobaric hypoxia (NH), hypobaric hypoxia (HH) and normobaric normoxia (NN) after exercise. **Methods:** Recreationally trained participants ($n = 15$; age = 24 ± 4 y; height = 178 ± 12 cm; weight = 72.47 ± 13.84 kg; body fat = 14 ± 7%; VO_{2max} = 3.60 ± 0.83 L · min^{-1}, W_{max} = 274 ± 72 W) each completed three trials of 1-h cycling at 70% of W_{max}. Following exercise, participants sat in an environmentally controlled chamber for a 4-h recovery period in NH (4,420 m), HH (4,420 m), or NN (975 m) environmental conditions. Blood oxygen saturation was measured using pulse oximetry at baseline, 30 min into exercise, immediately after exercise, and 30 min into each hour of recovery. Muscle biopsies were taken from the *vastus lateralis* pre-exercise and after a 4-h exposure period. Samples were analyzed using qRT-PCR to assess gene expression related to mitochondrial development. **Results:** Arterial oxygen saturation was lower in HH and NH trials compared to the NN trial ($p < 0.001$) and lower in the HH compared to NH ($p = 0.001$). PGC-1α, GABPA, ERRα, and NRF1 mRNA were not different between the three conditions or from pre-exercise ($p = 0.804$, 0.650, 0.956, 0.563, respectively). TFAM mRNA increased in NH from pre-exercise to post-exercise ($p = 0.036$) and was higher than NN ($p = 0.011$). **Conclusion:** These data indicate that gene expression related to mitochondrial development is only marginally affected (TFAM) by the type of hypoxic environment after a 4-h treatment despite differences in arterial oxygen saturation.
Funding provided by the Department of Defense United States Army Medical Research and Materiel Command (DOD USAMRMC: W81XWH-15-2-0075).

Exercise Induced Oxidative Stress During Normobaric and Hypobaric Hypoxic Exercise Recovery.

John Quindry[1], Tiffany Quindry[1], Dustin Slivka[2], John Cuddy[1], Walter Hailes[1], Charles Dumke[1], Brent Ruby[3]; [1]University of Montana, Missoula, MT, [2]University of Nebraska, Omaha, NE.

Purpose: Altitude exposure and exercise provoke an acute oxidative stress response in muscle and blood tissues. Prior work indicates that redox-sensitive exercise recovery responses are attenuated above 1500m, although the independent impact of hypobaria and hypoxia on these responses are unknown. Moreover, given that the wealth of existing exercise and altitude data are conducted primarily in males, the current study was designed to understand exercise recovery responses in males and females exposed to various hypoxia and hypobaria conditions following a common bout of aerobic exercise. **Methods:** Sixteen active males (n=8) and females (n=8) between the ages of 18-40 performed cycle ergometer exercise for 60 minutes at 70% watts max at a base elevation of 975m. In a randomized counter-balanced crossover design subjects recovered in an environmental chamber for 4 hours in three conditions; 1000m normobaric normoxia (NN, 675mmHg, 18.8%FiO2), a simulated 4400m normobaric hypoxia (NH, 675mmHg, 12% FiO2), or a simulated 4400m hypobaric hypoxia (HH, 440mmHg, 12% FiO2). Pulse oximetry was used to measure O2 saturation throughout the exercise trials and to confirm hypoxia during recovery. Six muscle biopsies obtained from the vastus lateralis at baseline and following each exercise recovery were examined for hypoxia and redox sensitive transcripts including endothelial PAS domain protein-1 (EPAS-1), hemeoxygenase-1 (HMOX1), superoxide dismutase-2 (SOD2), and nuclear factor erythroid-derived 2-like 2 (NFE2L2). **Results:** No sex-dependent differences in gene transcripts were observed for any markers examined. No differences were observed for EPAS-1 or NFE2L2. Time-, but not trial-, dependent differences existed for HMOX1 and SOD2 and indicate a similar redox stimulus was present 4 hours post exercise in all three recovery condition. **Conclusion:** These data suggest exercise recovery in simulated conditions of NH and HH do not impact EPAS-1, HMOX1, SOD2 or NFE2L2. Additional redox-sensitive markers in blood and muscle should be examined to determine whether additional adaptive responses are impacted by NH and HH recovery conditions.
Funding provided by the Department of Defense United States Army Medical Research and Materiel Command (DOD USAMRMC: W81XWH-15-2-0075).

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Montana

Name: Brent Ruby
Project Role: PI
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Dr. Ruby coordinated study design, implementation, sample and data collection, and reporting.
Funding Support:

Name: Walter Hailes
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Mr. Hailes coordinated study participant recruitment and management and organized/conducted data collection.
Funding Support:

Name: John Cuddy
Project Role: Research Associate
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Mr. Cuddy contributed to study participant recruitment and management and organized/conducted data collection.
Funding Support:

Nebraska

Name: Dustin Slivka
Project Role: Co-PI
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Dr. Slivka assisted in study design, implementation, sample analysis, statistical analysis, and reporting.
Funding Support:

Name: Roksana Zak
Project Role: Graduate Student (doctoral)
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Ms. Zak performed skeletal muscle gene expression analysis
Funding Support:

Name: Caleb Ross
Project Role: Graduate Student (masters)
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: Mr. Ross assisted in the muscle processing and analysis.
Funding Support:

Auburn

Name: John Quindry
Project Role: Co-investigator
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 2
Contribution to Project: Dr. Quindry is organizing data analyses for the oxidative stress markers.
Funding Support:

8. SPECIAL REPORTING REQUIREMENTS

Quad Chart: See attached.

Evaluation of the Physiological Challenges in Extreme Environments: Implications for Enhanced Training, Operational Performance and Sex-Specific Responses

W81XWH-15-2-0075

PI: Brent C. Ruby, Ph.D., FACSM **Org:** The University of Montana **Award Amount:** 2,652,591

Study/Product Aim(s)

- To determine the physiological differences between hypobaria and hypoxia using markers of mitochondrial biogenesis and oxidative stress (including an evaluation of sex differences).
- To determine the effect of environmental temperature on exercise response and adaptation.
- To determine the effectiveness of pharmacological interventions at mitigating the deleterious effects of altitude (and perhaps heat).
- To implement laboratory protocols in the field to ensure translation to the training/operational environment.

Approach

The overall aim of the proposed research is to determine the outcomes of specific training and pharmacological countermeasures to the known performance decrements in extreme environments. This project series extends our previous DOD funded research describing the negative physiological consequences of operations in extreme environments to include novel countermeasures to mitigate these effects. Additionally, this project adds novel insight into sex-differences during performance in hostile environments.

Accomplishment: Data collection has been completed for study I and sample analyses are underway for skeletal muscle genes and oxidative stress markers. The Institutional IRB application has been approved for study II and is being prepared for Army HRPO submission

Timeline and Cost

Activities / CY	16	17	18	19
Study I (hypobaria vs. hypoxia)				
Study II (Environ. and adaptations)				
Study III (Pharm and altitude adaptations)				
Text (Major aim/study/milestone)				
Estimated Budget ($K)	**$658**	**$637**	**$646**	**$712**

Updated: (June 2, 2016)

Goals/Milestones (Example)

CY16 Goal – Complete Study I – Hypobaria vs. Hypoxia (including a sex differences evaluation)

☑ Data collection

☐ Sample/data analyses and presentation/pub/annual report

CY17 Goals – Complete Study II – Environmental impact on muscle adaptations.

☐ HRPO approval, recruitment, data collection

☐ Sample/data analyses and presentation/pub/annual report

CY18 Goal – Complete Study III – Pharm interventions and altitude

☐ HRPO approval, recruitment, data collection

☐ Sample/data analyses and presentation/pub/annual report

CY19 Goal – Complete Study IV – Field translation study

☐ HRPO approval, recruitment, data collection

☐ Sample/data analyses and presentation/pub/annual report

Comments/Challenges/Issues/Concerns

The most difficulty challenge has been female study participant recruitment due to the exclusion criteria of exogenous hormone use (birth control).

No timeline adjustments necessary.

Budget Expenditure to Date

Projected Expenditure: $320,000

Actual Expenditure: $$285,718