THE EFFECTS OF NORMOBARIC INTERMITTENT HYPOXIC TRAINING ON HYPOBARIC PERFORMANCE

By

JOHN H. SELLERS

Bachelor of Science in Business Administration
Oklahoma State University
Stillwater, OK
2008

Master of Science in Health and Human Performance
Oklahoma City University
Oklahoma City, OK
2010

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
May, 2016

THE EFFECTS OF NORMOBARIC INTERMITTENT HYPOXIC TRAINING ON HYPOBARIC PERFORMANCE

Dissertation Approved:

Dr. Bert Jacobson

Dissertation Adviser

Dr. Doug Smith

Dr. Jason DeFreitas

Dr. Mwarumba Mwavita

Outside Committee Member

Name: JOHN H. SELLERS

Date of Degree: MAY, 2016

Title of Study: THE EFFECTS OF NORMOBARIC INTERMITTENT HYPOXIC TRAINING ON HYPOBARIC PERFORMANCE

Major Field: HEALTH, LEISURE, & HUMAN PERFORMANCE

Abstract: The purpose of the present study was to examine the effects of a normobaric intermittent hypoxic training (NIHT) intervention protocol, when compared to normobaric normoxia (NN) training, on maximal aerobic endurance performance in both (NN) and hypobaric hypoxia (HH). Eleven male Reserve Officers' Training Corps (ROTC) cadets (age 19.55 ± 1.44 y, mass 75.80 ± 8.82 kg, stature 177.45 ± 6.67 cm) completed the 6 week training intervention in either the NIHT (EXP, n = 6) or NN (CON, n = 5) conditions. Pre- and post-testing included assessments of peak oxygen uptake (VO_{2peak}) in both NN and HH conditions with the NIHT group also completing a follow-up VO_{2peak} assessment after a 1 week detraining period. Participants also completed blood draws to assess any changes to the blood's O_2-carrying capacity. Mixed ANOVA was performed to analyze differences between the within-subjects factor (time) and between-subjects factor (EXP and CON). Repeated measures ANOVA were also performed to analyze differences for all variables between the pre-, post-, and follow-up results of the EXP group. The present study revealed that NIHT failed to elicit greater aerobic endurance performance in either NN or HH conditions when compared to NN endurance training. Further, NIHT did not induce significant adaptations of the blood's O_2-carrying capacity compared to endurance training in normoxia. However, there was a significant main effect of time ($P < .05$) on endurance performance in the NN condition as demonstrated by a 5.44% increase in VO_{2peak}. There was also a significant main effect of time ($P < .01$) on endurance performance in the HH condition as demonstrated by an 11.48% increase in VO_{2peak}. Further, there was also a significant interaction of time x training group ($P < .05$) for resting arterial O_2 saturation as measured via pulse oximetry (SpO_2) as a result of a 2.39% increase in SpO_2 values for the EXP group and a simultaneous decrease of 2.72% in SpO_2 values for the CON group from the pre- to post-testing measurements conducted in the HH chamber. These findings may have critical relevance for military personnel conducting operations in high altitude locations.

TABLE OF CONTENTS

Chapter Page

I. INTRODUCTION 1

Background 1
Statement of Problem 5
Rationale 7
Statement of Purpose 9
Hypotheses 9
Definition of Terms 11
Assumptions 13
Limitations 13
Delimitations 14

II. REVIEW OF LITERATURE 15

Physiological Responses to Hypoxic Exposure 15
Altitude Training Strategies 32
Live high-Train high 32
Live high-Train low 37
Intermittent Hypoxic Exposure 45
Live low-train high 50
Intermittent Hypoxic Training 50

III. METHODOLOGY 57

Subjects 57
Pre-testing Procedures 60
Intervention Training Protocol 64
Post-testing Procedures 68
Follow-up-testing Procedures 72
Statistical Analysis 74

Chapter Page

IV. RESULTS 75

Subject Characteristics 75
Training Volume 75
Hematology 77
Normobaric Normoxia Maximal Aerobic Capacity 79
Hypobaric Hypoxia Maximal Aerobic Capacity 83

V. DISCUSSION 92

Training Intervention 92
Effects of NIHT on Hematological Parameters 94
Effects of NIHT on Endurance Performance in Normobaric Normoxia 96
Effects of NIHT on Endurance Performance in Hypobaric Hypoxia 100

VI. CONCLUSION 106

REFERENCES 109

APPENDICES 124

Appendix A Research Design 125
Appendix B Normobaric Normoxia VO_{2max} Testing Setup 126
Appendix C Hypobaric Hypoxia VO_{2max} Testing Setup 127
Appendix D Health History Questionnaire 128
Appendix E IRB Approval 131
Appendix F Informed Consent Form 132
Appendix G Recruitment Script 136
Appendix H UHS Blood Draw Letter 138

LIST OF TABLES

Table Page

Table 1 Modified Astrand-Saltin Protocol.....61
Table 2 Intervention Training Protocol.....64
Table 3 Subject Characteristics.....75
Table 4 Intervention Protocol Training Volume.....76
Table 5 Hematological Parameters.....79
Table 6 EXP Group Hematological Parameters.....79
Table 7 Normobaric Normoxia VO_2 Test Parameters.....83
Table 8 Hypobaric Hypoxia VO_2 Test Parameters.....90
Table 9 EXP Group Hypobaric Hypoxia VO_2 Test Parameters.....91

LIST OF FIGURES

Figure Page

Figure 1 Cardiovascular Responses to Acute Hypoxia....16
Figure 2 Recruitment of Participants....59
Figure 3 EXP Group Training Mask Setup....65
Figure 4 CON Group Training Mask Setup....66
Figure 5 Training Session Average SpO_2....77
Figure 6 NN Maximal V_E....81
Figure 7 HH Peak O_2 Uptake....85
Figure 8 HH Relative Peak O_2 Uptake....86
Figure 9 HH Maximal V_T....87
Figure 10 HH Resting SpO_2....89

CHAPTER I

INTRODUCTION

French physiologist Claude Bernard is credited with being the first individual to observe the ability of the human body's *milieu intéieur*, or internal environment, to maintain relative consistency within itself despite alterations in the external environment. In 1932, Walter Cannon introduced the term *homeostasis* to define this internal stability in his book *The Wisdom of the Body*, in which he went on to propose that certain physiological mechanisms exist in order to both preserve and restore homeostasis when challenged by deviations in either the internal or external states. The physiological mechanisms to which Cannon was referring would later come to be known as the feedforward and feedback systems (Fox, 1987). However, despite the human body's capacity to maintain homeostasis, chronic exposure to external stimuli may prohibit a return to equilibrium even with the acute physiological responses.

Under such circumstances when an individual remains in a setting, i.e. environmental altitude, that elicits acute physiological responses in an attempt to maintain homeostasis, these short-term responses eventually give way to more permanent processes (Sherwood, 2011). The specific environmental stressor at altitude is the reduced availability of oxygen (O_2) due to the decline in the partial pressure of O_2 (PO_2).

While the percentage of O_2, which may also be referred to as the fraction of inspired O_2 (FiO_2), is a constant at 20.9% at any elevation, as altitude increases, the barometric pressure (P_B) decreases, resulting in a subsequent decline in PO_2. At sea level, P_B is 760 mmHg, PO_2 is 158.84 mmHg (760 mmHg x 0.209), and arterial oxygen partial pressure (PaO_2) is 100 mmHg. For comparison, at an elevation of 10,000 ft, or 3048 m, P_B is 522.7 mmHg, PO_2 is 109.24 mmHg (522.7 mmHg x 0.209), and PaO_2 is 60 mmHg. Due to the reduced P_B encountered in environmental altitude, an individual's maximal aerobic capacity, or VO_{2max}, is compromised, which in turn leads to a reduction in both endurance performance and the ability to recover between bouts of activity. Further, it has been shown that trained individuals display greater decreases in VO_{2max} at moderate altitudes when compared to untrained individuals (Pascal Mollard et al., 2007). As VO_{2max} is a product of multiple physiological systems related to O_2 supply, transfer, delivery, and use, there are a number of adaptations, both acute and chronic, that may occur due to altitude acclimatization. These adaptations may lead to potential enhancements in aerobic capacity while at increased elevations (Ponsot et al., 2006).

Acute changes may include, but are not limited to, increased heart rate (HR) and increased breathing rate, both of which represent an effort to increase O_2 availability to the body (Sherwood, 2011). The longer-term adaptations that typically occur after continued residence of 1-3 weeks (Martin Burtscher, 2005; Krueger, 1993; B. D. Levine, 2002; Muza, 2007) at natural altitude are ordinarily categorized as either hematological or non-hematological. Some of the most highly researched hematological adaptations to altitude include, but are not limited to, increases in arterial oxygen saturation (SaO_2), increased hemoglobin (Hb) concentration via increased erythropoietin (EPO) levels, and decreased

plasma volume (PV) (M Burtscher, Faulhaber, Flatz, Likar, & Nachbauer, 2006; Fulco, Beidleman, & Muza, 2013). Commonly examined and widely debated non-hematological adaptations to sustained stays at altitude are improvements in the efficiency of movement and muscle buffering capacity (Cheung, 2010; B. D. Levine & Stray-Gundersen, 2005). Current guidelines for acclimatization recommend ascents at a rate of 300-600 m per day (Krueger, 1993; Muza, 2007) and although acclimatization occurs over a lengthier time period than the onset of physiological adjustments to acute altitude exposure, these modifications are more enduring, but not necessarily permanent (Beidleman et al., 1997; Muza, Beidleman, & Fulco, 2010).

In 1963 the International Olympic Committee (IOC) awarded the 1968 Summer Olympics to Mexico City. Due to Mexico City's elevation (2250 m), there was an increase in research efforts investigating the potential benefits of training at elevation and subsequent impact on athletic performance at altitude as well as sea level. Despite the escalation in research efforts following the IOC's decision (Daniels, 1979), significant findings in this field had already been made prior to 1963. However, the majority of the aforementioned research had concerned itself with either high altitude residents or mountaineering expeditions, with little to no regard for the relationship between elite athletic competition and altitude. Further, these early inquiries led some investigators to begin examining the practice of *discontinuous exposure* for altitude acclimation (Stickney & Van Liere, 1953; Van Liere, 1943), the process now referred to as intermittent hypoxic training (IHT). Fueled by the participating nations' desire for Olympic glory and founded on the results of the preliminary investigations, the field of altitude training and associated research expanded to bring about numerous philosophies.

The original altitude training strategy included Live High-Train High (LHTH), wherein the athletes would both live and train in mountainous locales. More modern training protocols include Live High-Train Low (LHTL), where the athletes reside in natural or simulated altitudes and train in low-altitude settings, and Live Low-Train High (LLTH), in which individuals live in low altitude settings and train in simulated altitude conditions. While the advancements in this field may have been accelerated in preparation for the 1968 Mexico City Olympic Games, these same techniques have been adopted by elite athletes seeking a competitive advantage when competing not only at altitude, but also at low elevation contests (Gregoire P Millet, Roels, Schmitt, Woorons, & Richalet, 2010). Though it should be noted that each of the aforementioned altitude training methods are still being employed today, LHTL has gained the most notoriety based on both anecdotal and research-based evidence; however, much of the benefit of LHTL is observed during endurance performance at or near sea level (SL) (Wilber, 2007b). Further, the LLTH strategy, along with the development of simulated altitude technologies utilizing both hypobaric hypoxia (HH), a state in which ambient PO_2 is lowered through a decrease in P_B, and normobaric hypoxia (NH), a state in which FiO_2 is decreased via an increase in the percentage of nitrogen (N_2) in ambient air, has born about two additional acclimation strategies, intermittent hypoxic exposure (IHE) and the previously mentioned IHT. IHT exposes the user to brief periods of hypoxic conditions, typically 1-2 h in length and is performed while the user is exercising, allowing them to live in low elevation locations and train at higher elevation (Krueger, 1993; Powell & Garcia, 2000). However, despite the growth and new ideas, there still remains speculation concerning the best practices and application for altitude

training, specifically, the efficacy of IHT to improve performance at moderate and high altitudes.

Statement of Problem

Presently, the United States (U.S.) military finds itself in a transition period. As a result of limited financial resources, when compared to past defense budgets, and a transforming geo-political climate, an ambiguous future awaits (Braun III & Allen, 2014). Additionally, the U.S. national defense strategy is influenced both by the actions and decisions of not only enemies, but also American allies (Laird, Timperlake, & Delaporte, 2014). However, despite these limitations, the U.S. military must maintain combat readiness at all times. Whether it be in times of peace, preparing to face enemies of the state, or assisting allies in joint military endeavors, U.S. armed forces attempt to maintain peak readiness at all times. Recent and current events have led to military personnel deployments to locations in the Middle East; locales that place additional physiological burdens related to extreme environments such as high altitude on personnel (Nindl et al., 2013). For instance, Afghanistan has several mountain passes with elevations exceeding 3000 m. Severe environmental conditions pose additional threats to the health of soldiers and their ability to carry out missions. Specifically, operations conducted at high altitude will increase the relative workload for personnel and unacclimatized soldiers may suffer from acute mountain sickness (AMS) or more severe forms of AMS such as high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE), both of which may be life-threatening (Krueger, 1993; Muza, 2007; Nindl et al., 2013). Further, prior investigations have reported significant mental detriments in the form of increased mood states such as anger and fatigue in soldiers completing high-altitude field training exercises (Bardwell, Ensign, & Mills, 2005).

Therefore, it is imperative that all potentially beneficial options to prepare soldiers for high altitude operations should be explored. However, the majority of studies examining the effects of the various methods of altitude training focus on elite level athletes, with the lion's share of the aforementioned work concentrating on performance at elevations at or near sea level. Consequently, researching the potential implications of simulated altitude training on the performance of military personnel at altitude is of increasing importance.

However, multiple altitude acclimatization, or adaptations brought about by exposure to terrestrial altitude, and acclimation, or adaptations induced via exposure to simulated altitude, methods exist, each with their own advantages and disadvantages in regards to efficacy, accessibility, and costs (Beidleman, Fulco, Staab, Andrew, & Muza, 2014; Cheung, 2010; B. D. Levine, 2002; Gregoire P Millet et al., 2010). Therefore, this investigation attempts to provide greater insight regarding the potential efficacy of normobaric IHT (NIHT) to elicit both hematological and non-hematological adaptations, as well as performance enhancements when testing under HH conditions. Specifically, the questions that have been attempted to be answered within this investigation are: 1) Is the prescribed NIHT training volume of 18 h over a period of 6 weeks sufficient to elicit significant hematological changes within the experimental (EXP) group when compared to the control (CON) group? 2) Is NIHT effective at improving VO_{2max} in an HH setting? 3) 4) If NIHT does produce significant physiological changes, how similar, it at all, are said changes to those previously identified using hypobaric IHT (HIHT) research designs? 5) If there were any significant hematological and/or nonhematological adaptations as a result of NIHT, will follow-up testing following a detraining period of 2 weeks demonstrate any resiliency of said alterations?

Rationale

Environmental conditions have impacted the outcome of military endeavors as long as there has been war, and while progress continues to be made in minimizing the effects of altitude on soldier health and performance, there remains room for improvement (Nindl et al., 2013). To date, there have been significant efforts, and tangible gains, to alleviate the occurrence of AMS in soldiers through acclimatization efforts utilizing simulated altitude via both NH and HH (Beidleman et al., 2014; Raphael Faiss et al., 2013; Feriche et al., 2014; Fulco et al., 2011; Neya, Enoki, Kumai, Sugoh, & Kawahara, 2007; Ponsot et al., 2006; Richard & Koehle, 2012; Schommer et al., 2010). However, as sustained combat operations often consist of endurance activities consisting of low to high intensity periods of work (Henning, Park, & Kim, 2011), combined with the evidence that both submaximal and maximal endurance capabilities are significantly diminished even at altitudes of 1500-2500 m (Fulco et al., 2013; Muza, 2007; Muza et al., 2010), research efforts should continue to investigate possible means of improving soldiers' aerobic capacity at altitude. The primary concern of any efforts to improve soldier performance at altitude is and must remain the efficacy of said training.

However, as has been previously mentioned, the U.S. national defense budget remains an area of contention, thus the financial feasibility of such endeavors must be considered. Further, other considerations such as relocation, travel, and ease of implementation should also be taken into account when attempting to select the most appropriate acclimatization effort. That being said, this paper does not dispute the disparity that has been reported between NH and HH (Beidleman et al., 2014; Dufour et al., 2006; Raphael Faiss et al., 2013; Feriche et al., 2014; Fulco et al., 2011; Richard & Koehle, 2012).

Yet, as Muza (2007) noted, much of the prior research has utilized hypobaric chambers, which are not readily accessible for military personnel use. Further, hypobaric chambers are not only extremely expensive in terms of financial cost, but also require skilled technicians to maintain and operate as well as the presence of registered nurses (RN) and medical doctors when in use, all of which add to the effective cost of usage.

IHT utilizing NH equipment is one potential method that would serve to be more economically feasible than hypobaric chambers, as well as more user friendly and convenient for military personnel. Additionally, while HH has been shown to be superior to NH in terms of generating acclimation to environmental altitude (Beidleman et al., 2014; Raphael Faiss et al., 2013; Feriche et al., 2014; Fulco et al., 2011; Richard & Koehle, 2012), there is evidence that NH does enhance acclimation to altitude, as well as stimulate other physiological adaptations considered beneficial for performance in natural altitude settings (Dufour et al., 2006; Geiser et al., 2001; Mackenzie, Watt, & Maxwell, 2008; Vogt et al., 2001). Based on prior research efforts, it does appear reasonable to believe that NIHT has the potential to be an effective altitude acclimation strategy for military personnel in terms of physical performance, financial cost, and accessibility. Due to the target population, even if significant changes are not induced as a result of the NIHT training protocol, any enhancements in soldier endurance performance at altitude would be of importance as the smallest increases in performance may lessen the impact of the challenges triggered during combat operations in high altitude settings (Henning et al., 2011; Krueger, 1993; Nindl et al., 2013). Therefore, further research such as the current investigation is justifiable in an effort to add to the discussion of NIHT's efficacy and applicability when attempting to prepare soldiers for deployments to mountainous locales.

Statement of Purpose

The purpose of the present study was to examine the effects of 6 weeks of NIHT on erythrocyte (RBC) volume, hemoglobin (Hb) levels, hematocrit (Hct) levels, serum erythropoietin (EPO) production, and maximal aerobic endurance performance both in normoxic and hypobaric hypoxic conditions when compared to normoxic training in ROTC cadets.

Hypotheses

1. H_0: There will be no difference in erythrocyte (RBC) volume percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: The EXP group will demonstrate a significantly greater RBC volume percent change compared to the CON group upon completion of the 6 week intervention training period.

2. H_0: There will be no difference in the hemoglobin (Hb) level percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: The EXP group will demonstrate a significantly greater Hb level percent change compared to the CON group upon completion of the 6 week intervention training period.

3. H_0: There will be no difference in the hematocrit (Hct) level percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: The EXP group will demonstrate a significantly greater Hct level percent change compared to the CON group upon completion of the 6 week intervention training period.

4. H_0: There will be no difference in serum erythropoietin (EPO) level percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: The EXP group will demonstrate a significantly greater serum EPO level percent change compared to the CON group upon completion of the 6 week intervention training period.

5. H_0: There will be no difference in the time-to-exhaustion (TE) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: There will be a significant difference in the TE percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

6. H_0: There will be no difference in the peak oxygen uptake (VO_{2peak}) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: There will be a significant difference in the VO_{2peak} percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

7. H_0: There will be no difference in the relative peak oxygen uptake (RVO_{2peak}) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: There will be a significant difference in the RVO_{2peak} percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

8. H_0: There will be no difference in the minute ventilation (V_E) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: There will be a significant difference in the V_E percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

9. H_0: There will be no difference in the respiratory frequency (*f*) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

   H_A: There will be a significant difference in *f* percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

10. H_0: There will be no difference in the tidal volume (V_t) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

    H_A: There will be a significant difference in the V_t percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

11. H_0: There will be no difference in the end-tidal pressure of O_2 ($PetO_2$) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

    H_A: There will be a significant difference in the $PetO_2$ percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

12. H_0: There will be no difference in the end-tidal pressure of CO_2 ($PetCO_2$) percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

    H_A: There will be a significant difference in the $PetCO_2$ percent change between the EXP and CON groups upon completion of the 6 week intervention training period.

Definition of Terms

Acclimation: Adaptive physiological responses to experimentally induced changes in particular climate factors

Acclimatization: Physiological adjustments brought about through chronic exposure to a different environment

Acute: Short-term

Acute mountain sickness: A syndrome characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise

Adaptation: Changes to the human system induced by exposure to an environmental stressor

Aerobic capacity: Highest rate at which an individual can consume and utilize O_2 from the air

Anoxia: An absence of O_2

Barometric pressure: The pressure exerted by the weight of the air in the atmosphere on objects on Earth's surface

Chronic: Long-term; continuing over time

Deacclimatization: Process involving the loss of high-altitude acclimatization upon return from environmental altitude including, but not limited to, hematologic, respiratory, cardiovascular, and nervous systems

Extreme altitude: 5500-8850 m (18,045-29,035 ft)

Hematological: Of, or related to, blood

High altitude: 1500-3500 m (4921-11,483 ft)

High altitude cerebral edema: A potentially fatal complication of acute mountain sickness; symptoms may include confusion, ataxia of gait, unconsciousness, and/or coma

High altitude pulmonary edema: A potentially fatal complication of acute mountain sickness; symptoms may include excessive pulmonary vasoconstriction and/or pulmonary hypertension

Homeostasis: Maintenance of a relatively stable internal environment

Hypercapnia: Above-normal CO_2 levels in arterial blood

Hyperventilation: Increased pulmonary ventilation in excess of metabolic demands

Hypobaric hypoxia: A state in which PO_2 is lowered through a decrease in barometric pressure

Hypocapnia: Below-normal CO_2 levels in arterial blood

Hypoxia: Condition of having insufficient O_2 at the cellular level

Intermittent hypoxic exposure: Discontinuous use of hypoxia, either hypobaric or normobaric, in a passive, resting state

Intermittent hypoxic training: Discontinuous use of hypoxia, either hypobaric or normobaric, in an exercise training setting

Live High-Train High: The practice of residing and performing exercise training at a moderate elevation, typically greater than 1500 m, for multiple weeks

Live High-Train Low: The practice of residing at moderate elevations, typically 2000-2700 m, for at least 8-10 h each day and performing exercise training at elevations less than 1000 m

Live Low-Train High: The practice of employing hypoxia during exercise training while individuals reside in normoxia

Low altitude: 500-1500 m (1640-4921 ft)

Normobaric hypoxia: A state in which PO_2 is lowered through a decrease in the fraction of inspired oxygen

Normoxia: The partial pressure of O_2 in the inspired gas is equal to that of air at sea level

Sea level: 0-500 m (0-1640 ft)

Stressor: Any stimulus that tends to disturb an individual's homeostasis

Very high altitude: 3500-5500 m (11,483-18,045 ft)

Assumptions

1. The samples are normally distributed and representative of their respective populations.
2. Participants' responses to the health history questionnaire were accurate and valid.
3. All participants gave a maximal effort during all testing and training sessions.
4. The equipment is appropriately calibrated and functioning properly.
5. That there were no data collection, data analyses, data entry, nor statistical processing errors.

Limitations

1. Differences in the participants' diets both between and within the groups may have had an effect on the responses to the training intervention.
2. Differences in the participants' sleeping habits both between and within the groups may have had an effect on the responses to the training intervention.
3. Participants were only provided a HR range within which to keep their HR during the different portions of each training session, therefore, differences in motivation levels between participants may have had an effect on the response to the training intervention protocol both between and within groups.
4. While there was no significant difference in total time in min exercising outside of the training intervention protocol between the EXP and CON groups ($p > .05$), differences in the participants' exercise training intensity outside of the intervention

training protocol both between and within the groups may have had an effect on the responses to the training intervention.

Delimitations

This study was delimited to Reserve Officers' Training Corps (ROTC) cadets between the ages of 18-22 years of age. Additionally, all participants were required to be male and highly trained as determined by their initial VO_{2max}.

This study was carried out in a single-blind manner in an attempt to minimize or eliminate the risk of the nocebo effect. All participants wore nearly identical training masks during all training sessions so as to inhibit the ability of participants to determine whether they were in the EXP or CON groups based on their training sessions.

In an attempt to increase the applicability of this investigation's results to current military personnel, this study was designed to utilize the NIHT sessions as complementary exercise training and not the sole form of exercise training for the ROTC cadets. This strategy allowed for ROTC cadets to continue performing high-intensity exercise training during PT while also receiving the supplementary NIHT sessions. This is of importance as a common drawback of only using NIHT is the decreased intensity with which individuals are able to perform during training, thus, potentially offsetting any benefits that may have been derived as a result of the NIHT. Further, all training sessions were conducted at approximately the same time of day for each participant, thus attempting to minimize any diurnal variations between training sessions.

CHAPTER II

REVIEW OF LITERATURE

The purpose of this review of literature is to present and integrate the existing and relevant research in the areas of human acclimatization and acclimation to environmental and synthetic hypoxia, respectively. Further, the influence of acclimatization and acclimation efforts to enhance aerobic endurance performance in hypoxic settings will also be scrutinized.

Physiological Responses to Hypoxic Exposure

Acute exposure to altitude, whether it be environmental or simulated, brings about a number of immediate physiological responses in order to adapt to the decreased ambient PO_2. This reduction in PO_2 results in declines in inspired PO_2 (PiO_2), alveolar PO_2 (PAO_2), PaO_2, and SaO_2. These detriments ultimately lead to hypoxemia at the cellular level, stimulating the general response to the decreased availability of O_2 (Gallagher & Hackett, 2004). While there are a number of physiological adjustments in response to high altitude exposure, see Figure 1 developed by Peter Bärtsch and Gibbs (2007), only those related to the focus of this investigation will be discussed. These specific adaptations include increased ventilation, the stimulation for EPO production and release, and alterations in cardiac output (CO) as a result of adjustments in HR and stroke volume (SV), and finally, the impact of said adaptations on aerobic endurance performance.

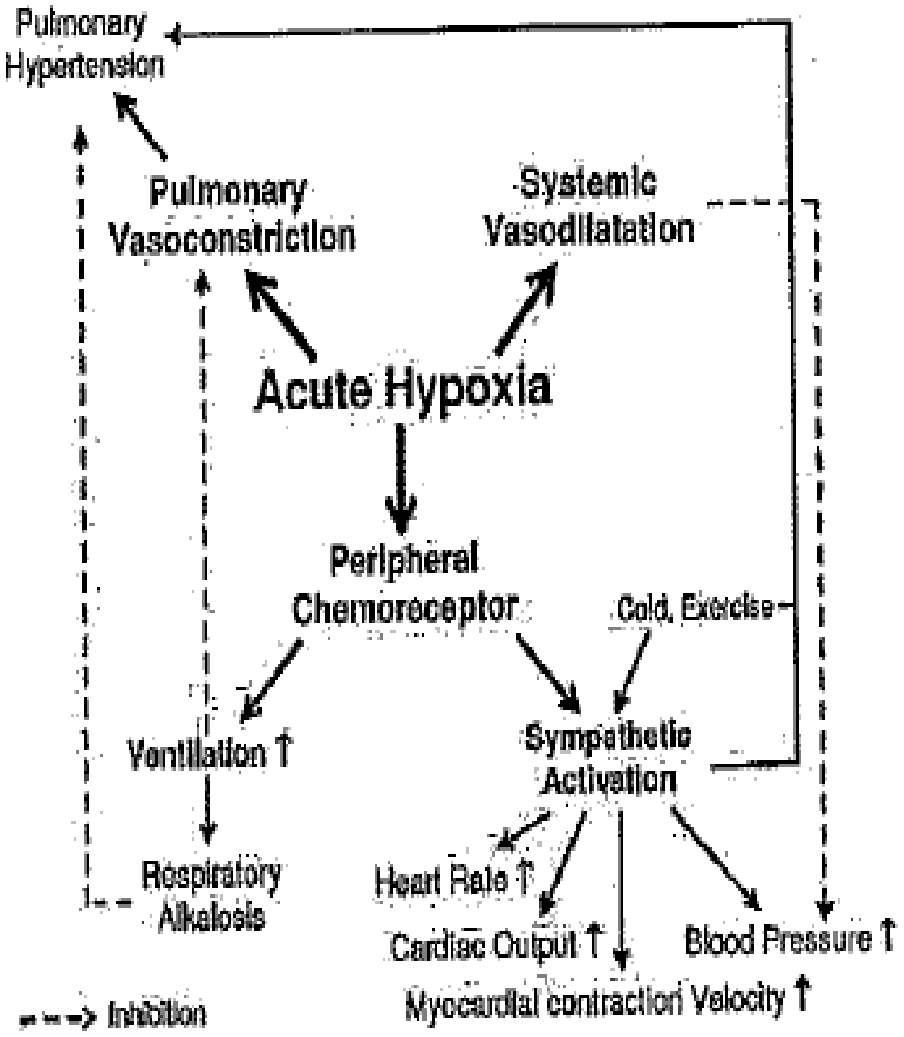


Figure 1. Cardiovascular responses to acute hypoxic exposure (Peter Bärtsch & Gibbs, 2007)

Upon continued exposure, further adjustments occur and include hematological changes such as a decrease in plasma volume, resulting in an increase in the relative levels of Hb and Hct. The rate and significance of the aforementioned changes are relative to the level of hypoxia to which one is exposed and continue to occur until one becomes acclimatized (Note: "acclimatization" will be used to indicate both acclimatization and acclimation in regards to adaptations brought about by exposure to

natural and simulated environments, respectively) to the severity of the respective decline in PO_2 (S. A. Gallagher & Hackett, 2004). Sojourns to high altitude locales lasting more than 2-3 d require the human body to employ more enduring adjustments to the reduced P_B and ambient PO_2. The purpose of such undertakings is to curtail the effects of hypoxia in an attempt to restore some level of homeostasis for every organ system affected by the change in O_2 availability. Together, these developments that take place remain to be fully understood. Adding to the difficulty of the development of a true comprehension of acclimatization is the inter-individual variability of responses to continued or repeated exposure to reductions of PO_2 (Hennis, O'Doherty, Levett, Grocott, & Montgomery, 2015). Yet, with adequate exposure, most humans are capable of becoming acclimatized to altitudes as high as 5500 m (S. A. Gallagher & Hackett, 2004). While the amount of time to be considered adequate may differ among individuals, the majority of prior studies seem to agree that 1-3 wk is typically sufficient for acclimatization to take effect (Fulco et al., 2013; Fulco, Rock, & Cymerman, 1998; Muza, 2007; Muza et al., 2010).

However, despite the almost immediate onset of physiological adjustments, the risk of adverse health effects upon initial introduction to altitude remains. One of the more common dangers of acute altitude exposure is the development of an high-altitude illness. High-altitude illness is used to describe three conditions brought about by acute exposure to a reduction in ambient PO_2, AMS, HACE, and HAPE, the latter two of which can be fatal. For example, it has been reported that 8% of casualties suffered during the initial 9 months of Operation Enduring Freedom in Afghanistan resulted from cases of high-altitude illness (Tannheimer et al., 2009). Further, the risk for each of the aforementioned conditions depends not only on individual variabilities but also the

variables specific to each ascent such as ascent rate, destination altitude, base camp level or altitude at which one sleeps, exposure duration, physical exertion level, ambient temperature and P_B, altitude of residence and/or acclimatization efforts prior to initial ascent, pre-existing conditions and associated medications, and personal history of high-altitude illness development, if any (Fulco et al., 2013; S. A. Gallagher & Hackett, 2004; Muza, 2007).

AMS has the greatest occurrence rate of the high-altitude illnesses with prior research reporting such rates ranging from approximately 10-90% globally. This extensive range is due to the wide array of variables that impact the onset of AMS, with symptoms typically arising approximately 6-10 h after exposure and may present as early as 1 h after initial exposure (Richard et al., 2014) as well as variations in the methodologies used to conduct the aforementioned research (S. A. Gallagher & Hackett, 2004). Initial symptoms of AMS typically include headaches, nausea, decreased hunger, dizziness, inability to sleep, and increased feelings of fatigue, with more severe cases of AMS displaying increased intensity of the aforementioned symptoms as well the potential for vomiting. Undiagnosed or untreated cases of AMS may progress to either HACE or HAPE, which is amplified if the affected individual continues to ascend to higher elevations without a sufficient acclimatization period (S. A. Gallagher & Hackett, 2004; Norris et al., 2012; Schommer, Menold, Subudhi, & Bärtsch, 2012).

It is widely accepted that continuous residence at high altitude leads to altitude acclimatization, thus reducing and potentially eliminating the risk of AMS; yet, the risk of high-altitude illness is still present upon the initial exposure during preacclimatization efforts and returns upon ascent to a greater elevation than the one at which the individual

had become acclimatized (Fulco et al., 2013; Muza, 2007; Muza et al., 2010). Further, there is emerging evidence that intermittent exposure to simulated altitude may reduce the risk of AMS, however, while these results have demonstrated a decrease in the risk for AMS, each study has reported varying degrees of efficacy, likely due to both the severity of hypoxia utilized and the individual variability present in AMS cases (Beidleman et al., 2004; M Burtscher, Brandstätter, & Gatterer, 2008; Fulco et al., 2013; Muza, 2007). Additionally, prior research has demonstrated that AMS symptoms are more severe in HH than NH at equivalent PO_2 levels. Based on these previous results, utilization of HH, when compared to NH, during acclimatization efforts has been shown to be more likely to achieve preacclimatization for exposure to terrestrial altitude (Fulco et al., 2011; Richard et al., 2014; R. C. Roach, Loeppky, & Icenogle, 1996; Schommer et al., 2010).

High-altitude illnesses, including AMS, HAPE, and HACE, display their most severe symptoms between 24-48 h (Fulco et al., 2013) but individuals may remain susceptible up to 3-5 d (S. A. Gallagher & Hackett, 2004) after initial exposure to altitudes greater than 2500 m. The persistence of symptoms beyond these time periods may suggest a diagnosis other than an high-altitude illness or signal the necessity for treatments to diminish symptoms including immediate descent of at least 1000 m, provision of O_2 to elicit an SaO_2 of at least 90%; in more severe cases such as HAPE and HACE, medications, if available, may be necessary (Fulco et al., 2013; S. A. Gallagher & Hackett, 2004; Muza et al., 2010; Norris et al., 2012). Due to the time lag between initial exposure and the onset of high-altitude illness symptoms, individuals attempting to perform rapid ascents may subject themselves to greater risk of HACE and HAPE. The

aforementioned circumstance is of particular concern for military personnel who are often required to make rapid ascents with no opportunity to descend if symptoms do occur (Tannheimer et al., 2009). Further, risk of illness is intensified as such operations require soldiers to perform strenuous work (R. Roach et al., 2000).

Continuous exposure, and/or gradual ascents, to altitude remain the most successful strategies to alleviate any high-altitude illness symptoms an individual may experience. However, as previously mentioned, there is emerging evidence that pre-acclimatization strategies employing intermittent, simulated altitude exposures may be adequate to prevent or minimize the effects of AMS and its more severe forms (Beidleman et al., 2004; M Burtscher et al., 2008; Fulco et al., 2013; Muza, 2007). There remain questions to be answered regarding the efficacy of such acclimatization strategies; nevertheless, two trends for acclimatization practices have emerged. First, multiple works have demonstrated the greater efficacy of HH, utilizing both objective and subjective measures, to prevent and minimize AMS symptoms (Fulco et al., 2011; Richard et al., 2014; R. C. Roach et al., 1996; Schommer et al., 2010). Second, in a 2010 review by Muza and colleagues, minimum standards for altitude severity and exposure time to induce acclimatization were proposed; in regards to continuous exposure, 6 d of continuous residence at 2200 m decreased risk of AMS and enhanced performance when participants were subjected to 4300 m. Further, prior investigations utilizing altitudes greater than 3000 m, combined with exposure durations of 5 d or more, have reported that such acclimatization strategies preceding sojourns to elevations greater than 4500 m significantly reduced AMS prevalence. Additionally, the perseverance of acclimatization appears to be correlated to the level of acclimatization achieved as acclimatization

significantly diminishes approximately 3 d after returning to low altitude for less acclimatized persons and after 7 d for more acclimatized individuals (Muza et al., 2010).

It is well documented that one of the more immediate physiological responses to a decrease in PiO_2 and ensuing hypoxemia is a change in ventilation. The subsequent commencement of hyperventilation typically occurs after an introduction to altitudes above 1500 m, whether terrestrial or synthetic. This adaptation, which can occur within minutes of altitude exposure, is referred to as the hypoxic ventilatory response (HVR) and leads to a nearly instantaneous decrease in alveolar PCO_2 ($PACO_2$) and an increase in both PAO_2 and SaO_2, although there is considerable inter-individual variation in HVR (Chapman, Stray-Gundersen, & Levine, 1998; Fulco et al., 2013; S. A. Gallagher & Hackett, 2004). Individuals with a more pronounced HVR are referred to as responders and those with a lower HVR are classified as non-responders. Evidence suggests that responders display decreased risk and severity of symptoms of high-altitude illnesses, with the opposite true for non-responders (Chapman et al., 1998). In addition to research-based evidence of the differences between responders and non-responders, anecdotal evidence exists in mountaineering as some climbers require supplemental O_2 to complete ascents of moderate to high peaks while other climbers are capable of completing the ascents by breathing only ambient air (Michael J Hamlin, Draper, & Hellemans, 2013). Multiple works utilizing healthy, but not trained, individuals reported significant changes in at least one of the following ventilatory variables of minute ventilation (V_E), tidal volume of ventilation (V_t), and breathing frequency (f) (M Burtscher et al., 2008; Raphael Faiss et al., 2013; S. A. Gallagher & Hackett, 2004; Loeppky et al., 1997; Muza et al., 2010; Sharma & Brown, 2007). Furthermore, the HVR may be altered by the

consumption of foods or medications containing respiratory stimulants or depressants (S. A. Gallagher & Hackett, 2004).

Additionally, and of particular note for the current investigation, is the difference in the HVR between HH and NH environments that has been reported in multiple works (Raphael Faiss et al., 2013; Hemmingsson & Linnarsson, 2009; Loeppky et al., 1997; Grégoire P Millet, Faiss, & Pialoux, 2012; Savourey, Launay, Besnard, Guinet, & Travers, 2003). Investigations performed by Loeppky et al. (1997) and Faiss et al. (2013) described similar results in that each study displayed comparable increases for V_E in both HH and NH settings within the initial hour of exposure; however, after continued exposure, V_E in the HH condition declined whereas V_E in the NH condition remained elevated, leading to the significant differences between the two conditions. Furthering the evidence of the different physiological responses to acute exposure of HH and NH settings is the difference in V_T. Faiss et al. (2013) described significantly reduced V_T levels in HH compared to NH beginning 8 h after introduction to the respective hypoxic conditions corresponding to 3000 m and continuing through the remainder of the 24 h experiment. Savourey et al. (2003), utilizing a PO_2 equivalent to 4500 m, reported significantly lower V_T and greater *f* during the HH condition compared to the NH condition. These variances presented during only a 40 min exposure, implying more shallow breathing may occur rather quickly upon exposure to HH. Loeppky et al. (1997) detailed similar, although not significant, increases of V_T during 9 h of NH exposure, FiO_2 = 14.2%, compared to HH exposure, P_B = 432.

Moreover, there is sufficient evidence that aerobic exercise exacerbates the differences in V_E between normoxic and hypoxic conditions. Authors investigating

changes in V_E under multiple FiO_2 values during graded exercise tests (GXT) performed on a treadmill revealed significant increases in V_E during the hypoxic condition, FiO_2 = 17%, compared to both the normoxic and hyperoxic conditions, FiO_2 = 21% and 66%, respectively (Mateika & Duffin, 1994). Later inquiries demonstrated pronounced increases in V_E throughout stationary cycling incremental exercise tests performed in normoxic (FiO_2 = 21%) and two NH conditions (FiO_2 = 15%, 12%), with differences reported between the normoxic and both hypoxic conditions as well as a significant increase in V_E from the mild to moderate hypoxic condition. Likewise, during the same inquiry, the authors also reported a significant escalation in V_E during moderate steady state exercise from the normoxic to moderate hypoxic conditions but not between the normoxic and mild hypoxic conditions (Engelen et al., 1996). However, more recent research reported no differences in V_E neither during nor after maximal exertion treadmill running tests completed at 2800 m and 180 m (Stang, Bråten, Caspersen, Thorsen, & Stensrud, 2014).

As previously mentioned, the HVR occurs rather rapidly in response to reductions of PO_2 and subsequent cellular hypoxemia. The HVR continues to occur until an individual becomes fully acclimatized to the corresponding severity of altitude to which they have been exposed, either through continuous residence or repeated exposure. From the initiation of the HVR, V_E continues to increase for approximately 1-2 wk (P Bärtsch & Saltin, 2008; Fulco et al., 2013; S. A. Gallagher & Hackett, 2004). While the HVR leads to ventilatory acclimatization that nearly restores PAO_2, PaO_2, PCO_2, and other markers of gas exchange to their respective SL equivalents within a relatively short period, prior works have shown that exposures lasting multiple years continue to increase

the HVR compared to shorter stays, which tends to support the idea that a direct relationship between length of stay and level of HVR does indeed exist (Fulco et al., 2013).

Beyond the HVR, altitude exposure leads to hematological adjustments in an attempt to counter the decreased PO_2 and subsequently lower PaO_2, which lead to a series of regulatory devices that attempt to restore the PaO_2 to homeostatic levels. The earliest of these responses is the secretion of EPO. Renal peritubular cells, which are sensitive to PO_2 levels within the body, signal the production and release of EPO from the kidneys (Mackenzie et al., 2008; Rasmussen, Siebenmann, Diaz Molina, & Lundby, 2013). This process is controlled by the O_2-regulated EPO genetic transcription, which is controlled by the hypoxia-inducible factor-1 (HIF-1). During normoxia, HIF-1, which is present in all tissues, has a half-life of approximately 5 min, but under hypoxic cellular conditions, the HIF-1 half-life increases to roughly 30 min. This increase in the stability of HIF-1 is ultimately responsible for the EPO response, and numerous other physiological responses, to hypoxic conditions, thus, HIF-1 may provide a potential genetic explanation for the large inter-individual response to hypoxia (Christopher John Gore, Clark, & Saunders, 2007; Rusko, Tikkanen, & Peltonen, 2004; Semenza, 2000).

In one of the earlier works investigating the regulation of EPO in humans exposed to acute altitude, results demonstrated the relationship between both the severity of altitude and total exposure time and the ensuing release of EPO. The investigators revealed that significant increases in serum EPO levels occurred after only 114 and 84 min of HH exposure at simulated altitudes equitable to 3000 m and 4000 m, respectively (Eckardt et al., 1989). Since that time, a number of studies have yielded similar

relationships between the altitude severity, time course of exposure, and EPO release, as evidenced in multiple reviews. However, as is noted in said reviews, while there does appear to be growing consensus regarding the magnitude of the decrease in ambient PO_2 and the minimal exposure time necessary to induce EPO secretion, there have also been various works reporting conflicting results (Ge et al., 2002; B. D. Levine, 2002; Mackenzie et al., 2008). However, there does appear to be some consensus amongst the various investigations. First, the minimal altitude required to elicit an increase in serum EPO appears to be approximately 2000 m. Second, a duration of at least 2 h is required to stimulate EPO production and release. One potential reason for the contrasting results is the differences in methodologies utilized including, but not limited to, the type of altitude, NH versus HH, the type of exposure, rest as opposed to exercise, as well as the measurement techniques employed (Mackenzie et al., 2008).

Plasma EPO concentration has been reported to reach its apex approximately 3-4 d after initial exposure, upon which time it begins to slowly descend until steadying to proportions marginally exceeding those reported at SL (Rasmussen et al., 2013). Increases in EPO do not immediately result in the production of red blood cells (RBCs), or the process known as erythropoiesis (Ostadal & Kolar, 2007). As a result of the sizeable variations reported in EPO release, RBC production also displays high variability in response to altitude exposure. A recent systematic review of altitude-induced RBC production suggested that for altitudes exceeding 4000 m, the minimum exposure time required to elicit significant RBC increases was 2 wk, indicating lengthy time lag between the increase of serum EPO levels and subsequent increase in RBC volume. Further, the authors proposed that if erythropoiesis is a primary objective,

utilizing altitude less 3000 m may be a fruitless endeavor as 4 wk exposures at this altitude did not significantly increase RBC volume. Finally, and in contrast to other acclimatization effects, the authors reported finding no evidence to suggest that significant differences exist in RBC production between investigations using HH or NH (Rasmussen et al., 2013).

Other potential hematological mechanisms occurring during altitude exposure to combat the diminished ambient PO_2 include an increase in both Hb and Hct concentrations, both of which lead to increases in the blood's O_2 carrying capacity (Ostadal & Kolar, 2007) . Though, both of these increases appear to be the result of a decreased plasma volume via renal diuresis, with significant changes typically not seen until after exposure times surpass multiple days in length (Wagner, 2000; Wyatt, 2014). Moreover, it appears more likely that Hb concentration (Hb_{con}), rather than Hb mass (Hb_{mass}), is elevated during exposure to altitudes as low as 1500 m. This provides further evidence of the reduction in plasma volume occurring within 24-48 h of initial ascent. Indeed, at more severe altitudes in the range of 3000-4000 m, an increase in Hb_{con} rises approximately 0.5-1.0 g/mL of blood, corresponding to a reduction of 0.2-0.3 L plasma volume (P Bärtsch & Saltin, 2008; Calbet et al., 2004). However, while an increased Hb_{con} in and of itself would provide greater O_2-carrying capacity, prior studies have reported that such changes would lead to elevated blood viscosity, which may negatively impact CO, thus potentially negating any benefit of a rise in hemoconcentration (Christopher John Gore et al., 2007; Naeije, 2010; Wagner, 2000). Although there is evidence of a strong relationship between Hb_{mass} and VO_{2max}, the correlation between the two is weak and only capable of explaining 14% of the variance in VO_{2max} (Saunders,

Garvican-Lewis, Schmidt, & Gore, 2013). Yet, even in the absence of a significant increase in Hb_{mass}, there may still be a potential increase in the systematic transport of O_2 due to an increase in the enzyme 2,3- diphosphoglycerate (2,3-DPG). Hypoxic conditions lead to increased levels of circulating 2,3-DPG to lower O_2's affinity to Hb, which would serve to expedite the dissociation of O_2 and Hb, thus increasing PAO_2 and ultimately CaO_2 (S. A. Gallagher & Hackett, 2004; Hahn & Gore, 2001). Further, the reduction to plasma volume, and thus, blood volume, has been reported to persist for 2-4 months after introduction to altitude (Calbet et al., 2004). A potential side effect, and one of particular concern for individuals during the initial days of altitude exposure is that the combination of the HVR, thus an increased amount of water vapor loss due to respiration, and renal diuresis may increase the risk of dehydration, primarily for those individuals training at altitude (Hahn & Gore, 2001; Wyatt, 2014).

Additionally, a series of adjustments related to cardiovascular function are believed to occur during acute altitude introduction, namely the change in CO via an altered HR. It has previously been reported that within the first few hours upon introduction to high altitude settings, there occur significant elevations in resting HR (Eckardt et al., 1989; Kato et al., 2004); still, more current work points to the contrary (Ofner et al., 2014). As a result of the elevated HR, CO would be elevated, relative to normoxic conditions, in response to the decrements to PO_2 and resultant drop in arterial O_2 content (CaO_2) (Wyatt, 2014). Conversely, there does appear to be some unanimity in the belief that CO actually decreases during high altitude conditions, although uniformity as to the effect of moderate altitudes on CO has yet to be attained (Pascal Mollard et al., 2007; Wagner, 2000). However, recent reviews suggested that while moderate levels of

hypoxia do indeed precede the onset of tachycardia, and ensuing rise in CO, a response which appears to be sufficient to counter the drop in PO_2 present in moderate hypoxia, both exercise and more austere hypoxic conditions prove too demanding for a similar, equitable increase in CO to offset the severity of hypoxemia (Naeije, 2010; Siebenmann & Lundby, 2015). However, despite the inconsistencies in results related to the hypoxic effect on both HR and CO, prior works do appear to agree that SV remains unaltered and that any change in CO that may or may not present under acute hypoxic stress is related to changes in HR (Pascal Mollard et al., 2007; Siebenmann & Lundby, 2015; Wagner, 2000).

As altitude contact time increases, either through continued stays or repeated, intermittent exposures, cardiovascular adaptations carry on to bring about further acclimatization. With an exposure time surpassing 2-3 d, the majority of research suggests CO returns to near baseline levels (Farinelli, Kayser, Binzoni, Cerretelli, & Girardier, 1994; Hainsworth & Drinkhill, 2007; Naeije, 2010). Yet, other studies have reported findings conflicting with this theory (Ostadal & Kolar, 2007). However, while HR may decline in comparison to HR values upon initial introduction to altitude; HR, both at rest and during submaximal exercise, remains somewhat elevated compared to SL values. Further, both CO_{max} and HR_{max} at altitude has been shown to be significantly lower when compared to SL control values, even in acclimatized individuals (Farinelli et al., 1994; Favret, Henderson, Richalet, & Gonzalez, 2003; Naeije, 2010; Wagner, 2000). One potential explanation for the alterations in HR upon altitude exposure may be related to enhanced sympathetic nervous system activity with acute exposure and parasympathetic activity increases during the acclimatization process, possibly and

partially explaining the initial rise and eventual fall in resting HR values (Farinelli et al., 1994; Naeije, 2010; Wagner, 2000). Further evidence for this theory was presented during the comparison of gradual and rapid ascents to altitude, whereas gradual ascents over 2 wk resulted in a 25% increase in resting HR, but a rapid ascent to the same altitude resulted in only a 9% increase in resting HR (Hainsworth & Drinkhill, 2007).

The likely mechanism behind CO returning to near SL values while HR remains elevated is a decrease in SV. While SV begins to decline during acute altitude exposure, as exposure time increases and the acclimatization process unfolds, PV decreases as a result of diuresis, which leads to the drop in SV. This decline in SV occurs during approximately the initial 7 d of exposure, and begins to steady during sojourns extending beyond such lengths. The decline in plasma volume is dependent upon the severity of the hypoxic exposure with greater levels of hypoxia resulting in more significant declines in PV (Peter Bärtsch & Gibbs, 2007; Hainsworth & Drinkhill, 2007; Naeije, 2010; Wagner, 2000). Further, there is evidence to suggest the aforementioned cardiovascular adaptations do remain relatively consistent with longer acclimatization periods as it has previously been reported that individuals remaining at elevation for significant periods of time as well as high-altitude natives have similar resting CO compared to SL controls while the long-term visitors and residents of high-altitude locations were also shown to display higher HR and lower SV than their lowland counterparts (Naeije, 2010). Finally, while there is some evidence that both NH and HH induce similar cardiovascular adaptations during altitude acclimatization, as the review by Ostadol & Kolar (2007) suggest, the plethora of methodologies utilized and presence of inter-individual variations have led to a lack of consensus on the matter.

In response to aerobic exercise during acute hypoxic conditions, similar patterns of inconsistency for HR have emerged. Previous investigations have reported significant increases in HR during both sub-maximal and maximal aerobic testing (Engelen et al., 1996; Wagner, 2000); however, more recent works have reported either no differences or decreases in HR during sub-maximal and maximal efforts (Beidleman et al., 2014; C. A. Gallagher, Willems, Lewis, & Myers, 2014; Lundby, Araoz, & Van Hall, 2001; Pascal Mollard et al., 2007; Ofner et al., 2014).

Similar to other physiological responses to exercise during acute altitude, some of the differences in HR alterations may be related to the training status of the participants in the aforementioned studies. One potential explanation for the varied responses between trained and untrained individuals may be related to SaO_2 levels. The occurrence of exercise induced arterial hypoxemia (EIH), which presents in approximately 40-50% of highly-trained individuals ($RVO_{2max} > 60$ mL $\cdot$ $kg^{-1} \cdot min^{-1}$) (Chapman, Emery, & Stager, 1999) during endurance exercise is a potentially determining factor of aerobic exercise performance during acute altitude exposure (Chapman et al., 1999; Christopher J Gore et al., 1996; Rusko et al., 2004; Terrados, Mizuno, & Andersen, 1985). This desaturation, defined as an SaO_2 less than 92%, tends to be accentuated by an abrupt drop in ambient PO_2, furthering the decrement to pulmonary gas exchange and consequently, reducing the availability of O_2 for the working musculature (Amann & Calbet, 2008; Calbet et al., 2003a; Chapman et al., 1999; Pascal Mollard et al., 2007). However, even if highly trained individuals do not display SaO_2 levels below the EIH threshold, prior evidence has suggested that trained individuals still display significantly lower SaO_2 levels than their untrained counterparts (Benoit, Busso, Castells, Geyssant, & Denis, 2003). Prior

investigations have reported that the body is capable of tolerating PaO_2 levels in the range of 75-80 mm Hg with minimal falls in SaO_2, however, any drop in PaO_2 below that minimal threshold of approximately 75 mm Hg will tend to have a more substantial impact on SaO_2 and thus negatively affect maximal exercise capacity (Bebout et al., 1989; Chapman et al., 1999). Intriguingly, and in contrast to the varied effects between HH and NH on HVR, HR may not exhibit different responses between the two forms of hypoxia as Beidleman and colleagues (2014) reported no differences in HR response between NH and HH for fit males performing cycling exercise intensities of 45% and 65% of their VO_{2max} at a simulated altitude equivalent to 4300 m. In support of the aforementioned findings, a recent systematic review of crossover trials revealed ambiguous HR results between HH and NH conditions (Coppel, Hennis, Gilbert-Kawai, & Grocott, 2015).

Despite the lack of clear evidence as to which physiological systems, and to what extent they influence the human body's ability to respond to a sudden decline in PiO_2, there does appear to be consistency in the evidence that maximal aerobic capacity is significantly diminished upon acute exposure to altitude. While there is some evidence that the decline in aerobic capacity may be observed with ascents to low altitudes of approximately 600-700 m (Chapman et al., 1999; Hahn & Gore, 2001; Wyatt, 2014), a more accepted theory is that significant detriments to VO_{2max}, and thus aerobic endurance performance, occur in a linear manner beginning at an altitude, or its synthetic equivalent, of 1500 m (Peter Bärtsch & Gibbs, 2007; M Burtscher et al., 2006; Chapman et al., 1999; Muza, 2007; Ofner et al., 2014). Further, a pattern of considerable interest to the current investigation has emerged in that trained individuals are prone to a more significant

decline in VO_{2max} during acute exposure than their untrained counterparts (Raphael Faiss, von Orelli, Deriaz, & Millet, 2014; Lawler, Powers, & Thompson, 1988; Mollard et al., 2008; P Mollard et al., 2007). As Calbet et al. (2002) so succinctly described, the detrimental consequence of hypoxia related to maximal aerobic capacity appears to be the result of a decline in ambient PO_2 and ensuing reduction in the PiO_2, diminishment of pulmonary gas exchange, and degradation of CO_{max}, which, combined, account for the deterioration of $VO_{2max.}$

Submaximal and maximal aerobic exercise performance continue to recover from initial decrements suffered during early exposure periods as improvements to both the former and the latter are brought about via crucial adaptations in pulmonary ventilation, hemoconcentration, and cardiovascular function, as well as other exercise related adaptations associated with continued or repeated exposures to altitude (Beidleman et al., 2004; Fulco et al., 2013; N. Garcia, S. R. Hopkins, & F. L. Powell, 2000; Muza, 2007; Muza et al., 2010; Ostadal & Kolar, 2007; Saunders et al., 2013; Saunders et al., 2004; Schommer et al., 2012). These longer-term adaptations related to endurance exercise performance will be the focus of the next segment of this review of literature as the efficacy of the multitude of both past and present altitude training strategies will be examined.

Altitude Training Strategies

The traditional method employed for altitude training involves both living and training at high altitude settings (1500-3000m), or Live high-Train high (LHTH). This classical model first emerged nearly six decades ago (Christopher John Gore et al., 2007; Gregoire P Millet et al., 2010) and is still frequently utilized by endurance athletes and

mountaineers, both by SL dwelling athletes and permanent residents of moderate to high altitude locations (Hahn & Gore, 2001; Michael J Hamlin et al., 2013; Wilber, 2007a; Wolfarth, 2005). Despite equivocal results to date concerning the efficacy of LHTH, this model has been utilized both to provide altitude acclimatization and to provide an additional training stimulus, the former being crucial for performance at altitude and the latter for performance at or near SL (Friedmann-Bette, 2008; Christopher John Gore et al., 2007; Igor, Vladimir, Milos, & Goran, 2011; Wilber, 2001, 2007a; Wolfarth, 2005).

For SL athletes travelling to moderate to high altitude locations for exercise training purposes, these training camps are typically scheduled 2-3 times per year, with each trip lasting approximately 2-4 wk (Hahn & Gore, 2001; Gregoire P Millet et al., 2010). Due to the complexity of altitude acclimatization (P Bärtsch & Saltin, 2008; M Burtscher et al., 2008; Fulco et al., 2013; S. A. Gallagher & Hackett, 2004; Muza et al., 2010) and the inter-individual variation of acclimatization (Chapman, 2013; Chapman et al., 1998; Tannheimer et al., 2009), LHTH camps typically adhere to similar schedules in an attempt to provide the most effective training stimulus for the athletes. These schedules include an acclimatization phase (7-10 d), the primary training phase (2-3 wk), and the recovery phase (2-5 d). For athletes returning to near SL for competition, an additional phase is necessary to allow the athletes to re-acclimate. The ideal duration of this phase is currently under debate, with the various strategies ranging from 2-21 d following the departure from the altitude training site (Bonetti & Hopkins, 2009; Chapman, Stickford, Lundby, & Levine, 2014; Gregoire P Millet et al., 2010). However, despite continued residence at altitude being the most effective strategy to induce acclimatization, the LHTH method does present certain aspects which may counteract the

primary purpose for such training endeavors (Gregoire P Millet et al., 2010; Wilber, 2007a).

A notable concern for the implementation of LHTH is the detriment to training intensity due to elevation (Christopher John Gore et al., 2007; B. Levine & Stray-Gundersen, 1992; Gregoire P Millet et al., 2010; Rusko et al., 2004; Wilber, 2007a). This issue has been reported both anecdotally and scientifically as elite athletes returning from LHTH camps displayed diminished training intensities at altitude as well as performance decreases of 3-8% upon return to SL, supporting the idea that the potential training benefit of hypoxia is outweighed by the decline in training intensity (B. D. Levine & Stray-Gundersen, 1997; Wilber, 2007a). This decline in training intensity may be brought about via a combination of mechanisms related to exercise under hypoxic conditions. The previously described EIH known to effect elite endurance athletes may substantially decrease submaximal training intensities and speeds (Christopher J Gore et al., 1996; Hahn & Gore, 2001; B. D. Levine & Stray-Gundersen, 1997; Rusko et al., 2004). Further, the alterations in HR and CO that present under hypoxic conditions, both to submaximal and maximal values, is likely to impact training at altitude (Rusko et al., 2004). Additionally, body mass (BM) losses may occur during prolonged stays at altitude, especially when physical activity levels are high, as is the case with endurance athletes and mountaineers. It has previously been reported that BM losses of up to 4% may occur, with two-thirds of said loss resulting from declines in lean BM, with the authors noting that similar values have been reported in similar studies (Zaccagni, Barbieri, Cogo, & Gualdi-Russo, 2014). Moreover, recovery may be negatively impacted as sleep quality is inhibited during LHTH camps. These sleep disruptions in the form of disordered

breathing and arousals may last up to two weeks upon arrival to altitude (Christopher John Gore et al., 2007; Sargent et al., 2013). Further, multiple reviews examining the efficacy of altitude training strategies have cited numerous works reporting impairments to immune function in athletes traveling to and training at altitude (Friedmann-Bette, 2008; Christopher John Gore et al., 2007; Rusko et al., 2004).

One of the original purposes for supplementing altitude training into normal endurance training programs was/is the credence that hypoxic exposure will lead to increases in RBC volume, theoretically leading to improvements in VO_{2max} and consequently an improved race performance (Friedmann-Bette, 2008; Hahn & Gore, 2001; Gregoire P Millet et al., 2010; Wilber, 2007a; Wolfarth, 2005). Based on the aforementioned time schedules and altitude severity adhered to during the majority of LHTH camps, the evidence as to whether such endeavors are efficacious at improving the variables related to endurance performance of elite athletes has been equivocal to date. The meta-analysis conducted by Rasmussen et al. (2013) suggested that an exposure duration greater than 2 wk at an elevation of 4000 m is necessary to induce significant RBC volume increases while also proposing that for altitudes less than 3000 m, 4 wk sojourns may not lead to substantial increases in RBC volume. However, prior works have reported significant increases in RBC volume both in elite biathletes after only a 3 wk stay at only 2050 m (Wolfarth, 2005) and while an earlier investigation reported significant increases in RBC volume of elite runners after a 4 wk residence at an altitude of 2500 m (B. D. Levine & Stray-Gundersen, 1997). However, there does appear to be consensus concerning an individual's training status and the length of stay at altitude necessary to elicit significant increases in RBC volume as multiple works have suggested

that highly-trained individuals may require longer stays as they are closer to their physiological ceiling and thus require greater amounts of stimulation to elicit the desired hematological adaptations (Rasmussen et al., 2013; Wolfarth, 2005).

As previously mentioned, altitude acclimatization processes require approximately 1-3 wk (Fulco et al., 2013; Fulco et al., 1998; Muza, 2007; Muza et al., 2010); however, endurance training performances may necessitate even longer exposure durations before standard training intensities may be resumed and the full benefit of the hypoxic training stimulus can be exploited (Calbet et al., 2003b; Fulco et al., 2013; Hahn & Gore, 2001). To this point, prior works have shown that 2-3 wk of altitude exposure have led to 20-60% increases of submaximal endurance performance at altitude compared to initial exposure. Yet, there is little to no evidence that similar exposure durations bring about enhancements of VO_{2max} in hypoxic settings (Beidleman et al., 2007). Further, there is evidence to suggest that even with a proper acclimatization period VO_{2max} remains compromised due to factors other than O_2 delivery to working musculature (Calbet et al., 2003b; Hahn & Gore, 2001). In an attempt to expedite the acclimatization process, there are medications available to reduce one's risk and/or symptoms of AMS and other high-altitude illnesses; but, these medications present a number of adverse side effects as well as aggravate the reduced exercise tolerance at altitude, limiting their usefulness for athletes (Fulco et al., 2013).

As multiple reviews of altitude training strategies have noted, continued residence at altitude, as is utilized during LHTH, is regarded as a decidedly effective acclimatization practice, yet other factors such as detriments to both health and aerobic exercise capacity have proved disadvantageous in attempts to enhance endurance

performance, specifically at SL (Hahn & Gore, 2001; Gregoire P Millet et al., 2010; Wilber, 2007a). Further, resources such as time and money have also impacted the implementation of LHTH camps. Collectively, these factors guided efforts to develop other altitude training methods (B. D. Levine, 2002; Wilber, 2001).

As a result of the aforementioned complications resulting from the classical LHTH altitude training model, a more contemporary approach was introduced in the early 1990s. This newer altitude training strategy of Live high-Train low (LHTL), which employed the potential benefits of altitude acclimatization, or living high, and endurance training without compromising intensity, or training low, was developed jointly by Dr. Benjamin Levine and Dr. Stray-Gundersen (Christopher John Gore et al., 2007; Gregoire P Millet et al., 2010; Wilber, 2007a). However, many athletes faced geographical limitations and were unable to carry out LHTL camps without significant costs, financial and otherwise (Christopher John Gore et al., 2007). Such restrictions eventually led to technological advancements that have born multiple methods to fulfill the LHTL strategy are now available. There are multiple comprehensive reviews detailing the various strategies currently employed (Bonetti & Hopkins, 2009; Gregoire P Millet et al., 2010; Wilber, 2001, 2007a) but for this review, LHTL will be used to refer to all possible methods; however, where applicable to the present investigation, distinctions between studies utilizing HH and NH will be presented.

Despite the abundance of studies investigating the efficacy of LHTL to improve SL performance (Bonetti & Hopkins, 2009; Chapman, Stickford, et al., 2014; Raphaël Faiss, Girard, & Millet, 2013; Fulco, Rock, & Cymerman, 2000; Christopher John Gore et al., 2007; Hahn & Gore, 2001; Humberstone-Gough et al., 2013; Gregoire P Millet et

al., 2010; Wilber, 2001; Wilber, Stray-Gundersen, & Levine, 2007), there remains a paucity of research efforts regarding the benefits or detriments of LHTL related to endurance performance in hypoxic conditions (Fulco et al., 2013; Hahn & Gore, 2001; Siebenmann et al., 2012). Further, empirical evidence regarding the ability of LHTL protocols to reduce either the prevalence or severity of high-altitude illnesses is extremely limited. Individuals participating in LHTL protocols are at greater risk of developing symptoms of AMS rather than HACE or HAPE, which are typically not a concern as LHTL protocols are conducted at altitudes or their simulated equivalents below the threshold for the development of either the former or the latter (Schommer et al., 2012). The initial symptoms of AMS typically occur within the first hours of exposure to an altitude exceeding 2400 m (S. A. Gallagher & Hackett, 2004; Muza et al., 2010; Richard et al., 2014). Yet, according to multiple review articles pertaining to LHTL (Bonetti & Hopkins, 2009; Hahn & Gore, 2001; Gregoire P Millet et al., 2010), as well as more recent original work (Chapman, Karlsen, et al., 2014), the recommended maximum altitude severity for such endeavors is equivalent to approximately 2500 m, which may attenuate any concerns regarding AMS.

While the current literature may be slight regarding the efficacy of LHTL protocols to elicit HVR adaptations (Hahn & Gore, 2001; Wilber, 2007a), current LHTL recommendations do appear to be sufficient to provoke such responses. The initiation of the HVR is brought about via the hyperventilation that commences nearly instantaneously upon introduction to altitude (Hahn & Gore, 2001; Townsend et al., 2002). Utilizing NH during an LHTL investigation, researchers have shown that resting blood pH is significantly increased after 10 d of 16 h per day of exposure, indicating the

presence of respiratory alkalosis, which is often the result of increased V_E (Nummela & Rusko, 2000). Further, a prior study has also reported that LHTL protocols with total exposure time of at least 88 h (11 d x 8 h per night) is sufficient to significantly reduce the partial pressure of CO_2 (PCO_2). Additionally, the same research team reported significant increases in SpO_2 of elite athletes after only 4 d of sleeping 8-11 h per night in NH equivalent to altitude ranges of approximately 2650-3000 m (Hahn & Gore, 2001). However, others have reported no change in resting V_E upon completion of a 20 d LHTL protocol using NH equivalent to 2650 m in which the researchers utilized two LHTL protocols, one in which participants slept 8-11 h per night for 20 d consecutively at the aforementioned simulated altitude, referred to as the continuous group, and another LHTL group, which performed four cycles of sleeping 5 d in NH followed by 2 d in normoxia, referred to as the intermittent group. These authors did report significantly lower resting end-tidal pressure of CO_2 ($PetCO_2$) levels compared to the control group in both the continuous and the intermittent groups. Intriguingly, they also reported a significant decline in $PetCO_2$ from the initial measure to the measurement taken after 15 d of sleeping in NH in the intermittent group, as well as a lower, but not significant, $PetCO_2$ observed in the continuous group. Based on these findings, the authors proposed that the HVR response was more distinct in the continuous group as compared to the intermittent LHTL group (Townsend et al., 2002). Additional studies have also reported significantly differences in V_E during submaximal but not maximal running in highly trained runners. During a terrestrial altitude LHTL investigation the responses of trained runners living at four different locations with altitudes of 1780, 2085, 2454, and 2800 m, respectively. The authors reported that while there was no difference in maximal V_E

following the 4 wk protocol, submaximal V_E was significantly decreased in the group living at 1780 m, while V_E displayed lower, albeit nonsignificant, for the 2085 m group. Further, submaximal V_E was significantly greater in the 2454 m group as well as elevated, but not significantly, in the 2800 m group. Additionally, after a 2 wk deacclimatization period, submaximal V_E was still significantly depressed for the athletes who resided at 1780 m, while the athletes living at the two highest altitudes still exhibited greater, but not significant, V_E levels during submaximal exercise (Chapman, Karlsen, et al., 2014).

In addition to shorter-term ventilatory responses, there is also evidence of genetic HVR adaptations. When comparing the two high-altitude native populations of the Andes and Tibet, it has been reported that the former has adapted to the altitude via hematological changes while the former have adapted via a resting V_E 1.5 times that of their Bolivian counterparts. Further, it has also been reported that the Tibetan natives have an HVR that is twice that of the Andean residents. Such responses have led some researchers to conclude that individuals such as Tibetan Sherpas are more capable than most during high-altitude expeditions due to the elevated HVR, correlating to more efficient O_2 delivery (Christopher John Gore et al., 2007). Interestingly, and of particular consequence for practitioners of LHTL, the HVR may be a key beneficial adaptation for strenuous activity in mountainous regions, but it may also be detrimental to athletes competing at or near SL. Based on the findings from their LHTL investigation utilizing four separate natural altitude locations, Chapman, Karlsen, et al. (2014) proposed that an enhanced HVR brought about during altitude acclimatization may have a potentially negative impact on endurance performance at or near SL via the increased energy and O_2

costs of breathing. This proposal may be supported via prior work reporting that endurance trained athletes display lower HVRs than untrained, but otherwise healthy individuals (Townsend et al., 2002).

In contrast to the dearth of empirical evidence related to ventilatory acclimatization, the current literature is replete with data related to hematological adaptations resulting from LHTL. Nevertheless, the sheer quantity of available evidence regarding EPO, Hct, Hb, and RBC changes has failed to produce consistently positive results, possibly related to the multitude of methodological differences, which only serves to fuel the controversy surrounding the efficacy of LHTL (Bonetti & Hopkins, 2009; Christopher John Gore et al., 2007; Wilber, 2001, 2007a).

One of the more popular justifications for implementing LHTL, or any form of altitude training for that matter, is the theoretical increase in EPO and thus, the eventual enhancement of the O_2-carrying capacity of the blood (Brocherie et al., 2015; Gregoire P Millet et al., 2010; Wilber, 2001, 2007a). In contrast to the other hematological variables to be discussed, there does appear to be consensus regarding the effects of hypoxic exposure on the increased production of EPO as it is well established that after approximately 2 h of introduction to hypoxic conditions, EPO concentration begins to rise and reaches peak levels after 3-4 d of exposure, after which it generally settles to levels slightly elevated compared to baseline measures (Ashenden et al., 2000; S. A. Gallagher & Hackett, 2004; Christopher John Gore et al., 2007; Rasmussen et al., 2013). Further, multiple LHTL studies and comprehensive reviews have reported EPO concentration increases employing both HH (Chapman, Karlsen, et al., 2014; Hahn & Gore, 2001) and NH (Ashenden et al., 2000; Siebenmann et al., 2012; Wilber, 2007a)

protocols following the aforementioned time paradigm for EPO levels relative to hypoxic exposure.

Following the rationale of the predominant model for the hematological adaptations resulting from exposure to hypoxic conditions, the production and subsequent increased EPO levels initiate the generation of RBCs in bone marrow (Clark et al., 2009; Saunders et al., 2013). However, while the pathway is a well-accepted theory, whether or not the hypoxic stimulus brought about via altitude training practices such as LHTL models is sufficient to yield such a response remains widely debated (Clark et al., 2009; Rasmussen et al., 2013; Robach et al., 2012; Saunders et al., 2013; Schmidt & Prommer, 2010). Additionally, the distinction between Hb_{mass} and Hb_{con} has become increasingly relevant as changes in Hb_{mass} would indicate changes in RBC volume whereas changes in Hb_{con} are likely to only be an indication of a change in total blood volume, with the former being the true adaptation researchers and endurance coaches are interested in with respect to its implications on VO_{2max} and the latter signaling acclimatization without necessarily impacting aerobic capacity (Hahn & Gore, 2001; Rasmussen et al., 2013; Saunders et al., 2013; Wilber, 2007a).

In addition to EPO, Hb and the concomitant RBC volume are also of particular interest during LHTL investigations due to their role in systematic O_2 transport (Brocherie et al., 2015; Humberstone-Gough et al., 2013; Siebenmann et al., 2012). However, the disparity regarding the effects of elevated EPO levels after hypoxic exposures centers on whether or not said increases lead to increases in Hb_{mass} (Robach et al., 2012; Saunders et al., 2013; Schmidt & Prommer, 2010; Siebenmann et al., 2012) and RBC volume (Chapman, Karlsen, et al., 2014; Rasmussen et al., 2013). Inquiries of the

standard LHTL model, which were conducted in geographically feasible locations in order for participants to both live and train in naturally high and low altitudes, respectively, have previously produced positive results for both Hb_{con} and Hb_{mass} compared to their fitness-matched control groups. Participants, who were sub- and elite-level athletes for their respective sports, completed 24-28 d LHTL protocols while living at 2500 m and training at altitudes ranging from 1000-1800 m (Wilber, 2007a).

Prior studies investigating the effects of LHTL via NH on highly-trained athletes failed to demonstrate significant changes in Hb_{con} and reticulocyte levels (Ashenden et al., 2000) or Hb_{mass} (Ashenden, Gore, Martin, Dobson, & Hahn, 1999; Robach et al., 2012; Saunders et al., 2004; Siebenmann et al., 2012). Adding to the lack of clarity on the matter, multiple studies reporting no changes in Hb_{mass} also reported significant escalations of reticulocyte counts (Aulin, Svedenhag, Wide, Berglund, & Saltin, 1998; Robach et al., 2012; Siebenmann et al., 2012). Each of the aforementioned studies included a control group and followed the generally accepted LHTL guidelines for both altitude severity and total exposure time. The importance of conducting LHTL studies with a control group when evaluating the effects on blood parameters has previously been addressed due to the potential of endurance training to increase said variables (Ashenden et al., 2000). Contrasting with the above-mentioned works, others have described substantial increases in Hb_{mass} after completion of NH-based LHTL procedures. Multiple placebo-controlled inquiries reported significant increases in Hb_{mass} following their respective LHTL protocols (Brocherie et al., 2015; Brugniaux, Schmitt, Robach, Nicolet, et al., 2006; Humberstone-Gough et al., 2013). Yet, Brugniaux et al. (2006) performed follow-up testing after a 15 d deacclimatization period and indicated that Hb_{mass} had

returned to baseline levels.

Similar inconsistencies as to the effectiveness of LHTL methods to significantly improve both VO_{2max} and endurance performance measures have been reported. However, as the majority of the current literature has focused on augmenting the performance of sub- and elite-level athletes from long-distance running to orienteering, even minute improvements may be of consequence (Brocherie et al., 2015; Raphaël Faiss et al., 2013; Fulco et al., 2000; Christopher John Gore et al., 2007; Gregoire P Millet et al., 2010; Wilber, 2001). To demonstrate, while the empirical evidence concerning the efficacy of LHTL to improve SL performance remains somewhat inconclusive due to statistical insignificance, anecdotal support remains steadfast as a result of more applied findings (Bonetti & Hopkins, 2009; Chapman, Karlsen, et al., 2014; Chapman, Stickford, et al., 2014; Raphaël Faiss et al., 2013; Fulco et al., 2000; Hahn & Gore, 2001; McLean, Gore, & Kemp, 2014; Wilber, 2007a). Further, as a primary objective of LHTL practices is to improve endurance performance at or near SL, minimal attention has been given to the efficacy of LHTL to enhance aerobic performance at moderate to high altitudes. To this point, authors of a comprehensive review conducted 10 yr after the initial introduction of LHTL failed to identify a single study examining the effects of LHTL on VO_{2max} or endurance performance in a hypoxic setting (Hahn & Gore, 2001). Further, for the studies that have examined aerobic endurance performance in hypoxic conditions following an LHTL protocol, inconclusive results have been reported as a 3 wk LHTL investigation employing terrestrial altitude described an 8.9% improvement in VO_{2max} at 2340m, albeit without the benefit of a control group (Schuler, Thomsen, Gassmann, & Lundby, 2007). However, an NH-based LHTL methodology failed to elicit any aerobic

capacity improvements (Siebenmann et al., 2012), which appears to support earlier research that despite the enlargement in other indicators of acclimatization such as Hb and SaO_2, VO_{2max} remains compromised (Bebout et al., 1989; Calbet et al., 2003b). Based on the empirical evidence currently available, while current LHTL practices utilizing living altitudes ranging from 2000-3000 m for 2-4 wk may be sufficient to elicit some facets of altitude acclimatization, whether or not this particular form of altitude training is adequate to dramatically improve performance at moderate to high altitudes remains to be seen (Calbet et al., 2003a; Calbet et al., 2003b; Fulco et al., 2011; Siebenmann et al., 2012).

While the advancement of altitude training technologies all but eliminated the geographical and reduced the financial limitations, respectively, of the LHTL strategy, certain obstructions remained for some individuals wishing to carry-out this particular form of altitude training. The conversion of residences into nitrogen houses or sleeping in hypoxic tents potentially remained too burdensome, and time-consuming, for some athletes (Michael John Hamlin & Hellemans, 2007). In an effort to expedite the acclimatization process, and theoretically enhance athletic performance, a subset of LHTL emerged and discontinuous exposure to hypoxic conditions, or IHE, was established (B. D. Levine, 2002; Mekjavic, Debevec, Amon, Keramidas, & Kounalakis, 2012; Muza, 2007; Powell & Garcia, 2000). Further, since LHTL involving natural altitude requires the individuals to relocate to mountainous regions, this aspect diminishes the military's capabilities for the rapid deployment of personnel (Muza, 2007). Though IHE may be a seemingly recent development related to athletic performance (B. D. Levine, 2002), its potential to induce altitude acclimatization (Stickney & Van Liere,

1953) as well as its effectiveness and logistical necessity to prepare mountaineers for ascents of peaks exceeding 8000 m (Powell & Garcia, 2000) have been investigated and practiced, respectively, for many years. Indeed, the mountaineering procedure of ascending and then returning to a base camp established at a lower elevation to sleep, eat, and collect more supplies stemmed from pure necessity but led to inadvertently greater altitude acclimatization via shorter-term exposures while climbing to higher elevations followed by recovery periods at base camp (Powell & Garcia, 2000).

Altitude acclimatization appears likely to correspond to the dosage of altitude exposure, which is a product of the total exposure duration (the duration of each IHE session x the total number of IHE sessions) and the severity of hypoxia. If IHE is to elicit a similar level of acclimatization as LHTL, then the severity of altitude must be increased as a result of the decreased total exposure times. For the purposes of this review, IHE will refer to protocols utilizing ≤ 8 h $\cdot$ d^{-1} of hypoxic exposure during resting conditions as the majority of LHTL protocols employed daily exposure durations typically exceeding 8 h $\cdot$ d^{-1} (Bonetti & Hopkins, 2009; Brugniaux, Schmitt, Robach, Jeanvoine, et al., 2006; Nathalie Garcia et al., 2000; Gregoire P Millet et al., 2010; Muza, 2007; Wilber, 2001, 2007a). In a comprehensive review of hypoxic training strategies, Muza (2007) elucidates this inverse relationship between IHE duration and hypoxia severity. One potential justification for the selection of either LHTL of IHE may be related to the overall benefits desired. If the desired outcome is to improve athletic performance at or near SL, then hematological outcomes are of primary interest and longer exposure durations such as those utilized during LHTL protocols are typically selected. If ventilatory adaptations related to acclimatization for a future ascent to terrestrial altitude are of primary interest,

then IHE may be sufficient to reduce the risk of AMS (Beidleman et al., 2004; M Burtscher et al., 2008; Fulco et al., 2013) and possibly augment exercise in hypoxic conditions (Faulhaber, Dünnwald, Gatterer, Bernardi, & Burtscher, 2012; Katayama et al., 2001).

The current literature regarding the efficacy of IHE, as defined above, protocols to reduce the risk of AMS appear to be limited, but promising. A pivotal study on the subject revealed that 60 h of HH exposure time (15 d of 4 h · d^{-1} exposure duration) was sufficient to both reduce the risk and severity of AMS during a 30 h exposure to HH equivalent to 4300 m (Beidleman et al., 2004). While prior works have suggested that acute exposure to HH induces a greater physiological strain than NH, and thus HH would be more effective at reducing the risk of AMS upon exposure to terrestrial altitude (Loeppky et al., 1997; R. C. Roach et al., 1996) others have reported contrasting results (Richard et al., 2014). To further illustrate, an NH-based LHTL procedure consisting of only 5 nightly exposures during sleep at an altitude equivalent of 4300 m significantly decreased the occurrence of AMS after the initial two exposures (Kolb, Ainslie, Ide, & Poulin, 2004).

Multiple studies using HH-based IHE protocols have demonstrated their respective usefulness to induce ventilatory adaptations consistent with acclimatization including a rise in resting HVR in hypoxic conditions (Beidleman et al., 2004; Faulhaber et al., 2012; Fulco et al., 2013; Katayama, Sato, Ishida, Mori, & Miyamura, 1998; Katayama et al., 2001), as well as other implications of acclimatization including, but not limited to, an increased resting (Beidleman et al., 2004; Katayama et al., 1998; Rodríguez et al., 2000) and exercise (Beidleman et al., 2007; Chapman et al., 1998; Katayama et al.,

2001; Ricart et al., 2000) SaO_2 levels. Yet other works have detailed no significant changes to variables associated with altitude acclimatization. A 4 wk HH-based IHE protocol of 3 h · d^{-1} of 5 d · wk^{-1} did not increase submaximal (Truijens et al., 2008) or maximal (Rodriguez et al., 2007) V_E in trained runners and swimmers.

The efficacy of NH-based IHE studies remains somewhat unclear as only limited evidence is currently available supporting the use of NH-IHE protocols of less than 8 h·d^{-1} exposure duration to elicit acclimatization and/or hypoxic performance enhancements (Michael John Hamlin & Hellemans, 2007; Mekjavic et al., 2012; Muza, 2007). Although sparse, and contrary to the majority of prior works reporting significant differences of the physiological responses observed between HH and NH conditions (Raphael Faiss et al., 2013; Loeppky et al., 1997; R. C. Roach et al., 1996; Savourey et al., 2003; Tucker, Reeves, Robertshaw, & Grover, 1983) there is some evidence that the timeline for the HVR response during NH-based IHE sessions does appear to follow the time elapse pattern of HVR during exposure to terrestrial altitude, with the NH-induced HVR stabilizing within a few days of the initial exposure (Sheel & MacNutt, 2003). Previous work has demonstrated a significant increase in individual HVR as early as 5 d after the initial IHE session, yet also reported no changes in group mean HVR from baseline after an additional 7 d, 12 d total, of IHE using an NH equivalent of 3800 m (N. Garcia, S. Hopkins, & F. Powell, 2000). A more recent inquiry reported that only four IHE sessions over a 4 d period using the NH equivalent of 4200 m induced significant improvements of 15% and 4% for V_E and SpO_2, respectively, during a constant power test (Debevec & Mekjavic, 2012). Further complicating the matter is the interaction of the physiological systems involved in acclimatization, as the potentially beneficial

ventilatory alterations may be at least partially undone via metabolic adjustments during submaximal exercise in hypoxic settings (M Burtscher, Gatterer, Faulhaber, Gerstgrasser, & Schenk, 2010). Additionally, neither submaximal cycling exercise V_E nor SaO_2 levels were improved after a 7 d protocol at NH equivalent of 4500 m for individuals at NH equivalents to 2000, 3000, or 4000 m (Faulhaber et al., 2012).

IHE-induced hematological adaptations have not been as pronounced as the ventilatory adaptations and while not conclusive, current evidence tends to indicate that IHE protocols do not provide a sufficient stimulus to induce erythropoiesis (Debevec & Mekjavic, 2012; Christopher J Gore et al., 2006; B. D. Levine, 2002; Muza, 2007; Powell & Garcia, 2000) due to the time course of increased erythropoietin levels resulting from a hypoxic stimulus (Eckardt et al., 1989). However, prior works have reported results somewhat to the contrary using IHE sessions of $\leq$ 2 h per exposure to elicit increased hemoconcentration via HH (Rodríguez et al., 2000) and increases to both hemoconcentration (M Burtscher et al., 2010) and reticulocyte count (N Garcia et al., 2000) via NH-based IHE protocols.

IHE-induced enhancements of endurance performances during hypoxia is another topic of which the current literature is sparse. Katayama et al. (2001) reported no change in VO_{2max} in a hypobaric chamber setting equivalent to 4500 m after seven 1.5 h exposures to the same simulated altitude. Further, no endurance performance enhancements in NH, FiO_2 = 12% or 4200 m, were observed following either a shorter (4 $h \cdot d^{-1}$ x 4 d) (Debevec & Mekjavic, 2012) or more prolonged (1 $h \cdot d^{-1}$ x 5 $d \cdot wk^{-1}$ x 4 wk) (Mekjavic et al., 2012) protocols. Though the empirical evidence may be limited, the results have been consistent in that IHE during rest does not augment endurance

performance in hypoxia; yet, it is by no means conclusive (M Burtscher et al., 2008; Faulhaber et al., 2012; Muza, 2007; Muza, Fulco, & Beidleman, 2009).

The final altitude training strategy to be discussed is the Live low-Train high (LLTH) method, which may also be referred to as IHT. IHT allows the individuals to live at or near SL while conducting some or all of their training sessions in simulated NH or HH. IHT sessions are approximately 5-180 min in duration (Gregoire P Millet et al., 2010; Wilber, 2007a) with the severity of altitude ranging from approximately 2000-5500 m (Bonetti & Hopkins, 2009; Gregoire P Millet et al., 2010; Wilber, 2001, 2007a). IHT may be preferable to the previously mentioned altitude training strategies by eliminating the majority of the potentially burdensome aspects of the LHTH and/or LHTL strategies. Some prospective benefits of utilizing IHT would be the additional time spent in normobaric normoxia (NN) for rest and recovery purposes between training sessions (Hendriksen & Meeuwsen, 2003) as well eliminating any potential lean body mass reductions that may occur with prolonged stays at altitude (Mizuno, Savard, Areskog, Lundby, & Saltin, 2008; Zaccagni et al., 2014). Further, IHT may also reduce the burden of monetary and time resources that more traditional altitude training methods require (Raphaël Faiss et al., 2013; Michael J Hamlin et al., 2013). Finally, and possibly the strongest argument to be made in favor of IHT is the preservation of high-intensity training sessions. By only conducting some training sessions each week in the simulated hypoxic conditions, athletes' regular training patterns may be maintained, thus drastically reducing the risk of a downturn in overall training volume (Dufour et al., 2006; Hoppeler, Klossner, & Vogt, 2008; Ponsot et al., 2006). However, despite these perceived advantages of IHT, enhanced performance was the original and remains the primary

objective of such endurance training practices; therefore, it should be noted that only a minute number of studies utilizing a control group have reported significant endurance performance enhancements for the IHT group compared to their control group counterparts (Raphaël Faiss et al., 2013).

Based on the current literature, it does not appear that true IHT sessions, during which exercise is performed the entire duration of the exposure to simulated altitude, are sufficient to stimulate a sustained HVR or other markers of ventilatory acclimatization. In one of the seminal works in this area, it was reported that untrained participants performing cycle ergometer training for 30 min · d^{-1} x 6 d · wk^{-1} x 4 wk at neither 2250 m nor 3450 m significantly increased maximal V_E over the SL control group during maximal exercise testing at either altitude (Roskamm et al., 1969). Yet, more recent results point to the contrary. While neither $PetO_2$ nor $PetCO_2$ was significantly different between the control and experimental groups of healthy, untrained individuals at either pre- or post-testing, there was a significant difference in the HVR as a result of a slight increase in HVR for the IHT group and a significant decrease in HVR for the control group following 30 min · d^{-1} x 5 d · wk^{-1} x 2 wk of cycle ergometer training in a HH setting equivalent to 4500 m. However, after a 2 wk detraining period, the differences in HVR dissipated and were no longer significant (Katayama et al., 1999). Furthermore, IHT may not only appear to be an insufficient stimulus for ventilatory acclimatization, it may also be detrimental to ventilatory acclimatization. Upon completion of a 1 h · d^{-1} x 6 consecutive days at the HH equivalent to 4500 m during which the control group remained sedentary and the experimental group performed bicycle ergometer exercise for 30 min of the 1 h exposure sessions, the control group demonstrated an increase in SaO_2

twice that of the IHT group, 14% versus 7%. Further, the authors also reported that the control group displayed a significant resting HVR increase of 30%, whereas the IHT group displayed no change in HVR (Katayama et al., 1998). As a result of the deleterious effects of IHT reported in the aforementioned study, it has been suggested that if IHT is to be performed in an attempt to augment performance at altitude, there should be an accompanying duration of IHE that is sufficient to stimulate ventilatory acclimatization (Muza, 2007).

The empirical evidence of IHT protocols to elicit the hematological adaptations commonly associated with altitude training is minimal and remains inconclusive. Several investigations, as reported in multiple comprehensive reviews of altitude training strategies including IHT, have reported no significant differences in blood parameters often associated with aerobic capacity such as serum EPO, Hb_{con}, Hb_{mass}, Hct, and RBC volume (Gregoire P Millet et al., 2010; Muza, 2007; Wilber, 2007a). Based on the current literature, it does not appear that there is any difference between NH- and HH-based protocols to stimulate erythropoiesis. Further, the current findings appear to be in line with prior works that have proposed that 2 h may be the minimal duration necessary to stimulate an increase in EPO (Rasmussen et al., 2013) as well as approximating the half-life of serum EPO to be less than 6 h, thus, current IHT practices would be an insufficient stimulus for the initiation of erythropoiesis (Hahn et al., 2001).

In one of the more influential works investigating IHT, the authors analyzed the effects of 60-90 min $\cdot$ d^{-1} x 4-5 d $\cdot$ wk^{-1} x 3-4 wk in 8 competitive cyclists and reported no significant differences of Hb_{con} or Hct, neither between the experimental and control groups, nor from pre- to post-testing values (Terrados, Melichna, Sylvén, Jansson, &

Kaijser, 1988). Further, a 1 h · d^{-1} x 3 d · wk^{-1} x 3 wk protocol utilizing the HH equivalent of 4000 m failed to elicit any hematological changes in elite triathletes (Vallier, Chateau, & Guezennec, 1996). Further, a lengthier protocol of 30 min · d^{-1} x 3 d · wk^{-1} x 6 wk in HH equivalent to 3200 m also yielded no significant differences in Hb_{con}, Hct, or RBC count in highly-trained cyclists (N. Ventura et al., 2003). However, there is limited evidence that IHT may indeed bring about hematological adaptations. One of the few studies of IHT to report hematological parameter increases utilized a cross-over design and was conducted using 16 triathletes competing at either the national and international levels. The investigators reported a significant difference in Hct between the HH group and the control group 9 d after the completion of the 105 min · d^{-1} x 10 consecutive days design in HH equal to 2500 m. Interestingly, the authors also reported significant increases in Hb_{con}, which the authors state could not be accounted for via a decline in PV, for both the HH and control groups 2 d after completion of the training, but not after 9 d (Hendriksen & Meeuwsen, 2003).

NH-based IHT protocols have fared much the same as HH-based IHT methods to enhance the O_2-carrying capacity of blood. A 5 wk double-blind, high-intensity training program in NH, FiO_2 = 15.3% or 2500 m, failed to elicit significant changes in either Hb or Hct in trained swimmers (Truijens, Toussaint, Dow, & Levine, 2003). A 30 min · d^{-1} x 3 d · wk^{-1} x 4 wk protocol using cycle ergometer training at an NH equivalent of 2750 m on trained team sport athletes was insufficient to produce any changes in either Hb_{con} or Hct (Morton & Cable, 2005). Further, an examination of the effects of 6 wk of high-intensity and moderate duration IHT, FiO_2 = 14.5% or 3000 m, did not educe Hb_{con} or Hct in highly-trained runners (Dufour et al., 2006). Another research team also utilizing

the NH equivalent of 3000 m, reported no significant changes in serum EPO, $Hb_{con,}$ Hct, or RBC volume in trained cyclists and triathletes after a 115 min · d^{-1} x 2 d · wk^{-1} x 7 wk IHT protocol (Roels et al., 2005).

In terms of cardiovascular adaptations following IHT, the empirical evidence remains scarce, as a minimal number of IHT inquiries have reported such information and the available data tend to indicate no significant changes. Multiple studies utilizing simulated altitude severities ranging from 2300-4000 m during IHT protocols reported no significant changes in HR_{max} for either normoxic or hypoxic testing conditions following either HH- (Hendriksen & Meeuwsen, 2003; Terrados et al., 1988; Vallier et al., 1996) or NH-based training (Dufour et al., 2006). Further, a previous inquiry into the cardiovascular response upon completion of IHT revealed no significant changes within or between the IHT and IHE groups for resting systolic or diastolic blood pressure measures, or resting HR (Katayama et al., 2000). Still, the combination of IHE and IHT may prove beneficial in terms of submaximal performance as 6 mountaineers displayed significant decreases in HR at submaximal but not maximal intensities following the completion of 3-5 h · d^{-1} x 17 d protocol in an HH setting equivalent to 4000-5500 m (M. VENTURA, JORDI, & FERRAN, 2000).

The efficacy of IHT to enhance aerobic performance at or near SL has been extensively researched with inconsequential results to date (Raphaël Faiss et al., 2013), however, the efficacy of IHT to improve aerobic performance at moderate to high altitudes remains somewhat limited and inconclusive (Muza, 2007). Although, there is a trend within the available literature that suggest current IHT practices may be adequate to lead to significant submaximal, but not maximal, aerobic endurance performance

increases at altitudes above 1500 m. For instance, a 40 min · d^{-1} x 2 d · wk^{-1} x 8 wk IHT protocol utilizing highly trained runners in an NH setting, FiO_2 = 16% or 2150 m, reported a significant decrease in both submaximal HR and VO_2 after IHT but not after normoxic training. Further, the authors also reported no changes in HR_{max} or VO_{2max} between the IHT and control groups after the 8 wk intervention (Holliss, Burden, Jones, & Pedlar, 2014). Interestingly, the aforementioned findings appear to be in line with previously reported results from a shorter, 3 wk vs 8 wk, protocol utilizing a more severe degree and different form of hypoxia, NH equivalent of 2150 m vs HH equivalent of 4000 m (Vallier et al., 1996). Additional results from studies that have conducted testing under hypoxic conditions have indicated both significant (Roskamm et al., 1969) and nonsignificant improvements in VO_{2max} (Hendriksen & Meeuwsen, 2003) as well as significant increases in hypoxic work capacity (Terrados et al., 1988) following HH-based IHT protocols. Equivocal results have also been reported for the limited number of investigations performing NH-based IHT protocols that also included NH testing as some have described significant improvements to VO_{2max} (Dufour et al., 2006) or aerobic power during incremental cycling tests to exhaustion (Roels, Bentley, Coste, Mercier, & Millet, 2007). Yet, additional results signified no change to VO_{2max} during testing in NH settings (Roels et al., 2007) following IHT compared to normoxic training.

While the more traditional altitude training methods such as LHTH and LHTL have received greater attention, both from an anecdotal and empirical evidence standpoint, the evidence supporting or refuting the effectiveness of more contemporary altitude training methods such as IHE and IHT to elicit not only altitude acclimatization but also aerobic performance enhancement under hypoxic conditions remains both

limited and inconclusive (Michael J Hamlin et al., 2013; Wilber, 2007a). Further, despite the increase in commercially available products for NH-based IHE and IHT practices, there remains a dearth of evidence of the effectiveness of NIHT to improve aerobic performance in an HH setting (Muza, 2007). There are a number of potential reasons for the inconclusive results to date related to altitude training, and more specifically, IHT, including but not restricted to, methodological and individual variances. As a result, it appears there is a necessity for further research in an attempt to provide a better understanding of the interaction of IHT methodologies including, but not limited to, exposure duration, simulated altitude severity, training intensity, and individual differences and their subsequent, combined effect on the hematological, cardiovascular, and maximal aerobic capacity variables related to submaximal and maximal aerobic performance in environmental altitude above 1500 m (Michael J Hamlin et al., 2013; B. D. Levine, 2002; Gregoire P Millet et al., 2010; Muza, 2007; Wilber, 2007a).

CHAPTER III

METHODOLOGY

Subjects

Eleven healthy, nonsmoking, college-aged male subjects (age 19.55 ± 1.44 y, mass 75.80 ± 8.82 kg, stature 177.45 ± 6.67 cm) with no history of respiratory disease participated in this study. Prior to participation, volunteers were fully informed of study procedures, risks, and benefits and completed an Institutional Review Board (IRB) approved informed consent document. Participants also completed a physical activity readiness questionnaire. All participants were current members of the Oklahoma State University (OSU) Army or Air Force ROTC detachments. Prior to and throughout the course of the study, all subjects resided in a location approximately 300 m above sea level. All potential participants were required to undergo a screening process that also served as the normoxic pre-testing procedures. For those participants that met the minimum peak aerobic capacity (VO_{2peak}) standards set forth in the informed consent document, their pre-screening results also served as their baseline measurements. As part of the pre-screening process, all potential participants completed a VO_{2peak} treadmill ergometer test in normoxic conditions ($VO_{2N\text{-}pre}$) using a modified Astrand-Saltin protocol (Chapman et al., 1998). A total of 27 ROTC cadets provided notification of their desire to participate in this study. Of these 27 potential participants, 20 completed the

pre-screening process, with 17 participants achieving a qualifying $VO_{2N\text{-}pre}$ of at least 49.2 mL · kg^{-1} · min^{-1}. This minimum standard utilized for participant selection purposes was chosen due to its usage as the minimum VO_{2peak} of young men considered to be in the "excellent" category according to the American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription (Thompson, 2010). Of the three potential participants that were not invited to continue their participation, two did not meet the minimum aerobic capacity standard and one was excluded due to the existence of a lower body injury. The remaining 17 participants were then notified of their selection to participate and scheduled to complete the remaining pre-testing procedures. Between the time of the $VO_{2N\text{-}pre}$ tests and the initial VO_{2peak} treadmill ergometer test in the HH chamber ($VO_{2HH\text{-}pre}$), 4 participants provided notification of their desire to end their participation in this study. Therefore, a total of 13 participants completed all aspects of the pre-testing procedures (Figure 1). These 13 participants were then pair-wise matched based on $VO_{2N\text{-}pre}$ results and assigned to either the experimental (n = 8; EXP) or control (n = 5; CON) groups. During the course of the training intervention period, 2 participants withdrew from the study due to injury unrelated to the study (n = 1) and other commitments (n = 1). An independent samples *t*-test was performed in SPSS and determined that the groups' $VO_{2N\text{-}pre}$ results, EXP = 61.53 and CON = 61.96 mL · kg^{-1} · min^{-1}, were not significantly different ($P > .05$). All subjects were instructed a to maintain their current dietary and sleeping habits and also completed weekly physical activity logs.

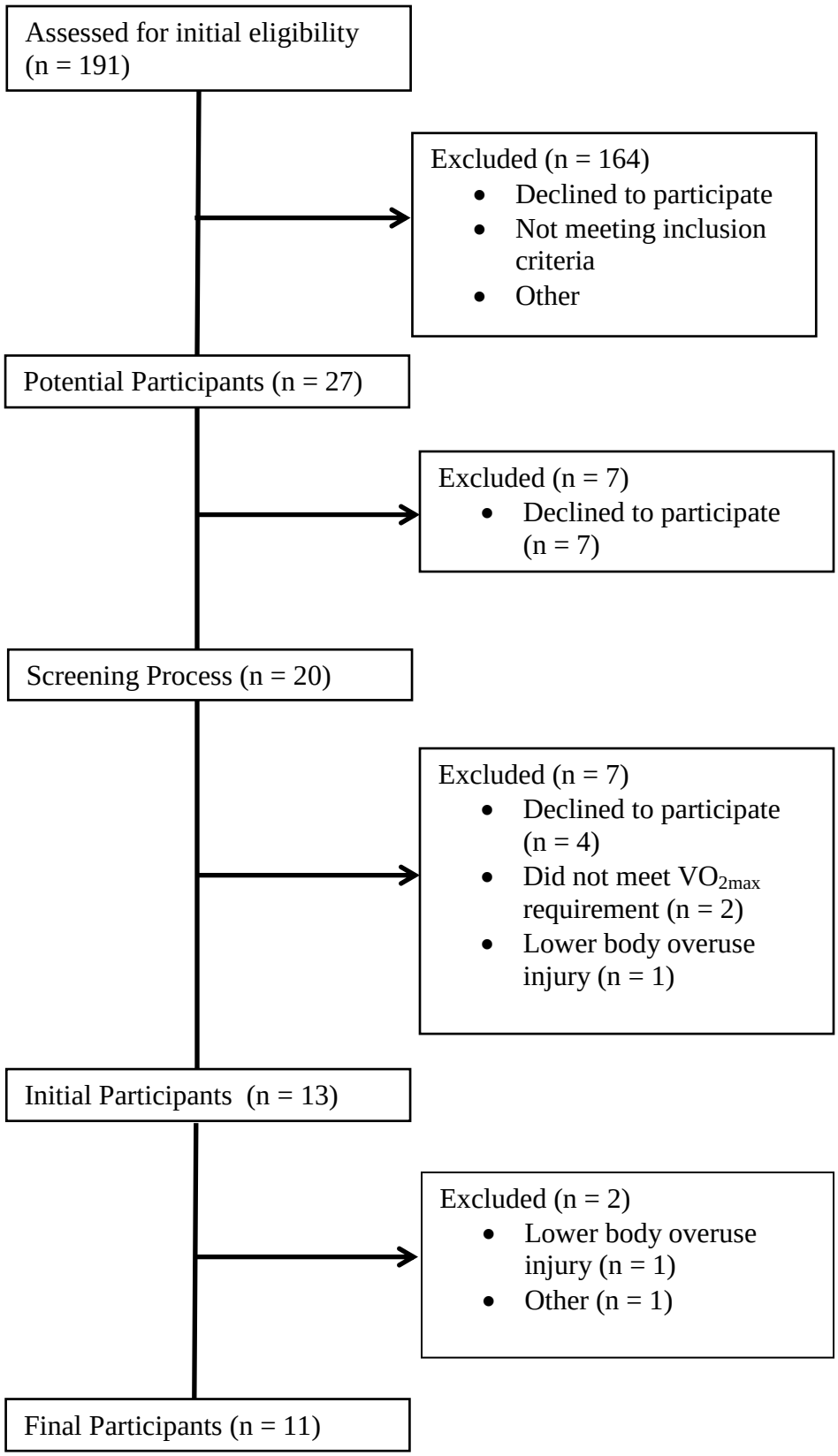


Figure 2. Recruitment of participants

Pre-Testing Procedures

Anthropometry

All participants underwent height and weight measurements. Both measurements were taken utilizing a Detecto Weigh Beam Eye-Level physician scale (Detecto Scale Company, Webb City, MO). The scale was calibrated prior to each use. Next, participants underwent a 7-site skinfold measurement test to analyze body composition. All skinfold measurements were performed by the primary investigator operating a Lange Skinfold Caliper (Beta Technology Incorporated, Cambridge, MD). Measurements were taken at the triceps, pectoral, midaxillary, subscapular, abdomen, suprailiac, and thigh locations and in that same order. A minimum of two measurements were taken at each skinfold site and the average of the two measurements was recorded. If there was a difference greater than ± 1mm between the initial two measurements, a third measurement was then taken and the average of the three measurements was recorded.

Hematological Measurements

Upon notification of selection to become a full participant in this study, all participants underwent an initial blood draw completed by OSU Health Services (OSUHS) employees at the OSUHS laboratory. Participants were provided documentation (Appendix H) to present to OSUHS employees to verify their participation in this study and to ensure that all accompanying costs were charged to the project's grant account. All participants completed the initial blood draw prior to their completion of the $VO_{2HH\text{-}pre}$ test. A complete blood count (CBC) analysis was performed by OSUHS laboratory technicians utilizing a Sysmex XS-1000*i* Automated Hematology Analyzer (Sysmex America, Inc., Lincolnshire, Illinois) to determine baseline measures

for the following variables: RBC volume, Hct volume, and Hb levels. Additional analysis was performed by Laboratory Corporation of America (Burlington, NC) to establish reference values of serum EPO for all participants utilizing the immunochemiluminometric assay (ICMA) methodology.

Normobaric Normoxia Maximal Aerobic Capacity

All potential participants completed a maximal aerobic capacity treadmill ergometer test in a normoxic setting ($VO_{2N\text{-}pre}$; $P_{B,}$ E 744 mm Hg; $FiO_{2,}$ 20.9%; Average temperature, 22.46° C; Average humidity, 42.23%) following a modified Astrand-Saltin protocol, a graded maximal aerobic capacity test consisting of 2-min stages (Table 1).

Table 1. Modified Astrand-Saltin protocol

Stage	Duration (sec)	Speed (km/h)	Pace (min/km)	Gradient (%)
Warm-up	300	9.66	6.21	0
1	120	14.48	4.14	0
2	120	14.48	4.14	2
3	120	14.48	4.14	4
4	120	14.48	4.14	6
5	120	14.48	4.14	8
6	120	14.48	4.14	10
Cool-down	120	2.41	24.90	0

Participants were instructed to abstain from strenuous exercise within 24 h of scheduled testing time as well as avoid caffeine consumption within 6 h of testing appointments. Prior to the commencement of the Astrand-Saltin protocol, arterial O_2 saturation as measured via pulse oximetry (SpO_2) was measured. The potential participants then completed a 5 min warm-up during which they ran on the treadmill ergometer at a speed of 6.0, the equivalent of a 10-min mi pace, and an incline gradient of 0%. Upon the completion of the warm-up, the testing protocol began and the treadmill ergometer speed increased to 9.0, the equivalent of a 6:40-min mi pace, while the incline gradient remained at 0%. The treadmill remained at this speed the duration of the test. At

the beginning of the second stage and each stage thereafter, the incline gradient increased by an amount of 2% until the participant reached exhaustion and ended the test. Upon the completion of the testing protocol, participants then completed a 2 min active recovery during which they walked on the treadmill at a speed of 1.5, the equivalent of a 40-min mi pace, and an incline gradient of 0%. All tests were completed on a Trackmaster treadmill (TMX 425C, Newton, KS) and expired gases were analyzed using a 4-breath average through a mixing chamber via a calibrated TrueOne® 2400 metabolic measuring system (Parvo Medics, Salt Lake City, UT). Per the work performed by Savourey et al. (2003), all volume measurements from VO_{2max} assessments were recorded under the body temperature pressure saturated (BTPS) condition. Additionally, HR was continuously monitored and maximum HR (HR_{max}) was recorded using a Polar HR monitor (Polar Electro FT1 and T31, Lake Success, NY). All subjects achieved at least two of the following criteria had been achieved: a plateau of O_2 consumption defined as a rise of less than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ between the final stages, a respiratory exchange ratio (RER) of 1.1 or greater, a blood lactate (BL) concentration $\geq$ 8.0 mmol/L, and HR_{max} within ± 10 beats/min of their age-predicted HR_{max} to meet the assumptions of a true maximal aerobic capacity test. The following variables from all normoxic and hypobaric hypoxic VO_{2peak} tests were recorded and analyzed: HR_{max} (BPM) time-to-exhaustion (TE; min), peak oxygen uptake (VO_{2peak}; $L \cdot min^{-1}$), peak carbon dioxide production (VCO_2; L/min), relative peak oxygen uptake (RVO_{2peak}; $mL \cdot kg^{-1} \cdot min^{-1}$), minute ventilation ($V_E$; $L \cdot min^{-1}$ – BTPS), tidal volume (V_T; $L \cdot min^{-1}$), breathing frequency (*f*; breaths per minute), end-tidal oxygen pressure ($PetO_2$; mmHg), and end-tidal carbon dioxide pressure ($PetCO_2$; mmHg).

Hypobaric Hypoxia Maximal Aerobic Capacity

Participants who met the VO_{2peak} minimum requirements during the pre-screening process in the normoxic environment then completed a maximal aerobic capacity treadmill ergometer test in the HH setting ($VO_{2HH\text{-}pre}$; Average $P_{B,}$ E 537.23 mm Hg; $F_iO_{2,}$ 20.9%; Average temperature, 26° C; Average humidity, 53.85%) at the OSU Center for Health Sciences (OSU-CHS) Center for Aerospace and Hyperbaric Medicine following a 2-7 d rest period after the $VO_{2N\text{-}pre}$ tests. Participants were instructed to abstain from strenuous exercise within 24 h of scheduled testing time as well as avoid caffeine consumption within 6 h of testing appointment. Prior to entering the HH chamber, all participants underwent blood pressure (BP), body temperature, and pulse readings performed by a RN. Participants then entered the HH chamber on an individual basis via an altitude elevator that was attached to the HH chamber, thus ensuring that the amount of simulated altitude exposure remained consistent for each participant prior to the start of each $VO_{2HH\text{-}pre}$ test. Approximately 5 min after entering the HH chamber, SpO_2 was measured. The same modified Astrand-Saltin protocol, as described in the previous paragraph and presented in Table 1, was utilized to carry out the $VO_{2HH\text{-}pre}$ testing. The test was completed on a Trackmaster treadmill (TMX 425C, Newton, KS) and expired gases were analyzed using a 4-breath average through a mixing chamber via a calibrated TrueOne® 2400 metabolic measuring system (Parvo Medics, Salt Lake City, UT). Per the work performed by Savourey et al. (2003), all volume measurements from VO_{2max} assessments were recorded under the BTPS condition. Additionally, HR was continuously monitored and HR_{max} was recorded using a Polar HR monitor (Polar Electro FT1 and T31, Lake Success, NY). All subjects achieved at least two of the

following criteria had been achieved: a plateau of O_2 consumption defined as a rise of less than 2 mL · kg^{-1} · min^{-1} between the final stages, an RER of 1.1 or greater, a BL concentration ≥ 8.0 mmol/L, and HR_{max} within ± 10 beats/min of their age-predicted HR_{max} to meet the assumptions of a true maximal aerobic capacity test. A board certified doctor of osteopathic medicine (DO) was present in the HH chamber for all VO_{2max} tests carried out in the hypobaric chamber. Upon exiting the HH chamber, each participant underwent BP, body temperature, and pulse readings performed by an RN.

Intervention Training Protocol

All subjects performed identical training protocols (Table 2) on Trackmaster TMX425 treadmill ergometers (Full Vision Inc., Kansas, USA), with the CON group performing the training sessions in a normoxic setting and the EXP group performing all training sessions in NH at a simulated altitude of 2750 m (FiO_2 = 15%).

Table 2. Intervention training protocol

	Warm-Up		Cardiovascular Training		Cool-Down	
Week	Duration (min)	Intensity (%HR_{max})	Duration (min)	Intensity (%HR_{max})	Duration (min)	Intensity (%HR_{max})
1	NA	NA	60	50-60%	NA	NA
2	10	50-60%	40	60-70%	10	50-60%
3	10	50-60%	40	70-77%	10	50-60%
4	10	50-60%	40	70-77%	10	50-60%
5	10	50-60%	10	60-70%	10	50-60%
			20	78-85%		
			10	60-70%		
6	10	50-60%	10	60-70%	10	50-60%
			20	78-85%		
			10	60-70%		

All normobaric hypoxic equipment was manufactured by Hypoxico Altitude Training Systems (New York, NY). As this research project was conducted with a single-blind experimental protocol in an attempt to reduce any nocebo effect, both the CON and

EXP groups completed the training sessions while wearing the High Altitude Training Masks (training masks). However, only the EXP participants' training masks (Figure 3) were connected to the Everest Summit II Altitude Generator (altitude generator).

Figure 3. EXP group training mask setup

Normobaric hypoxic conditions for the EXP group was simulated by diluting ambient air with nitrogen via the altitude generator. CON participants' training masks

were not connected to the altitude generator, thus allowing them to train under normoxic conditions (Figure 4).

Figure 4. CON group training mask setup

Participants were allowed to adjust the speed of the treadmill ergometer *ad libitum* so as to keep their HR within the prescribed HR ranges during the warm-up, exercise, and cool-down portions of each training session. The incline gradient of the treadmill ergometer was set to 2% for the duration of all training sessions. Prior to each

training session, each participant received their training prescription cards for the day and any necessary clarifications were provided prior to the start of the training session. Participants were then fitted with Polar HR monitors (Polar Electro FT1 and T31, Lake Success, NY) and the training masks. Training intensity for both groups was determined via a percentage of the HR_{max} achieved during the $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. The percentage of HR_{max} has been shown to be highly correlated to its respective percentage of VO_{2max} and thus an appropriate method for determining training intensities (Reis, Van den Tillaar, & Marques, 2011).

The training intervention was 6 wk in duration, with three 1 h training sessions per week for a total of 18 training sessions. All 3 training sessions during week 1 consisted of 60 min at 50-60% of VO_{2peak} as determined by $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. The 3 training sessions during the second week of the intervention period consisted of a 10 min warm-up and 10 min cool-down, both performed at 50-60% of $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. The work portion of all training sessions during week 2 was 40 min in duration with the intensity prescribed as 60-70% of $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. Training sessions for weeks 3 & 4 consisted of a 10 min warm-up and 10 min cool-down, both performed at 50-60% of $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. The work portion of all training sessions during weeks 3 and 4 was 40-min in duration with a prescribed intensity of 70-77% of $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. Training sessions for weeks 5 & 6 consisted of a stair-step design with a 10 min warm-up at 50-60%, 10 min at 60-70%, 20 min at 77-85%, 10 min at 60-70%, and 10 min cool-

down at 50-60% of $VO_{2N\text{-}pre}$ for the CON group and $VO_{2HH\text{-}pre}$ for the EXP group, respectively. There was a 24-48 h recovery period between each training session. As all subjects were current ROTC cadets, each participant continued their participation in their mandatory PT sessions throughout the duration of the intervention period. An independent samples *t*-test was performed in SPSS to determine if there were any differences in the average amount of time per participant performing PT between the CON and EXP groups. Distance travelled, elevation gain, average speed, and SpO_2 were recorded for all training sessions. In addition, FiO_2 was recorded for each training session completed by the EXP participants. All training sessions took place in the OSU Health & Human Performance (HHP) Laboratory under the supervision of the primary investigators or other HHP graduate assistants who held current cardiopulmonary resuscitation (CPR) certifications and had completed the necessary CITI Responsible Conduct of Research Training.

Post-Testing Procedures

Anthropometry

Post-testing procedures occurred 3-4 d after participants had completed their final training session. All participants completed a post-intervention weight measurement. Weight was taken utilizing a Detecto Weigh Beam Eye-Level physician scale (Detecto Scale Company, Webb City, MO). The scale was calibrated prior to each use. Next, participants underwent a 7-site skinfold measurement test to analyze body composition. All skinfold measurements were performed by the primary investigator operating a Lange Skinfold Caliper (Beta Technology Incorporated, Cambridge, MD). Measurements were taken at the triceps, pectoral, midaxillary, subscapular, abdomen, suprailiac, and thigh

locations and in that same order. A minimum of two measurements were taken at each skinfold site and the average of the two measurements was recorded. If there was a difference greater than ± 1mm between the initial two measurements, a third measurement was then taken and the average of the three measurements was recorded and used for analysis.

Hematological Measurements

Participants underwent a second blood draw completed by OSUHS employees at the UHS laboratory. Participants were provided documentation (Appendix H) to present to OSUHS employees to verify their participation in this study and to ensure that all accompanying costs were charged to the project's grant account. All participants completed the blood draw prior to their completion of the $VO_{2HH\text{-}post}$ test. A CBC analysis was performed by OSUHS laboratory technicians utilizing a Sysmex XS-1000*i* Automated Hematology Analyzer (Sysmex America, Inc., Lincolnshire, Illinois) to determine post-testing measures for the following variables: RBC volume, Hct volume, and Hb levels. Additional analysis was performed by Laboratory Corporation of America (Burlington, NC) to establish post-intervention values of serum EPO for all participants utilizing the ICMA methodology.

Normobaric Normoxia Maximal Aerobic Capacity

Participants completed a maximal aerobic capacity treadmill ergometer test in a normoxic setting ($VO_{2N\text{-}post}$; $P_{B,}$ E 744 mm Hg; $FiO_{2,}$ 20.9%; Average temperature, 22.46° C; Average humidity, 42.23%) following the identical modified Astrand-Saltin protocol utilized during the pre-testing procedures (Figure 2). Participants were instructed to abstain from strenuous exercise within 24 h of scheduled testing time as well as avoid

caffeine consumption within 6 h of testing appointment. Prior to the commencement of the Astrand-Saltin protocol, SpO_2 was measured. The participants then completed a 5 min warm-up during which they ran on the treadmill ergometer at a speed of 6.0, the equivalent of a 10-min mi pace, and an incline gradient of 0%. Upon the completion of the warm-up, the testing portion began and the treadmill ergometer speed increased to 9.0, the equivalent of a 6:40-min mi pace, while the incline gradient remained at 0%. The treadmill remained at this speed the duration of the test. At the beginning of the second stage and each stage thereafter, the incline gradient increased by an amount of 2% until the participant reached exhaustion and ended the test. Upon the completion of the testing protocol, participants then completed a 2 min active recovery during which they walked on the treadmill at a speed of 1.5, the equivalent of a 40-min mi pace, and an incline gradient of 0%. The test was completed on a Trackmaster treadmill (TMX 425C, Newton, KS) and expired gases were analyzed using a 4-breath average through a mixing chamber via a calibrated TrueOne® 2400 metabolic measuring system (Parvo Medics, Salt Lake City, UT). Per the work performed by Savourey et al. (2003), all volume measurements from VO_{2max} assessments were recorded under the BTPS condition. Additionally, HR was continuously monitored and HR_{max} was recorded using a Polar HR monitor (Polar Electro FT1 and T31, Lake Success, NY). All subjects achieved at least two of the following criteria had been achieved: a plateau of O_2 consumption defined as a rise of less than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ between the final stages, a RER of 1.1 or greater, a BL concentration $\geq$ 8.0 mmol/L, and HR_{max} within ± 10 beats/min of their age-predicted HR_{max} to meet the assumptions of a true maximal aerobic capacity test.

Hypobaric Hypoxia Maximal Aerobic Capacity

Participants also completed a VO_{2max} treadmill ergometer test in the HH chamber ($VO_{2HH\text{-}post}$; Average $P_{B,}$ E 537.23 mm Hg; $FiO_{2,}$ 20.9%; Average temperature, 26° C; Average humidity, 53.85%) at the OSU-CHS Center for Aerospace and Hyperbaric Medicine following a 3 d rest period. Participants were instructed to abstain from strenuous exercise within 24 h of scheduled testing time as well as avoid caffeine consumption within 6 h of testing appointment. Prior to entering the HH chamber, all participants underwent BP, body temperature, and pulse readings performed by an RN. Participants then entered the HH chamber on an individual basis via an altitude elevator that was attached to the HH chamber, thus ensuring that the amount of simulated altitude exposure remained consistent for each participant prior to the start of each $VO_{2HH\text{-}post}$ test. Approximately 5 min after entering the HH chamber, SpO_2 was measured. The same modified Astrand-Saltin protocol, as described previously, and presented in Figure 2, was utilized to carry out the $VO_{2HH\text{-}post}$ testing. The test was completed on a Trackmaster treadmill (TMX 425C, Newton, KS) and expired gases were analyzed using a 4-breath average through a mixing chamber via a calibrated TrueOne® 2400 metabolic measuring system (Parvo Medics, Salt Lake City, UT). Per the work performed by Savourey et al. (2003), all volume measurements from VO_{2max} assessments were recorded under the BTPS condition. Additionally, HR was continuously monitored and HR_{max} was recorded using a Polar HR monitor (Polar Electro FT1 and T31, Lake Success, NY). All subjects achieved at least two of the following criteria had been achieved: a plateau of O_2 consumption defined as a rise of less than 2 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} between the final stages, an RER of 1.1 or greater, a BL concentration $\geq$ 8.0 mmol/L, and HR_{max} within $\pm$ 10

beats/min of their age-predicted HR_{max} to meet the assumptions of a true maximal aerobic capacity test. A board certified DO was present in the HH chamber for all VO_{2max} tests carried out in the hypobaric chamber. Upon exiting the HH chamber, each participant underwent BP, body temperature, and pulse readings performed by an RN.

Follow-up Testing Procedures

Hematological Measurements

Follow-up testing occurred for EXP participants only. Upon completion of a 1 wk detraining period, which amounted to two weeks since the completion of participants' final IHT exposure, EXP participants underwent a third and final blood draw completed by OSUHS employees at the OSUHS laboratory. Participants were provided documentation (Appendix H) to present to OSUHS employees to verify their participation in this study and to ensure that all accompanying costs were charged to the project's grant account. All EXP participants completed the blood draw prior to their completion of the $VO_{2HH\text{-}FollowUp}$ test. A CBC analysis was performed by OSUHS laboratory technicians utilizing a Sysmex XS-1000*i* Automated Hematology Analyzer (Sysmex America, Inc., Lincolnshire, Illinois) to determine follow-up quantities for the following variables: RBC volume, Hct volume, and Hb levels. Additional analysis was performed by Laboratory Corporation of America (Burlington, NC) to establish follow-up values of serum EPO for EXP participants utilizing the ICMA methodology.

Hypobaric Hypoxia Maximal Aerobic Capacity

EXP participants (n = 6) completed a third and final VO_{2max} treadmill ergometer test in the HH chamber ($VO_{2HH\text{-}FollowUp}$; Average $P_{B,}$ E 537.23 mm Hg; $F_iO_{2,}$ 20.9%; Average temperature, 26° C; Average humidity, 53.85%) at the OSU-CHS Center for

Aerospace and Hyperbaric Medicine following a 1 wk detraining period, which established a 2 wk period between the final IHT exposure and the $VO_{2HH\text{-}FollowUp}$ tests. Participants were instructed to abstain from strenuous exercise within 24 h of scheduled testing time as well as avoid caffeine consumption within 6 h of testing appointment. Prior to entering the HH chamber, all participants underwent BP, body temperature, and pulse readings performed by an RN. Participants then entered the HH chamber on an individual basis via an altitude elevator that was attached to the HH chamber, thus ensuring that the amount of simulated altitude exposure remained consistent for each participant prior to the start of each $VO_{2HH\text{-}FollowUp}$ test. Approximately 5 min after entering the HH chamber, SpO_2 was measured. The same modified Astrand-Saltin protocol as was used for the pre- and post-testing procedures was utilized for the $VO_{2HH\text{-}FollowUp}$ testing. At the commencement of the recovery period, SpO_2 measurements were performed. The test was completed on a Trackmaster treadmill (TMX 425C, Newton, KS) and expired gases were analyzed using a 4-breath average through a mixing chamber via a calibrated TrueOne® 2400 metabolic measuring system (Parvo Medics, Salt Lake City, UT). Per the work performed by Savourey et al. (2003), all volume measurements from VO_{2max} assessments were recorded under the BTPS condition. Additionally, HR was continuously monitored and HR_{max} was recorded using a Polar HR monitor (Polar Electro FT1 and T31, Lake Success, NY). All subjects achieved at least two of the following criteria had been achieved: a plateau of O_2 consumption defined as a rise of less than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ between the final stages, an RER of 1.1 or greater, a BL concentration $\geq$ 8.0 mmol/L, and HR_{max} within ± 10 beats/min of their age-predicted HR_{max} to meet the assumptions of a true maximal aerobic capacity test. A board certified

DO was present in the HH chamber for all VO_{2max} tests carried out in the hypobaric chamber. Upon exiting the HH chamber, each participant underwent BP, body temperature, and pulse readings performed by an RN.

Statistical Analysis

Descriptive data will be presented as means ± standard deviation (SD) for participant characteristics and all testing variables. Mixed analysis of variance (ANOVA) will be performed on all variables to analyze differences between the within-subjects factor (time) and between-subjects factor (CON and EXP). Repeated measures ANOVA will be performed to analyze differences for all variables between the pre-, post-, and follow-up results of the EXP group. Significant main effects and interactions will be analyzed using Bonferroni correction. The level of statistical significance will be set at $p < 0.05$. Statistical analysis will be conducted using SPSS version 21.

CHAPTER IV

RESULTS

Subject Characteristics

There were no significant differences between the EXP and CON groups for height or age, P = 0.12 and P = 0.60, respectively. There was neither a significant main effect of time F(1,8) = 0.29, P = 0.60, nor training group of participants F(1,9) = 0.89, P = 0.37, nor was there a significant interaction of time x training group of the participants, F(1,9) = 0.12, P = 0.73 for BM. There was no significant main effect of time F(1,9) = 1.53, P = 0.25, nor training group of participants F(1,9) = 0.001, P = 0.98, nor was there a significant interaction of time x training group of the participants, F(1,9) = 3.11, P = 0.11 on the body fat percentages (BF%) of participants.

Table 3. Subject characteristics (Mean ± SD)

	CON		EXP	
Variable	Pre-test	Post-test	Pre-test	Post-test
Height (cm)	178.7 ± 8.17	N/A	176.42 ± 5.71	N/A
Body mass (kg)	78.59 ± 11.88	78.54 ± 12.25	73.54 ± 5.34	73.27 ± 5.73
Age (y)	18.80 ± 1.79	N/A	20.17 ± .75	N/A
Body fat (%)	8.59 ± 3.07	8.82 ± 3.68	9.43 ± 3.67	8.10 ± 2.83

N = 11 (CON, n = 5; EXP, n = 6) unless otherwise stated.

Training Volume

There was no significant difference between groups in training time (min) performed during PT, P = 0.56. Based on independent samples *t*-tests, there was no

significant difference in the average distance completed per training session (km) between groups for Week 1; however, the CON group completed significantly more km per training session during Week 2, 3.87 vs 3.58 km, P = 0.005, Weeks 3 & 4, 4.17 vs 3.92 km, P = 0.014, and Weeks 5 & 6, 4.22 vs 3.86 km, P = 0.002 (Table 4). Further, the average SpO_2 was, on average, significantly less in the EXP group than the CON group during each training session during Week 1, 84.79 vs 97.11%, P < 0.001, Week 2, 82.35 vs 96.85%, P < 0.001, Weeks 3 & 4, 82.30 vs 97.11%, P < 0.001, and Weeks 5 & 6, 84.24 vs 97.54%, P < 0.001 (Figure 5).

Table 4. Intervention protocol training volume (Mean ± SD)

		Week 1 Per Session	Week 2 Per Session	Weeks 3 & 4 Per Session	Weeks 5 & 6 Per Session	Totals
Distance Covered (km)	E	5.13 ± .58	5.76 ± .37^	6.30± .5*	6.22 ± .77^	95.9
	C	5.08 ± .47	6.23 ± .46	6.71 ± .62	6.79 ± .57	109.7
SpO_2 (50 min)	E	84.8 ± 3.16^	82.36 ± 2.68^	82.3 ± 2.68^	84.2 ± 2.15^	82.4
	C	97.1 ± 1.27	96.85 ± 1.76	97.11 ± 1.13	97.54 ± .58	97.2
Average Pace (min/km)	E	11:41	10:25	9:31	9:40	10:00
	C	11:49	9:38	8:57	8:50	9:17

* P < .05, ^ P < .01 for difference with CON.

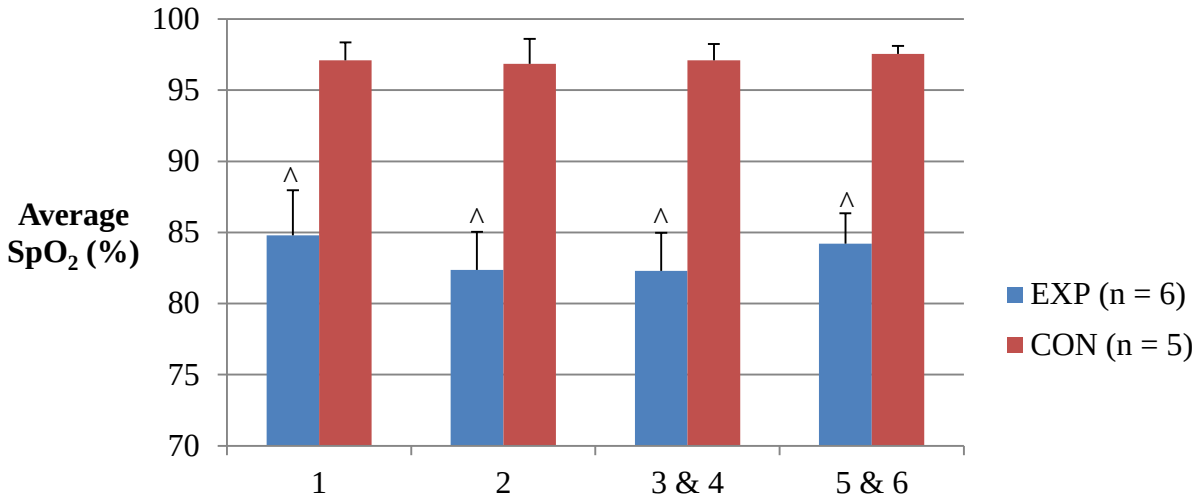


Figure 5. Training session average SpO_2. ^ $p < .01$, indicates the EXP group's SpO_2 was significantly lower than CON group. Values are mean ± SD.

Hematology

All hematological variables are summarized in Table 5. A summary of the repeated measures analysis of the pre-, post-, and follow-up testing for all hematological variables of the EXP group, as only the EXP group completed the follow-up testing procedures, is presented in Table 6.

Erythrocyte Volume

There was no significant interaction of time x training group of the participants, $F(1,8) = 0.24$, $P = 0.64$, nor main effect of training group of participants $F(1,8) = 4.61$, $P = 0.06$, nor was there a significant main effect of time $F(1,8) = 0.42$, $P = 0.54$, for RBC volume. Further, there was no significant difference at any time (pre-, post-, or follow-up testing) in RBC volume for the EXP participants, $F(2,1) = 5.68$, $P = 0.15$.

Hemoglobin Concentration

There was no significant interaction of time x training group of the participants, $F(1,8) = 0.47$, $P = 0.51$, nor was there a significant main effect of training group of

participants $F(1,8) = 2.99$, $P = 0.12$, nor was there a significant main effect of time $F(1,8) = 0.60$, $P = 0.46$, for Hb concentration. Further, there was no significant difference at any time (pre-, post-, or follow-up testing) in Hb concentration for the EXP participants, $F(2,1) = 4.81$, $P = 0.17$.

Hematocrit

There was no significant interaction of time x training group of the participants, $F(1,8) = 0.14$, $P = 0.72$, nor was there a significant main effect of training group of participants $F(1,8) = 3.61$, $P = 0.09$, nor was there a significant main effect of time $F(1,8) = 0.50$, $P = 0.50$, for Hct levels. Further, there was no significant difference at any time (pre-, post-, or follow-up testing) in Hct levels for the EXP participants, $F(2,1) = 4.51$, $P = 0.18$.

Serum Erythropoietin

There was no significant interaction of time x training group of the participants, $F(1,8) = 0.78$, $P = 0.40$, nor was there a significant main effect of training group of participants $F(1,8) = 0.64$ $P = 0.45$, nor was there a significant main effect of time $F(1,8) = 0.00$, $P = 0.99$, for serum EPO levels. Further, there was no significant difference at any time (pre-, post-, or follow-up testing) in EPO levels for the EXP participants, $F(2,1) = 0.93$, $P = 0.52$.

Table 5. Hematological parameters

		Pre-test			Post-test		
			95% CI			95% CI	
Variable	Group	Mean ± SD	Lower	Upper	Mean ± SD	Lower	Upper
RBC	EXP	5.10 ± .38	4.75	5.44	5.11 ± .46	4.75	4.46
(M/uL)	CON	4.63 ± .27	4.29	4.97	4.72 ± .17	4.36	5.07
	Mean	4.86 ± .40	4.62	5.11	4.91 ± .38	4.66	5.16
Hb (g/dL)	EXP	15.2 ± .77	14.44	15.96	15.22 ± 1.05	14.36	16.08
	CON	14.28 ± .69	13.52	15.04	14.6 ± .53	13.74	15.46
	Mean	14.74 ± .84	14.21	15.28	14.91 ± .85	14.30	15.52
Hct (%)	EXP	44.16 ± 2.70	41.91	46.41	44.36 ± 2.74	42.17	46.55
	CON	41.62 ± 1.48	39.37	43.87	42.28 ± 1.21	40.09	44.47
	Mean	42.89 ± 2.45	41.30	44.48	43.32 ± 2.28	41.77	44.87
Serum	EXP	8.48 ± 3.62	2.31	14.65	9.7 ± 3.80	5.12	14.29
EPO	CON	12.12 ± 7.65	5.95	18.29	10.94 ± 5.01	6.36	15.56
(mIU/mL)	Mean	10.3 ± 5.96	5.94	14.67	10.32 ± 4.24	7.08	13.56

N = 10 (EXP, n = 5; CON, n = 5) unless otherwise stated.

Table 6. EXP group hematological parameters (Mean ± SD)

Variable	Pre-test	Post-test	Follow-up
RBC (M/uL)	5.15 ± .42	5.19 ± .48	5.32 ± .38
Hb (g/dL)	15.25 ± .89	15.3 ± 1.20	15.78 ± .79
Hct (%)	44.05 ± 3.11	44.7 ± 3.04	45.83 ± 2.21
Serum EPO (mIU/mL)	9.3 ± 3.61	8.43 ± 2.90	8.35 ± 2.00

N = 4 unless otherwise stated.

Normobaric Normoxia Maximal Aerobic Capacity

Maximum Heart Rate

There was no significant interaction of time x training group $F(1,8) = 0.38$, $P = 0.55$, nor was there a significant main effect of time $F(1,8) = 0.04$, $P = 0.84$. However, there was a significant difference in HR_{max} measured during NN aerobic capacity pre- and post-testing (3.63% and 4%, respectively) between training groups, $F(1,8) = 11.87$, $P = 0.01$. HR_{max} and all other normoxic maximal aerobic capacity variables are summarized in Table 7.

Time-to-Exhaustion

There was no significant interaction of time x training group, $F(1,8) = 0.56$, $P = 0.48$, nor significant main effect of training group, $F(1,8) = 0.06$, $P = 0.81$, nor significant main effect of time $F(1,8) = 0.002$, $P = 0.97$, on TE measured during NN aerobic capacity testing.

Maximal Oxygen Uptake

There was no significant interaction of time x training group, $F(1,8) = 2.03$, $P = 0.19$, nor was there a significant main effect of training group, $F(1,8) = 3.65$, $P = 0.09$. However, there was a significant main effect of time $F(1,8) = 10.09$, $P = 0.01$ for VO_{2peak} as demonstrated by a 5.44% increase from pre- to post-testing measures.

Relative Maximal Oxygen Uptake

There was no significant interaction of time x training group, $F(1,8) = 5.18$, $P = 0.46$, nor was there a significant main effect of training group, $F(1,8) = 0.19$, $P = 0.68$. However, there was a significant main effect of time $F(1,8) = 6.88$, $P = 0.03$ for RVO_{2peak} as demonstrated by a 5.31% increase from pre- to post-testing measures.

Minute Ventilation

There was a significant, ordinal interaction of time x training group on V_E, $F(1,8) = 6.29$, $P = 0.04$. Further analysis utilizing a paired samples *t*-test revealed no difference ($P = 0.24$) in V_E for the CON group and a significant ($P = 0.04$) 3.92% decrease in V_E

from the pre- to post-testing for the EXP group.

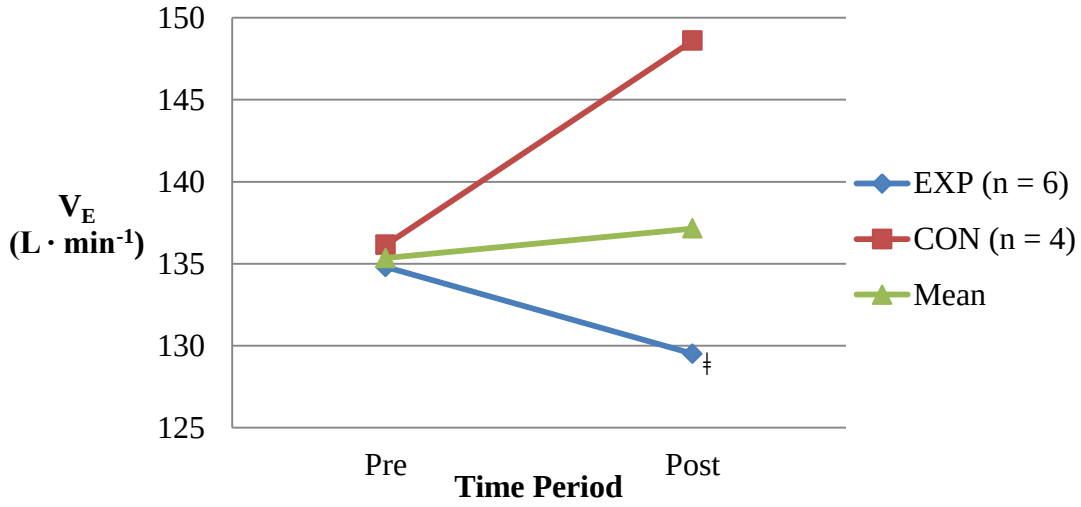


Figure 6. NN maximal V_E. ǂ $p < .05$, indicates a significant interaction of time x training group.

Breathing Frequency

There was no significant interaction of time x training group, F(1,8) = 1.61, P = 0.24, nor significant main effect of training group, F(1,8) = 0.002, P = 0.97, nor significant main effect of time F(1,8) = 0.42, P = 0.54, *f* measured during NN aerobic capacity testing.

Tidal Volume

There was no significant interaction of time x training group, F(1,8) = 0.07, P = 0.80, nor significant main effect of training group, F(1,8) = 0.29, P = 0.65, nor significant main effect of time F(1,8) = 1.39, P = 0.27, on V_T measured during NN aerobic capacity testing.

End-tidal Oxygen Pressure

There was no significant interaction of time x training group, F(1,8) = 0.95, P = 0.36, nor significant main effect of training group, F(1,8) = 1.28, P = 0.29, nor significant

main effect of time $F(1,8) = 1.22$, $P = 0.30$, on $PetO_2$ measured during NN aerobic capacity testing.

End-tidal Carbon Dioxide Pressure

There was no significant interaction of time x training group, $F(1,8) = 1.99$, $P = 0.20$, nor significant main effect of time $F(1,8) = 0.04$, $P = 0.84$, nor significant main effect of training group, $F(1,8) = 1.28$, $P = 0.29$ on $PetCO_2$ measured during NN aerobic capacity testing.

Arterial Oxygen Saturation

There was no significant interaction of time x training group $F(1,9) = 0.02$, $P = 0.90$ on SpO_2 levels. There was also no significant main effect of training group $F(1,9) = 0.54$, $P = 0.48$, however, there was a significant main effect of time $F(1,9) = 16.95$, $P = 0.003$ as demonstrated by a 1.89% decrease in mean SpO_2 from pre- to post-testing assessment in the NN condition.

Table 7. Normobaric normoxia VO_2 test parameters

		Pre-test		Post-test	
			95% CI		95% CI
Variable	Group	Mean ± SD	Lower, Upper	Mean ± SD	Lower, Upper
HR_{max}	EXP	199.50 ± 1.37	196.56, 202.44	200.00 ± 1.67	188.64, 195.87
(BPM)	CON	192.25 ± 4.79	196.29, 203.71	192.00 ± 6.06	187.46, 196.54
	Mean	196.60 ± 4.77	193.55, 198.20	196.80 ± 5.55	193.07, 198.93
TE	EXP	11.23 ± 1.90	9.49, 12.97	11.36 ± 1.90	9.82, 12.89
(min)	CON	11.64 ± 1.75	9.51, 13.78	11.50 ± 1.05	9.61, 13.38
	Mean	11.39 ± 1.76	10.06, 12.81	11.41 ± 1.54	10.21, 12.64
VO_{2peak}	EXP	5.64 ± .82	4.95, 6.32	5.83 ± .50	5.3, 6.36
($L \cdot min^{-1}$)	CON	6.26 ± .53	5.42, 7.09	6.76 ± .66	6.11, 7.41
	Mean	5.88 ± .76	5.41, 6.49	6.20 ± .72*	5.87, 6.71
RVO_{2peak}	EXP	61.55 ± 7.00	55.88, 67.23	64.01 ± 5.45	58.94, 69.08
($mL \cdot min^{-1} \cdot kg^{-1}$)	CON	62.01 ± 3.92	55.05, 68.96	66.54 ± 5.27	60.34, 72.75
	Mean	61.74 ± 5.69	57.29, 66.27	65.02 ± 5.24*	61.27, 69.28
V_E	EXP	134.80 ± 16.95	119.27, 150.33	129.51 ± 18.20ǂ	108.00, 151.02
($L \cdot min^{-1}$)	CON	136.15 ± 15.70	117.13, 155.17	148.61 ± 28.98	122.27, 174.95
	Mean	135.34 ± 15.57	123.20, 147.75	137.15 ± 23.69	122.06, 156.06
V_T	EXP	2.73 ± .63	2.24, 3.21	2.84 ± .55	2.32, 3.36
($L \cdot min^{-1}$)	CON	2.85 ± .24	2.25, 3.45	3.02 ± .55	2.39, 3.66
	Mean	2.78 ± .49	2.40, 3.17	2.91 ± .53	2.52, 3.34
f	EXP	50.68 ± 7.07	44.68, 56.69	46.73 ± 8.78	39.86, 53.59
	CON	47.90 ± 5.02	40.55, 55.26	49.19 ± 3.63	40.78, 57.60
	Mean	49.57 ± 6.18	44.54, 54.04	47.71 ± 6.99	42.53, 53.39
$PetO_2$	EXP	121.35 ± 2.51	119.00, 123.71	118.84 ± 3.12	114.76, 122.91
(mm Hg)	CON	117.99 ± 2.48	115.11, 120.87	117.83 ± 5.80	112.85, 122.82
	Mean	120.01 ± 2.93	117.81, 121.53	118.43 ± 4.11	115.12, 121.55
$PetCO_2$	EXP	34.45 ± 1.79	32.68, 36.22	35.60 ± 3.97	32.24, 38.95
(mm Hg)	CON	39.24 ± 2.03	37.07, 41.41	37.69 ± 2.75	33.59, 41.80
	Mean	36.37 ± 3.05	35.44, 38.25	36.44 ± 3.53	33.99, 39.30
SpO_2	EXP	98.58 ± .66	98.05, 99.12	96.67 ± 1.21	95.42, 97.92
(%)	CON	98.20 ± .45	97.62, 98.79	96.40 ± 1.52	95.03, 97.77
	Mean	98.41 ± .58	98.00, 98.79	96.55 ± 1.29^	95.61, 97.46

N = 10 (EXP, n = 6; CON, n = 4) unless otherwise stated.
TE, time-to-exhaustion; $VO_{2peak,}$ maximal oxygen uptake; RVO_{2peak}, relative oxygen uptake; V_E, minute ventilation (BTPS); V_t, tidal volume; *f*, breathing frequency; $PetO_2$, end-tidal O_2 pressure; $PetCO_2$, end-tidal CO_2 pressure.
* P < .05, ^ P < .01 for difference with Pre-test.
ǂ P < .05 for significant interaction of time x training group.

Hypobaric Hypoxia Maximal Aerobic Capacity

All hypobaric hypoxia maximal aerobic capacity variables are summarized in Table 8. A summary of the repeated measures analysis of the pre-, post-, and follow-up testing variables of the aerobic capacity tests in the hypobaric hypoxic conditions, as only the EXP group completed the follow-up testing procedures, is presented in Table 9.

Maximum Heart Rate

There was no significant interaction of time x training group $F(1,9) = 0.97$, $P = 0.35$, partial $\acute{\eta}^2 = 0.097$, nor was there a significant difference between training groups, $F(1,9) = 2.25$, $P = 0.17$, nor a significant main effect of time $F(1,9) = 0.71$, $P = 0.42$, in HR_{max} measured during the hypobaric hypoxia aerobic capacity testing. Further, there was no significant difference of HR_{max} in the EXP group between pre-, post-, and follow-up assessments in the hypobaric hypoxic chamber, $F(2,3) = 0.75$, $P = 0.53$.

Time-to-Exhaustion

There was no significant interaction of time x training group, $F(1,9) = 1.17$, $P = 0.31$, partial $\acute{\eta}^2 = 0.115$, nor significant main effect of training group, $F(1,9) = 0.03$, $P = 0.86$, nor was there a significant main effect of time $F(1,9) = 3.35$, $P = 0.10$, on TE measured during aerobic capacity testing in hypobaric hypoxia. Further, there was no significant difference of TE in the EXP group between pre-, post-, and follow-up assessments in the hypobaric hypoxic chamber, $F(2,3) = 3.99$, $P = 0.11$.

Maximal Oxygen Uptake

There was no significant interaction of time x training group, $F(1,9) = 2.12$, $P = 0.18$, partial $\acute{\eta}^2 = 0.19$, nor was there a significant main effect of training group, $F(1,9) = 2.84$, $P = 0.13$. However, there was a significant main effect of time $F(1,9) = 22.06$, $P = 0.001$ for VO_{2peak} as demonstrated by an 11.48% increase from pre- to post-testing measures of aerobic capacity testing in hypobaric hypoxia, as is seen in Figure 7. There was a significant difference in VO_{2peak} between the three aerobic capacity tests performed by the EXP group as further analysis revealed a significant increase of 15.99% from pre-

to post-testing, P = 0.03, with no significant difference between the pre- and follow-up tests, P = 0.07, nor between the post- and follow-up assessments, P = 0.55.

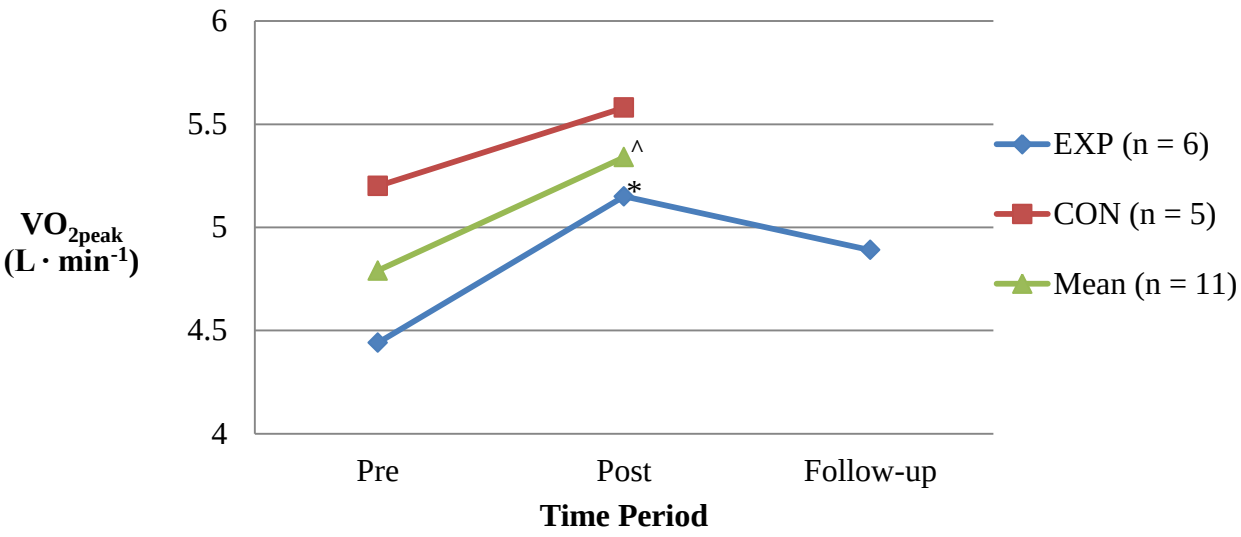


Figure 7. HH peak O_2 uptake. * p < .05, ^ p < .001, indicates a significant main effect of time.

Relative Maximal Oxygen Uptake

There was no significant interaction of time x training group, F(1,9) = 1.64, P = 0.23, partial $\acute{\eta}^2$ = 0.15, nor was there a significant main effect of training group, F(1,9) = 0.61, P = 0.45. However, there was a significant main effect of time F(1,9) = 6.88, P = 0.03 for RVO_{2peak} as demonstrated by an 11.13% increase from pre- to post-testing assessments of aerobic capacity testing in hypobaric hypoxia; however, Further, there was no significant difference of RVO_{2peak} in the EXP group between pre-, post-, and follow-up assessments in the hypobaric hypoxic chamber, F(2,3) = 6.53, P = 0.06. However, while neither reached statistical significance, there was a 14.71% increase from the pre- to post-test and a 4.79% decrease from the post-test to the follow-up test, resulting in a net gain of 9.21% of RVO_{2peak}.

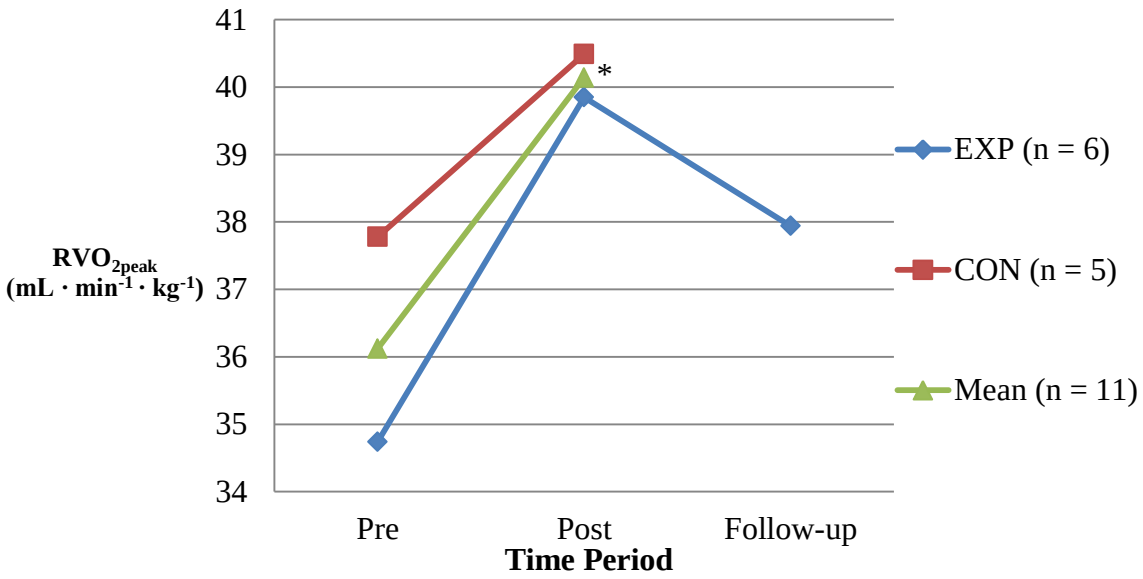


Figure 8. HH relative peak O_2 uptake. * $p < .05$, indicates a significant main effect of time.

Minute Ventilation

There was no significant interaction of time x training group, F(1,9) = 1.23, P = 0.30, partial $\acute{\eta}^2$ = 0.12, nor a significant main effect of training group, F(1,9) = 4.27, P = .07, nor significant main effect of time F(1,9) = 2.21, P = 0.17, on V_E measured during aerobic capacity testing in hypobaric hypoxia. There was no significant difference of V_E in the EXP group between pre-, post-, and follow-up aerobic capacity assessments in the hypobaric hypoxic chamber, F(2,3) = 5.33, P = 0.053.

Breathing Frequency

There was no significant interaction of time x training group, F(1,9) = 0.18, P = 0.68, partial $\acute{\eta}^2$ = 0.02, nor a significant main effect of training group, F(1,9) = 0.23, P = 0.64, nor was there a significant main effect of time F(1,9) = 0.35, P = 0.57, on *f* measured during aerobic capacity testing in hypobaric hypoxia. Additionally, there was no significant difference of *f* in the EXP group between pre-, post-, and follow-up assessments in the hypobaric hypoxic chamber, F(2,3) = 0.427, P = 0.679.

Tidal Volume

There was no significant interaction of time x training group, $F(1,9) = 0.07$, $P = 0.80$, partial $\acute{\eta}^2 = 0.05$ nor a significant main effect of training group, $F(1,9) = 0.29$, $P = 0.65$ on V_T. However, there was a significant main effect of time on V_T, $F(1,9) = 7.89$, $P = 0.02$, as demonstrated by an increase in V_T of 8.75% from pre- to post-assessment of aerobic capacity in hypobaric hypoxia. Further, the repeated measures analysis of V_T during the three testing times for the EXP group displayed a significant difference, $F(2,3) = 14.59$, $P = 0.02$, and further analysis revealed a significant increase in V_T of 10.48% from the pre-test to the follow-up test, $P < 0.01$.

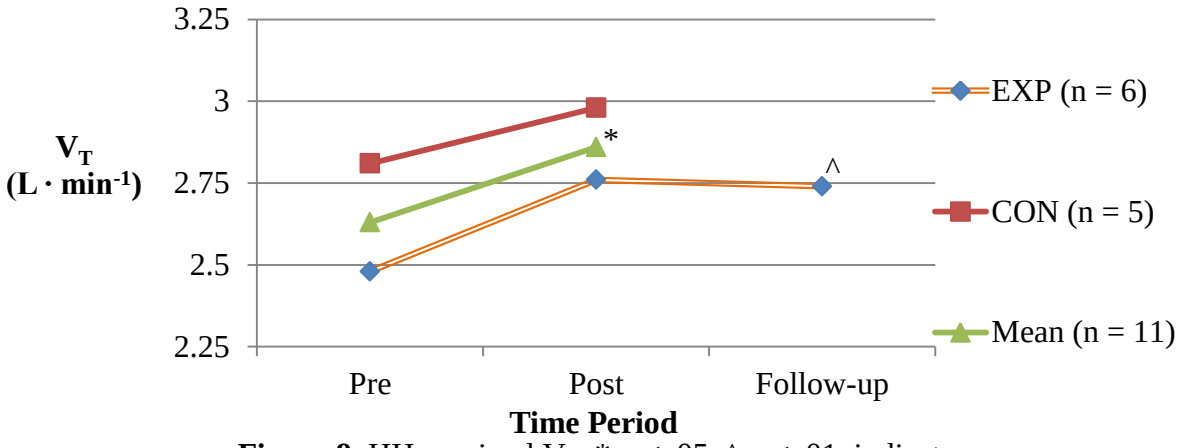


Figure 9. HH maximal V_T. * $p < .05$, ^ $p < .01$, indicates significant main effect of time.

End-tidal Oxygen Pressure

There was no significant interaction of time x training group, $F(1,9) = 0.02$, $P = 0.90$, partial $\acute{\eta}^2 = 0.002$, nor significant main effect of training group, $F(1,9) = 0.00$, $P = 1.00$, nor was there a significant main effect of time $F(1,9) = 0.49$, $P = 0.50$, on $PetO_2$ measured during aerobic capacity testing in hypobaric hypoxia. There was no significant difference in $PetO_2$ present in the EXP group between pre-, post-, and follow-up aerobic capacity assessments in the hypobaric hypoxic chamber, $F(2,3) = 3.59$, $P = 0.13$.

End-tidal Carbon Dioxide Pressure

There was no significant interaction of time x training group, $F(1,9) = 0.11$, $P = 0.75$, partial $\acute{\eta}^2 = 0.01$, nor a significant main effect of training groups, $F(1,9) = 0.10$, $P = 0.77$, nor was there a significant main effect of time $F(1,9) = 1.18$, $P = 0.31$, on $PetCO_2$ measured during aerobic capacity testing in hypobaric hypoxia. There was no significant difference in $PetCO_2$ present in the EXP group between pre-, post-, and follow-up aerobic capacity assessments in the hypobaric hypoxic chamber, $F(2,3) = 5.461$, $P = 0.07$.

Arterial Oxygen Saturation

There was a significant, disordinal interaction of time x training group $F(1,9) = 7.71$, $P = 0.02$, partial $\acute{\eta}^2 = 0.46$. Further analysis utilizing a paired samples *t*-test revealed a non-significant, $P = 0.18$, increase of 2.39% in SpO_2 values for the EXP group and a concurrent, significant, $P = .03$, decrease of 2.72% in SpO_2 values for the CON group from the pre- to post-testing measurements conducted in the HH chamber. Further, there was no significant difference in SpO_2 present in the EXP group between pre-, post-, and follow-up aerobic capacity assessments in the hypobaric hypoxic chamber, $F(2,3) = 1.733$, $P = 0.23$.

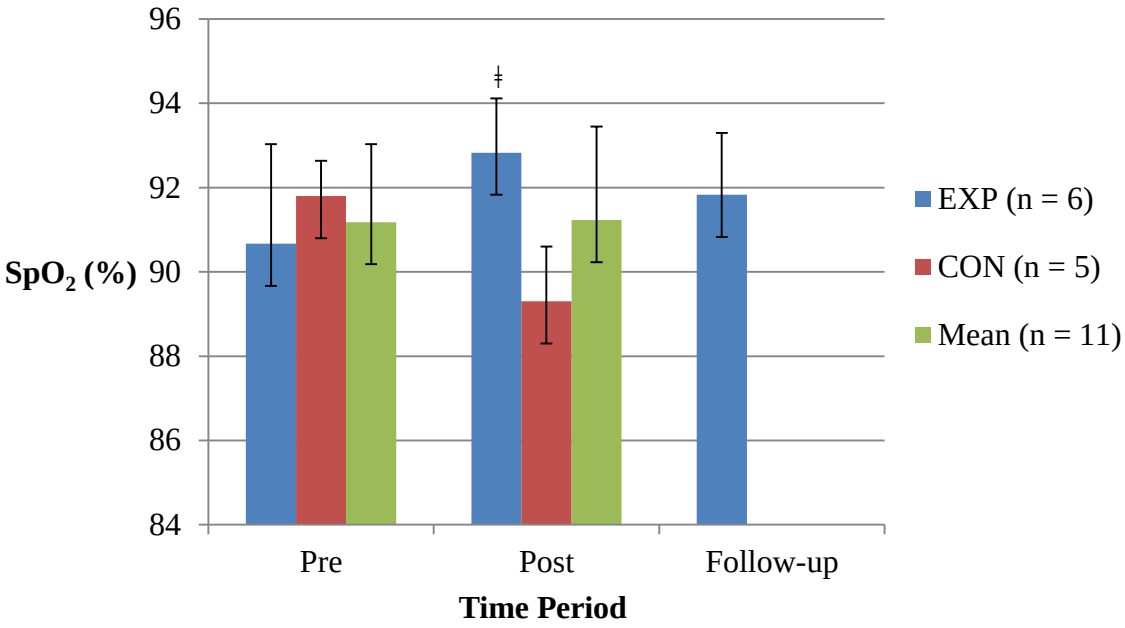


Figure 10. HH resting SpO_2. ǂ $p < .05$, indicates significant interaction of time x training group. Values are mean ± SD.

Table 8. Hypobaric hypoxia VO_2 test parameters

		Pre-test		Post-test	
			95% CI		95% CI
Variable	Group	Mean ± SD	Lower, Upper	Mean ± SD	Lower, Upper
HR_{max} (BPM)	EXP	192.17 ± 4.96	185.97, 198.37	187.00 ± 10.24	179.62,194.38
	CON	184.20 ± 8.41	177.41, 190.99	184.60 ± 3.58	176.51, 192.69
	Mean	188.55 ± 7.61	183.59,192.78	185.91 ± 7.69	180.33, 191.28
TE (min)	EXP	8.96 ± 1.29	7.82, 10.11	9.62 ± 1.65	8.23, 10.01
	CON	9.06 ± 1.18	7.81, 10.32	9.23 ± 1.30	7.71, 10.75
	Mean	9.01 ± 1.18	8.16, 9.86	9.45 ± 1.44	8.40, 10.46
VO_{2peak}	EXP	4.44 ± .50	3.86, 5.03	5.15 ± .63	4.60, 5.70
($L \cdot min^{-1}$)	CON	5.20 ± .77	4.56, 5.85	5.58 ± .54	4.97, 6.18
	Mean	4.79 ± .72	4.39, 5.26	5.34 ± .61^	4.95, 5.77
RVO_{2peak}	EXP	34.74 ± 3.86	30.72, 38.76	39.85 ± 3.01	36.15, 43.56
($mL \cdot min^{-1} \cdot kg^{-1}$)	CON	37.78 ± 4.90	33.38, 42.19	40.49 ± 4.99	36.43, 44.55
	Mean	36.12 ± 4.42	33.28, 39.24	40.14 ± 3.82^	37.42, 42.92
V_E	EXP	130.13 ± 18.58	109.16, 151.10	140.53 ± 14.98	125.78, 155.29
($L \cdot min^{-1}$)	CON	157.70 ± 26.98	134.73, 180.77	159.21 ± 17.15	143.04, 175.37
	Mean	142.66± 25.91	128.36, 159.46	149.02 ± 18.03	138.93, 160.82
V_T	EXP	2.48 ± .41	2.16, 2.80	2.76 ± .64	2.28, 3.25
($L \cdot min^{-1}$)	CON	2.81 ± .25	2.46, 3.16	2.98 ± .33	2.45, 3.51
	Mean	2.63 ± .37	2.41, 2.88	2.86 ± .51*	2.51, 3.23
f	EXP	53.00 ± 6.37	46.22, 59.78	52.66 ± 9.72	44.04, 61.27
	CON	56.11 ± 8.40	48.68, 63.54	54.02 ± 8.81	44.58, 63.46
	Mean	54.42 ± 7.15	49.53, 59.59	53.28 ± 8.88	46.95, 59.73
$PetO_2$	EXP	91.39 ± 1.09	89.98, 97.80	91.64 ± .97	90.51, 92.77
(mm Hg)	CON	91.33 ± 1.93	89.79, 92.88	91.71 ± 1.48	90.47, 92.94
	Mean	91.36 ± 1.45	90.32, 92.41	91.67 ± 1.16	90.84, 92.51
$PetCO_2$	EXP	18.40 ± 1.24	16.88, 19.93	18.72 ± .62	17.60, 19.84
(mm Hg)	CON	18.51 ± 2.06	16.83, 20.18	19.09 ± 1.68	17.86, 20.32
	Mean	18.45 ± 1.57	17.32, 19.59	18.89 ± 1.17	18.07, 19.73
SpO_2 (%)	EXP	90.67 ± 2.36	88.96, 92.37	92.83 ± 1.29ǂ	91.64, 94.03
	CON	91.80 ± .84	89.93, 93.67	89.30 ± 1.30	87.99, 90.61
	Mean	91.18 ± 1.85	89.97, 62.50	91.23 ± 2.22	90.18, 91.96

N = 11 (EXP, n = 6; CON, n = 5) unless otherwise stated.

TE, time-to-exhaustion; $VO_{2peak,}$ maximal oxygen uptake; RVO_{2peak}, relative oxygen uptake; V_E, minute ventilation (BTPS); V_T, tidal volume; *f*, breathing frequency; $PetO_2$, end-tidal O_2 pressure; $PetCO_2$, end-tidal CO_2 pressure.

* P < .05, ^ P < .01 for difference with Pre-test.

ǂ P < .05 for significant interaction of time x training group.

Table 9. EXP group hypobaric hypoxia VO_2 parameters (Mean ± SD)

Variable	Pre-test	Post-test	Follow-up
HR_{max} (BPM)	192.17 ± 4.96	187 ± 10.24	185 ± 10.28
TE (min)	8.96 ± 1.29	9.62 ± 1.65	9.28 ± 1.91
VO_{2peak} ($L \cdot min^{-1}$)	4.44 ± .50	5.15 ± .63*	4.89 ± .61
RVO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$)	34.74 ± 3.86	39.85 ± 3.01	37.94 ± 4.12
V_E ($L \cdot min^{-1}$)	130.13 ± 18.58	140.53 ± 14.98	143.23 ± 10.12
V_T ($L \cdot min^{-1}$)	2.48 ± .41	2.76 ± .64	2.74 ± .44^
f	53 ± 6.37	52.66 ± 9.72	53.15 ± 6.89
$PetO_2$ (mm Hg)	91.39 ± 1.09	91.64 ± .97	92.93 ± .94
$PetCO_2$ (mm Hg)	18.40 ± 1.24	18.72 ± .62	18.09 ± .73^
SpO_2 (%)	90.67 ± 2.36	92.83 ± 1.29	91.83 ±1.47

N = 6 unless otherwise stated.

TE, time-to-exhaustion; $VO_{2peak,}$ maximal oxygen uptake; RVO_{2peak}, relative oxygen uptake; V_E, minute ventilation (BTPS); V_t, tidal volume; *f*, breathing frequency; $PetO_2$, end-tidal O_2 pressure; $PetCO_2$, end-tidal CO_2 pressure.

* $P < .05$, ^ $P < .01$ for difference with Pre-test.

CHAPTER V

DISCUSSION

The primary findings of the current investigation revealed that NIHT failed to elicit significantly greater aerobic endurance performance enhancements in either the NN or HH condition when compared to NN endurance training. Further, NIHT did not induce significant adaptations of the blood's O_2-carrying capacity compared to endurance training in NN. However, the results do suggest that the NIHT protocol induced some level of altitude acclimatization via a significant interaction of time and training group as evidenced by a simultaneous 2.39% increase and 2.72% decrease in resting SpO_2 levels measured in HH for the EXP and CON groups, respectively. Additionally, while nonsignificant, the EXP group tended to display greater signs of HVR adaptations than the CON group as a result of increased V_E and V_T measurements in the HH chamber.

Training Intervention

There was no significant difference in reported PT training volume performed externally and in addition to the intervention training protocol ($P = 0.56$) between the EXP and CON groups, which tends to suggest that any reported differences during the post- and follow-up assessments were primarily the result of the differences in the EXP and CON endurance training programs. Further, while there was not a significant difference in the average distance (km) completed during Week 1, the EXP group

completed significantly fewer km per session during Weeks 2-6, leading to an average of 13.8 fewer km covered for each EXP participant compared to each CON participant. The detriment to training volume brought about by a decrease in O_2 availability is often cited as an argument against only performing endurance training in hypoxic conditions (Dufour et al., 2006; Hoppeler et al., 2008; Ponsot et al., 2006), as is the case with traditional altitude training strategies. Additionally, the average SpO_2 value recorded during each training session of EXP participants was significantly lower ($P < .01$) at 82.4% while the CON participants' average SpO_2 was 97.2%. These results indicate that the FiO_2 of 15% utilized during the NIHT sessions was sufficient to induce hypoxia. As the current study only required 3 h of NIHT each week, participants were also able to perform higher-intensity training sessions in addition to the intervention protocol. This may be advantageous in that the hypoxic stimulus remains supplementary to, and not deleterious to total training volume.

A potential benefit of NIHT and other discontinuous altitude exposures is the reduction of the risk of detrimental BM losses that may occur with extended altitude sojourns (Zaccagni et al., 2014). The results of the present study support the reduction of such a risk as no significant differences in either BM or BF% were found between the EXP and CON groups following the intervention training protocol. However, while prior works have reported other prospective detriments of prolonged training camps at higher elevations such as sleep disturbances and compromised immune function (Friedmann-Bette, 2008; Christopher John Gore et al., 2007; Rusko et al., 2004; Sargent et al., 2013), the current investigation did not examine such factors as they relate to NIHT and there remains a need for future inquiries in this area.

Effects of NIHT on Hematological Parameters

No changes in RBC, Hb, Hct, or serum EPO levels were observed following the completion of the training intervention; nor were any changes observed after the EXP group's 1 wk detraining period. Thus, the data appear to indicate that the currently prescribed NH exposure duration (60 min · d^{-1} x 3 d · wk^{-1} x 6 wk) and severity (FiO_2 = 15% or 2750 m) is insufficient to induce any alterations in the aforementioned hematological variables. The present results are in agreement with prior works that have reported no discernable changes in blood parameters following IHT protocols. While the current investigation utilized NH, the majority of HH-based IHT interventions have also reported a similar lack of efficacy of IHT to enhance the O_2-carrying capacity of blood. Prior investigations utilizing IHT protocols ranging in exposure times of 30-90 min · d^{-1} x 3-5 d · wk^{-1} x 3-6 wk and simulated altitudes ranging from 2300-4000 m have reported no changes to RBC, Hb_{con}, and/or Hct levels in highly-trained individuals (Terrados et al., 1988; Vallier et al., 1996; N. Ventura et al., 2003). However, there is precedence for HH-based IHT to stimulate hematological alterations. Following a protocol design of 105 min · d^{-1} x 10 consecutive days design and HH corresponding to 2500 m, the authors reported a significantly elevated Hb_{con} 2 d after the completion of the intervention, a change not correlated to a decreased PV. However, the elevated Hb_{con} proved short-lived as it returned to near baseline levels when participants were tested 1 wk later (Hendriksen & Meeuwsen, 2003).

In regards to NIHT protocols, the majority of the prior investigations have reported no significant alterations in RBC, Hb_{con}, and/or Hct, nor EPO levels. The NIHT exposure durations and simulated altitude severity are wide-ranging in nature, yet are in

agreement that the hypoxic stimulus was insufficient to induce hematological adaptations. To illustrate, previous studies employing NIHT protocols similar in nature to the present investigation and varying from 30-115 min · d^{-1} x 2-5 d · wk^{-1} x 4-7 wk and FiO_2 of 14.5-15.3%, equivalent to elevations of 2500-3000 m, all reported no changes to the hematology of participants. Based on the available evidence, it appears the both HH- and NH-based IHT interventions have been equally ineffective to induce any hematological adaptations often correlated to endurance performance.

However, factors other than the hypoxic stimulus may be at least partially responsible for the lack of any significant changes. For example, the majority of IHT protocols utilize training sessions shorter in duration than what has previously been recommended as the minimal amount of time of 2 h to stimulate EPO production (Eckardt et al., 1989; Hahn & Gore, 2001; Rasmussen et al., 2013). Further, EPO production reaches its apex approximately 3-4 d after exposure to the hypoxic stimulus; thus, the timing of both the blood draw and the analysis of the hematological parameters may be crucial. In the present study, participants' blood draws were performed 3-5 d after their final training session. If any changes were induced via the NIHT protocol, the time lag between the final training session and the post-testing blood draw may have proved too long for any change to be detected. Finally, it is also possible that current IHT practices do not employ a severity of hypoxia adequate to stimulate EPO production during the limited exposure times. For example, one of the earlier investigations into EPO production stimulation reported that by increasing the simulated altitude from 3000 m to 4000 m, the time required to elicit significant increases in EPO levels declines from 114 min to 84 min, respectively (Eckardt et al., 1989). However, the aforementioned

study was based on an IHE protocol, and not IHT, highlighting the tradeoff between altitude severity and workload intensity that separates IHE and IHT protocols. Therefore, if the primary objective is to increase the hematological variables correlated with aerobic endurance performance, altitude training strategies employing longer duration exposures and/or greater levels of hypoxia, such as LHTL and IHE, may prove more efficacious than IHT.

Effects of NIHT on endurance performance in normobaric normoxia

In regards to HR_{max} during aerobic capacity testing under NN conditions, the results of the present investigation are comparable to the majority of previous studies reporting no observable changes following IHT. Further, both HH-based (Hendriksen & Meeuwsen, 2003; Vallier et al., 1996) and NIHT (Dufour et al., 2006; Roels et al., 2007) protocols have failed to elicit adaptations to HR_{max} during maximal capacity testing. However, the effects of IHT on HR_{max} under NN conditions are far from conclusive. For example, it has been previously reported that 6 wk of NIHT was sufficient to lead to significant reductions in the HR_{max} achieved during a VO_{2max} performed on a cycle ergometer. However, the same study yielded a statistically stronger reduction in HR_{max} for the NIHT group ($P < 0.05$) compared to the NN-trained group ($P < 0.10$), leading the authors to proclaim that the reduction in HR_{max} for the NN-trained group was more of a statistical tendency (N. Ventura et al., 2003). Further, it should be noted that each of the aforementioned studies utilized trained- to highly-trained individuals, a population in which one would not expect to find significant reductions in HR_{max} after a relatively brief (i.e. less than 6 wk), intervention period. Contrarily, it has been well established that a reduction in HR after the completion of a training intervention by previously untrained

individuals is to be expected due to the added training stimulus. Therefore, it may be proposed that if the combination of hypoxia and training volume (intensity x duration) is sufficient, it may be possible to elicit similar reductions in HR_{max} of trained individuals following IHT protocols. While the current literature appear to refute such a possibility, the work by N. Ventura et al. (2003) demonstrated such an adaptation should not be ruled out as of yet. This may be of practical importance as a decreased HR_{max} could potentially indicate an ability to perform submaximal workloads at lower energy costs to the individual.

In the present study, while TE remained unaltered and unaffected by training group, both VO_{2peak} ($P = 0.01$) and RVO_{2peak} ($P = 0.03$) measured in the NN condition increased significantly after the 6 wk training intervention protocol. However, while there was no statistically significant difference between training groups ($P = 0.093$), the CON group tended to demonstrate more pronounced increases than the EXP group for both VO_{2peak} (7.99 vs. 3.37%) and RVO_{2peak} (7.31 vs. 4.0%). As a result, the findings from the current inquiry are in agreement with previous works utilizing trained participants and reporting no perceivable effect on endurance performance in NN between hypoxic or normoxic training groups. Hendriksen and Meeuwsen (2003), utilizing a cross-over design and highly-trained triathletes, reported insignificant improvements in SL VO_{2max} of 1.9% and 2.0% after a 9-10 d training intervention in HH and NN, respectively. Morton and Cable (2005), employing a 4 wk NIHT protocol of 30 min training sessions at the same FiO_2 utilized in the present study, 15%, reported a significant 7.2% increase in SL VO_{2max}, but no discernable difference between the NIHT and NN training groups. Further, a 4 wk NIHT program has previously been shown to improve both VO_{2max} and

time-trial cycling performance in elite cyclists in the NN condition, with no significant difference between training conditions. Similar to the current study, the aforementioned inquiry also allowed participants to complete their regular training agendas in addition to the supervised laboratory training sessions (Lecoultre et al., 2010).

However, not all NIHT protocols have proven effective at improving SL aerobic endurance performance. One such inquiry, which utilized trained cyclists and a 30 min · d^{-1} x 3 d · wk^{-1} x 6 wk and simulated altitude equivalent to 3200 m, characteristics that are similar in nature to the present investigation, reported no significant change to VO_{2max} measured at SL (N. Ventura et al., 2003). Contrary to the aforementioned study, there is limited evidence that NIHT may be more effective than normoxic training to improve SL aerobic endurance performance at or near SL. Dufour et al. (2006) reported significant increases in both VO_{2max} and TE in the NIHT group, but not the NN trained group after a 6 wk intervention. One potential explanation for the varying efficacy of IHT, whether utilizing HH or NH, appears to be the training volume performed under hypoxia. The implementation of various training intensities and hypoxic severities may prove vital in the outcome of IHT practices to improve aerobic endurance performance at SL and low altitudes.

Another interesting finding from the current investigation is the change seen in maximal ventilatory properties during aerobic capacity testing at SL. Maximal V_E during NN post-testing revealed a significant interaction ($P < .05$) of time x training group as demonstrated by a 9.15% increase in V_E for the CON group and a concurrent 3.92% decrease in V_E for the EXP group. The current results are in direct contrast to prior works reporting no changes of maximal V_E measured in NN following an either an NIHT

protocol (Dufour et al., 2006; Lecoultre et al., 2010; N. Ventura et al., 2003) or an HH-based IHT protocol (Vallier et al., 1996). Further, the present results represent a more drastic departure from previously reported alterations in resting ventilatory parameters. Katayama et al. (2000) reported a slight, insignificant increase in HVR at rest following IHT and a significant decline in HVR for the NN training group. Yet, there is one inquiry in which maximal V_E alterations similar to the current study were reported. Roels et al. (2007) reported an insignificant 9% increase of maximal V_E under NN testing conditions for the NN-trained group with virtually no change reported in the experimental group following a 3 wk NIHT protocol.

A potential explanation for the observed changes in V_E may be the result of alterations to *f* during testing. While insignificant, the results of the current study indicate a 7.79% decrease and simultaneous 2.69% increase in *f* for the EXP and CON groups, respectively. Further, V_T appears unlikely to have had such an influence as similar increases in V_T of 4.03% and 5.96% occurred in the EXP and CON groups, respectively. Adding to the intrigue of the is the similarity between the other ventilatory parameters, including $PetO_2$ and $PetCO_2$, neither of which were shown to be greatly impacted by the change in V_E. While Katayama et al. (1999) also reported no alterations in either $PetO_2$ or $PetCO_2$, their measurements were performed at rest and the results of the current study were obtained at the time VO_{2peak} was reached. However, together, these results may indicate that IHT does not impact such variables at rest nor during exercise, yet more evidence is needed before any conclusions may be drawn. The HVR typically results in the onset of hyperventilation to offset the reduction in PO_2, such a response to hypoxic conditions may potentially be detrimental to SL performance due to the increased energy

demands of respiration during high intensity exercise. However, the current results appear to indicate the opposite of the accepted rationale. It remains unclear what led to such a striking divergence from the accepted logic regarding ventilatory adaptations, thus future studies utilizing similar training protocols are warranted to either support or refute the current findings.

Effects of NIHT on endurance performance in hypobaric hypoxia

A primary interest of the current investigation was whether or not the prescribed NIHT protocol was adequate to induce significant alterations in aerobic performance parameters measured in an HH setting equivalent to an altitude of 3033 m (10,000 ft). Demonstrating the need for effective acclimatization methods, not only to present or reduce cases of high-altitude illnesses, but also to restore the endurance performance capabilities that are often lost upon acute altitude exposure. To that point, the current study revealed a 41.5% decrease in mean RVO_{2max} from the NN to the HH condition during pre-testing and a 38.27% decrement during post-testing. While the aforementioned results indicate a greater decrement than what has previously been reported (Peter Bärtsch & Gibbs, 2007; M Burtscher et al., 2006; Chapman et al., 1999; Muza, 2007), the individual variability that has been documented (Chapman, 2013) as well as the fact that hypoxia has been reported to lead to greater aerobic capacity detriments in trained than untrained individuals (Raphael Faiss et al., 2014). Therefore, exploring potential methods to induce acclimatization and offset such declines are of great importance to military personnel (Krueger, 1993; Muza, 2007).

HR_{max} remained unaltered for either group following the intervention protocol and the current findings are in agreement with the majority of prior studies indicating IHT

protocols are insufficient to induce such changes during acute hypoxic exposures (Beidleman et al., 2014; Dufour et al., 2006; Geiser et al., 2001; Hendriksen & Meeuwsen, 2003; Ofner et al., 2014). Although HR_{max} showed no sign of change following the training intervention, there was still a significant ($P < 0.01$) decline in mean HR_{max} of 4.09% and 5.53% during pre- and post-testing, respectively, from the NN to the HH conditions. Further, the current results are in agreement with previous work (Pascal Mollard et al., 2007).

Although there were no statistically significant changes in TE to report, the interaction's partial $\acute{\eta}^2$ value of 0.12 revealed a moderate effect size, thus, the potential for practical implications. While the mean TE only slightly improved, more marked differences between training groups were observed. Again, while not statistically significant, the EXP group's TE increased by 7.37% from pre- to post-testing, whereas the CON group only increased TE by 1.88%. The EXP group's increase represents an increase of approximately 40 s for TE in an HH setting, which would appear to have practical significance. As combat operations have been reported to consist of endurance activities of varying intensity levels (Henning et al., 2011), an increase in TE of 40 s during maximal exercise may provide the difference between success and failure of a mission.

Analogous to the observed aerobic capacity changes in NN, both VO_{2peak} ($P < 0.01$) and RVO_{2peak} ($P < 0.05$) significantly improved following the intervention training period. However, neither VO_{2peak} nor RVO_{2peak} revealed a statistically significant interaction or main effect of training group. Yet, based on the reported partial $\acute{\eta}^2$ value of 0.19, the results tend to indicate a difference that may be of practical significance. In the

present study, the VO_{2peak} achieved by the EXP group increased by 15.99%, whereas the CON only demonstrated an increase of 7.31%. In a similar fashion, RVO_{2peak} of the EXP group increased by 14.71% compared to only a 7.17% increase in the CON group. As the EXP group demonstrated increases in O_2 uptake more than twice the level of increase achieved by the CON group, the practical significance, partial $\acute{\eta}^2 = 0.15$, may indeed outweigh the lack of statistical significance, which is potentially a result of the low number of participants rather than the measured changes. The current findings are in agreement with the limited number of previous NIHT studies that reported significant improvements of aerobic performance under hypoxic conditions, yet no discernable differences between the control and experimental groups (Roels et al., 2007; N. Ventura et al., 2003). Further, prior works utilizing HH-based IHT protocols have also demonstrated equivocal aerobic performance outcomes under hypoxic conditions as some have reported significant enhancements (Roskamm et al., 1969; Terrados et al., 1988) while more recent works have reported no performance differences between the IHT and control groups (Holliss et al., 2014). The literature as it relates to LHTL strategies to improve hypoxic endurance performance is not only scarce, but also equivocal as previous studies have reported significant improvements in such parameters (Schuler et al., 2007) while others have failed to do so (Siebenmann et al., 2012). The ambivalent nature of altitude training strategies, excluding LHTH, to improve performance at altitude, may be due to the high degree of variability present in methodologies as differences such as the use of a control group, exposure duration, and exposure severity remain. While the available literature as it relates to IHT and subsequent VO_{2max} performance during hypoxic conditions remains somewhat limited (Muza, 2007; Roels et

al., 2007) and therefore difficult to formulate any concrete assumptions as to its efficacy, the aforementioned works and the findings from the present study appear to provide justification for continued research efforts in this area.

In terms of the ventilatory parameters during maximal exercise in the HH setting, an interesting pattern emerged, which may suggest a somewhat enhanced HVR for the EXP compared to the CON group. Similar to some of the aforementioned variables, maximal V_E did not reach statistical significance following the intervention period; however, based on the moderate effect size, partial $\acute{\eta}^2 = 0.12$, there is some evidence of practical significance for an elevated ventilatory response in the EXP group compared to the CON group. This is demonstrated by a 7.99% increase in V_E for the EXP group with only a 0.95% increase in V_E measured in the CON group. This alteration was most likely the result of the changes in V_T rather than *f*, as the former displayed a significant increase ($P < 0.05$) from pre- to post-assessments, while the latter revealed negligible changes. Further, and the likely cause of the discrepancy in V_E between training groups were the increases in V_T of 11.29% and 6.05% for the EXP and CON groups, respectively. This would appear to indicate that the EXP participants were able to take deeper breaths during maximal effort exercise in acute hypoxia.

The current results represent a direct contrast to what has been previously reported as multiple investigations detailed decreased V_T and increased *f* during hypoxic exposures. Further, each of these works examined the difference in physiological responses to NH compared to HH during rest, indicating both the decrease in V_T and increase in *f* are intensified by HH compared to NH. These varied responses have led to the acceptance that, in terms of simulated altitude, HH is preferable to NH to induce

acclimatization (Raphael Faiss et al., 2013; Loeppky et al., 1997; Savourey et al., 2003). Additional studies have examined the alterations in ventilatory parameters during exercise and reported that the same trends revealed during resting conditions tend to be exaggerated during submaximal exercise (Engelen et al., 1996; Mateika & Duffin, 1994), yet not during maximal exertion (Stang et al., 2014). The ventilatory adaptations observed in the present investigation are of particular interest for two specific reasons. First, the cause of the increase in V_E during the current study is likely an increase in V_T and not *f*, which is in direct contrast to previously reported results. This is of potential importance as it may indicate deeper breaths being taken, theoretically allowing greater time for O_2 extraction. However, based on $PetO_2$ and $PetCO_2$ measurements in the current study, this claim cannot be substantiated and therefore, additional examinations of this question appear warranted. Second, there may be some indication that NIHT potentially elicits physiological adaptations that transfer to an HH setting. Resting SpO_2 measurements revealed an interaction of both statistical ($P < .05$) and practical significance (partial $\acute{\eta}^2 = 0.46$) following the 6 wk intervention protocol. This interaction was exhibited via a 2.38% increase ($P = 0.18$) and 2.72% decrease ($P = 0.03$) in SpO_2 measured in the HH condition for the EXP and CON groups, respectively. As decreased SaO_2 levels have previously been shown to reduce endurance performance capabilities (Amann & Calbet, 2008; Calbet et al., 2003a; Pascal Mollard et al., 2007), increases to resting SaO_2 levels may potentially and positively impact endurance performance in hypoxic conditions. Although it should be noted that increasing SaO_2 levels in and of itself will not restore aerobic capacity to SL values (Calbet et al., 2003b), increases in

such physiological variables may still be encouraging indications of the potential ability of NIHT to induce acclimatization.

CHAPTER VI

CONCLUSION

Limitations

The current investigation utilized trained, male ROTC Cadets as participants. Our primary incentive for the use of said participants was to potentially increase the applicability of our results to military personnel that may be required to deploy to high-altitude locations without the benefit of a sufficient acclimatization period. However, as a result of the stringent inclusion criteria, the potential for a sufficient sample size, in terms of statistical power, to reduce the risk of Type II errors was compromised. To this point, none of the interactions achieved a $\beta > 0.26$. Further discussion of this study's limitations and delimitations may be found on pages 13-14.

Conclusions

The present study was designed to examine the hypothesis that a 6 wk NIHT protocol would elicit significant aerobic capacity enhancements and that these improvements would be greater in the EXP group compared to the CON group. A secondary aim was to determine if the prescribed intervention would be sufficient to induce hematological adaptations typically associated with aerobic performance. In terms of the latter, this hypothesis was not supported in this inquiry. In terms of the former, while there may have not been statistically significant results to support this hypothesis, some trends did emerge that may be of practical

importance. First, despite no significant differences in TE measured in the HH condition, EXP participants tended to display greater increases compared to their CON counterparts. In fact, EXP participants increased their TE by approximately 40 s, whereas the CON participants only increased TE by approximately 10 s. Further, while the mean VO_{2peak} and mean RVO_{2peak} both revealed significant increases from pre- to post-testing in the HH chamber, the EXP group demonstrated percentage increases that were more than twice that of the CON group. It should be noted that both groups displayed significantly greater aerobic capacity measures in the NN testing condition as well, but with more regularity of improvement between the training groups. Therefore, this may potentially indicate the NIHT protocol was somewhat, although not statistically, effective to improve endurance performance under hypoxic conditions. Finally, the EXP group displayed some tendencies that may indicate some form of ventilatory adaptation. The combination of a significantly reduced V_E during maximal exercise in the NN condition and the significant increase of SpO_2, as well as the tendency for an increased V_T during the hypoxic testing condition displayed by the EXP group may denote more efficient breathing during maximal exercise in both NN and HH settings following the NIHT protocol. To the authors' knowledge, this is the first study to examine the efficacy of endurance training in NH to improve aerobic endurance performance in HH utilizing trained ROTC cadets. The aforementioned improvements in aerobic capacity may have substantial performance and injury risk implications during military operations in high-altitude locations. Given the significance of aerobic capacity to sustain moderate intensity efforts as well as recover from bouts of maximal exertion, the decrements hypoxia poses to both the former and the latter are of great practical and functional importance for

present day military operations. Further, as military personnel operating in mountainous regions are already functioning near their VO_{2max} genetic ceiling, any enhancements may literally prove to be the difference between life and death. Due to the perceived potential for NIHT to improve endurance performance during acute hypoxic exposure, as well as the tremendous risks undertaken during combat operations, research efforts in this area must continue in an attempt to determine the ideal acclimatization strategy or strategies.

Future Investigations

The current investigation provides additional understandings of the potential effects of intermittent hypoxic training strategies to improve aerobic endurance performance in HH settings. Specifically, the potential for the utilization of NIHT to elicit endurance performance enhancements during acute exposure to an HH condition. While there are noted differences in the physiological responses to NH and HH, there are a limited number of investigations that have utilized the former for IHT sessions while testing in the latter. Further, the current findings displayed some signs of acclimatization related to the HVR, but not in regards to hematological changes related to blood's O_2-carrying capacity. Therefore, keeping in mind the generally lower costs (financial, ease of access, etc.) of NH compared to HH, further studies appear warranted. In particular, future research should seek to expand upon the currently available evidence related to the NIHT dosage necessary to elicit physiological changes related to altitude acclimatization. Additionally, prospective studies should seek to expand upon the existing evidence regarding the potential for the use of NIHT to enhance aerobic and anaerobic performance in both acute and extended altitude exposures.

REFERENCES

Amann, M., & Calbet, J. A. (2008). Convective oxygen transport and fatigue. *Journal of applied physiology, 104*(3), 861-870.

Ashenden, M. J., Gore, C. J., Dobson, G. P., Boston, T. T., Parisotto, R., Emslie, K. R., . . . Hahn, A. G. (2000). Simulated moderate altitude elevates serum erythropoietin but does not increase reticulocyte production in well-trained runners. *European journal of applied physiology, 81*(5), 428-435.

Ashenden, M. J., Gore, C. J., Martin, D. T., Dobson, G. P., & Hahn, A. G. (1999). Effects of a 12-day "live high, train low" camp on reticulocyte production and haemoglobin mass in elite female road cyclists. *European journal of applied physiology and occupational physiology, 80*(5), 472-478.

Aulin, K. P., Svedenhag, J., Wide, L., Berglund, B., & Saltin, B. (1998). Short-term intermittent normobaric hypoxia-haematological, physiological and mental effects. *Scandinavian journal of medicine & science in sports, 8*(3), 132-137.

Bardwell, W. A., Ensign, W. Y., & Mills, P. J. (2005). Negative mood endures after completion of high-altitude military training. *Annals of Behavioral Medicine, 29*(1), 64-69.

Bärtsch, P., & Gibbs, J. S. R. (2007). Effect of altitude on the heart and the lungs. *Circulation, 116*(19), 2191-2202.

Bärtsch, P., & Saltin, B. (2008). General introduction to altitude adaptation and mountain sickness. *Scandinavian journal of medicine & science in sports, 18*(s1), 1-10.

Bebout, D., Story, D., Roca, J., Hogan, M., Poole, D., Gonzalez-Camarena, R., . . . Wagner, P. (1989). Effects of altitude acclimatization on pulmonary gas exchange during exercise. *Journal of applied physiology, 67*(6), 2286-2295.

Beidleman, B. A., Fulco, C. S., Staab, J. E., Andrew, S. P., & Muza, S. R. (2014). Cycling performance decrement is greater in hypobaric versus normobaric hypoxia. *Extreme Physiol Med, 3*(8), 10.1186.

Beidleman, B. A., Muza, S. R., Fulco, C. S., Cymerman, A., Ditzler, D., Stulz, D., . . . Sawka, M. N. (2004). Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clinical Science, 106*(3), 321-328.

Beidleman, B. A., Muza, S. R., Fulco, C. S., Cymerman, A., Sawka, M. N., Lewis, S. F., & Skrinar, G. S. (2007). Seven intermittent exposures to altitude improves exercise performance at 4300 m. *MEDICINE, 195*, 9131i9108i4001-0141i9130.

Beidleman, B. A., Muza, S. R., Rock, P. B., Fulco, C. S., Lyons, T. P., Hoyt, R. W., & Cymerman, A. (1997). Exercise responses after altitude acclimatization are retained during reintroduction to altitude. *Medicine and science in sports and exercise, 29*(12), 1588-1595.

Benoit, H., Busso, T., Castells, J., Geyssant, A., & Denis, C. (2003). Decrease in peak heart rate with acute hypoxia in relation to sea level VO2max. *European journal of applied physiology, 90*(5-6), 514-519.

Bonetti, D. L., & Hopkins, W. G. (2009). Sea-level exercise performance following adaptation to hypoxia. *Sports medicine, 39*(2), 107-127.

Braun III, W. G., & Allen, C. D. (2014). Shaping a 21st-Century Defense Strategy. *JFQ, 73*(2nd Quarter).

Brocherie, F., Millet, G. P., Hauser, A., Steiner, T., Rysman, J., Wehrlin, J. P., & Girard, O. (2015). Live high-train low and high" hypoxic training improves team-sport performance. *Med Sci Sports Exerc. doi, 10*, 1249.

Brugniaux, J. V., Schmitt, L., Robach, P., Jeanvoine, H., Zimmermann, H., Nicolet, G., . . . Richalet, J.-P. (2006). Living high-training low: tolerance and acclimatization in elite endurance athletes. *European journal of applied physiology, 96*(1), 66-77.

Brugniaux, J. V., Schmitt, L., Robach, P., Nicolet, G., Fouillot, J.-P., Moutereau, S., . . . Chorvot, M.-C. (2006). Eighteen days of "living high, training low" stimulate erythropoiesis and enhance aerobic performance in elite middle-distance runners. *Journal of applied physiology, 100*(1), 203-211.

Burtscher, M. (2005). The athlete at high altitude: performance diminution and high altitude illnesses: review article. *International SportMed Journal: The Extreme Environment and Sports Medicine: Part 1, 6*(4), p. 215-223.

Burtscher, M., Brandstätter, E., & Gatterer, H. (2008). Preacclimatization in simulated altitudes. *Sleep and Breathing, 12*(2), 109-114.

Burtscher, M., Faulhaber, M., Flatz, M., Likar, R., & Nachbauer, W. (2006). Effects of short-term acclimatization to altitude (3200 m) on aerobic and anaerobic exercise performance. *International journal of sports medicine, 27*(8), 629-635.

Burtscher, M., Gatterer, H., Faulhaber, M., Gerstgrasser, W., & Schenk, K. (2010). Effects of intermittent hypoxia on running economy. *International journal of sports medicine, 31*(9), 644-650.

Calbet, J. A., Boushel, R., Rådegran, G., Søndergaard, H., Wagner, P. D., & Saltin, B. (2003a). Determinants of maximal oxygen uptake in severe acute hypoxia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 284*(2), R291-R303.

Calbet, J. A., Boushel, R., Rådegran, G., Søndergaard, H., Wagner, P. D., & Saltin, B. (2003b). Why is V˙ o 2 max after altitude acclimatization still reduced despite normalization of arterial O2 content? *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 284*(2), R304-R316.

Calbet, J. A., Rådegran, G., Boushel, R., Søndergaard, H., Saltin, B., & Wagner, P. D. (2004). Plasma volume expansion does not increase maximal cardiac output or VO2 max in lowlanders acclimatized to altitude. *American Journal of Physiology-Heart and Circulatory Physiology, 287*(3), H1214-H1224.

Chapman, R. F. (2013). The individual response to training and competition at altitude. *British Journal of Sports Medicine, 47*(Suppl 1), i40-i44.

Chapman, R. F., Emery, M., & Stager, J. (1999). Degree of arterial desaturation in normoxia influences VO~ 2~ m~ a~ x decline in mild hypoxia. *Medicine and science in sports and exercise, 31*, 658-663.

Chapman, R. F., Karlsen, T., Resaland, G. K., Ge, R.-L., Harber, M. P., Witkowski, S., . . . Levine, B. D. (2014). Defining the "dose" of altitude training: how high to live for optimal sea level performance enhancement. *Journal of applied physiology, 116*(6), 595-603.

Chapman, R. F., Stickford, A. S. L., Lundby, C., & Levine, B. D. (2014). Timing of return from altitude training for optimal sea level performance. *Journal of applied physiology, 116*(7), 837-843.

Chapman, R. F., Stray-Gundersen, J., & Levine, B. D. (1998). Individual variation in response to altitude training. *Journal of applied physiology, 85*(4), 1448-1456.

Cheung, S. S. (2010). *Advanced Environmental Exercise Physiology*. Champaign, IL: Human Kinetics.

Clark, S. A., Quod, M., Clark, M., Martin, D., Saunders, P., & Gore, C. (2009). Time course of haemoglobin mass during 21 days live high: train low simulated altitude. *European journal of applied physiology, 106*(3), 399-406.

Coppel, J., Hennis, P., Gilbert-Kawai, E., & Grocott, M. P. (2015). The physiological effects of hypobaric hypoxia versus normobaric hypoxia: a systematic review of crossover trials. *Extreme physiology & medicine, 4*(1), 1.

Daniels, J. (1979). Altitude and athletic training and performance. *The American journal of sports medicine, 7*(6), 371-373.

Debevec, T., & Mekjavic, I. B. (2012). Short intermittent hypoxic exposures augment ventilation but do not alter regional cerebral and muscle oxygenation during hypoxic exercise. *Respiratory physiology & neurobiology, 181*(2), 132-142.

Dufour, S. P., Ponsot, E., Zoll, J., Doutreleau, S., Lonsdorfer-Wolf, E., Geny, B., . . . Billat, V. (2006). Exercise training in normobaric hypoxia in endurance runners. I. Improvement in aerobic performance capacity. *Journal of applied physiology, 100*(4), 1238-1248.

Eckardt, K.-U., Boutellier, U., Kurtz, A., Schopen, M., Koller, E. A., & Bauer, C. (1989). Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. *Journal of applied physiology, 66*(4), 1785-1788.

Engelen, M., Porszasz, J., Riley, M., Wasserman, K., Maehara, K., & Barstow, T. J. (1996). Effects of hypoxic hypoxia on O2 uptake and heart rate kinetics during heavy exercise. *Journal of applied physiology, 81*(6), 2500-2508.

Faiss, R., Girard, O., & Millet, G. P. (2013). Advancing hypoxic training in team sports: from intermittent hypoxic training to repeated sprint training in hypoxia. *British Journal of Sports Medicine, 47*(Suppl 1), i45-i50.

Faiss, R., Pialoux, V., Sartori, C., Faes, C., Dériaz, O., & Millet, G. P. (2013). Ventilation, oxidative stress, and nitric oxide in hypobaric versus normobaric hypoxia. *Med Sci Sports Exerc, 45*(2), 253-260.

Faiss, R., von Orelli, C., Deriaz, O., & Millet, G. P. (2014). Responses to exercise in normobaric hypoxia: comparison of elite and recreational ski mountaineers. *International Journal of Sports Physiology and Performance, 9*(6), 978-984.

Farinelli, C., Kayser, B., Binzoni, T., Cerretelli, P., & Girardier, L. (1994). Autonomic nervous control of heart rate at altitude (5050 m). *European journal of applied physiology and occupational physiology, 69*(6), 502-507.

Faulhaber, M., Dünnwald, T., Gatterer, H., Bernardi, L., & Burtscher, M. (2012). Metabolic Adaptations May Counteract Ventilatory Adaptations of Intermittent Hypoxic Exposure during Submaximal Exercise at Altitudes up to 4000 m.

Favret, F., Henderson, K. K., Richalet, J.-P., & Gonzalez, N. C. (2003). Effects of exercise training on acclimatization to hypoxia: systemic O2 transport during maximal exercise. *Journal of applied physiology, 95*(4), 1531-1541.

Feriche, B., García-Ramos, A., Calderón-Soto, C., Drobnic, F., Bonitch-Góngora, J. G., Galilea, P. A., . . . Padial, P. (2014). Effect of Acute Exposure to Moderate Altitude on Muscle Power: Hypobaric Hypoxia vs. Normobaric Hypoxia. *PloS one, 9*(12), e114072.

Fox, S. I. (1987). *Human Physiology* (E. J. Jaffe Ed. 2nd ed.). Dubuque, Iowa: Wm. C. Brown Publishers.

Friedmann-Bette, B. (2008). Classical altitude training. *Scandinavian journal of medicine & science in sports, 18*(s1), 11-20.

Fulco, C. S., Beidleman, B. A., & Muza, S. R. (2013). Effectiveness of preacclimatization strategies for high-altitude exposure. *Exercise and sport sciences reviews, 41*(1), 55-63.

Fulco, C. S., Muza, S. R., Beidleman, B. A., Demes, R., Staab, J. E., Jones, J. E., & Cymerman, A. (2011). Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 300*(2), R428-R436.

Fulco, C. S., Rock, P. B., & Cymerman, A. (1998). Maximal and submaximal exercise performance at altitude. *Aviation, space, and environmental medicine, 69*(8), 793-801.

Fulco, C. S., Rock, P. B., & Cymerman, A. (2000). Improving athletic performance: is altitude residence or altitude training helpful? *Aviation, space, and environmental medicine, 71*(2), 162-171.

Gallagher, C. A., Willems, M. E., Lewis, M. P., & Myers, S. D. (2014). Effect of acute normobaric hypoxia on the ventilatory threshold. *European journal of applied physiology, 114*(8), 1555-1562.

Gallagher, S. A., & Hackett, P. H. (2004). High-altitude illness. *Emergency medicine clinics of North America, 22*(2), 329-355.

Garcia, N., Hopkins, S., & Powell, F. (2000). Effects of intermittent hypoxia on the isocapnic hypoxic ventilatory response and erythropoiesis in humans. *Respiration physiology, 123*(1), 39-49.

Garcia, N., Hopkins, S. R., & Powell, F. L. (2000). Intermittent vs continuous hypoxia: effects on ventilation and erythropoiesis in humans. *Wilderness & environmental medicine, 11*(3), 172-179.

Ge, R.-L., Witkowski, S., Zhang, Y., Alfrey, C., Sivieri, M., Karlsen, T., . . . Levine, B. (2002). Determinants of erythropoietin release in response to short-term hypobaric hypoxia. *Journal of applied physiology, 92*(6), 2361-2367.

Geiser, J., Vogt, M., Billeter, R., Zuleger, C., Belforti, F., & Hoppeler, H. (2001). Training high-living low: changes of aerobic performance and muscle structure with training at simulated altitude. *International journal of sports medicine, 22*(8), 579-585.

Gore, C. J., Clark, S. A., & Saunders, P. U. (2007). Nonhematological mechanisms of improved sea-level performance after hypoxic exposure *Medicine and science in sports and exercise* (Vol. 39, pp. 1600).

Gore, C. J., Hahn, A. G., Scroop, G. C., Watson, D., Norton, K. I., Wood, R., . . . Emonson, D. (1996). Increased arterial desaturation in trained cyclists during maximal exercise at 580 m altitude. *Journal of applied physiology, 80*(6), 2204-2210.

Gore, C. J., Rodriguez, F. A., Truijens, M. J., Townsend, N. E., Stray-Gundersen, J., & Levine, B. D. (2006). Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000–5,500 m). *Journal of applied physiology, 101*(5), 1386-1393.

Hahn, A. G., & Gore, C. J. (2001). The effect of altitude on cycling performance. *Sports medicine, 31*(7), 533-557.

Hahn, A. G., Gore, C. J., Martin, D. T., Ashenden, M. J., Roberts, A. D., & Logan, P. A. (2001). An evaluation of the concept of living at moderate altitude and training at sea level. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology, 128*(4), 777-789.

Hainsworth, R., & Drinkhill, M. J. (2007). Cardiovascular adjustments for life at high altitude. *Respiratory physiology & neurobiology, 158*(2), 204-211.

Hamlin, M. J., Draper, N., & Hellemans, J. (2013). Real and Simulated Altitude Training and Performance.

Hamlin, M. J., & Hellemans, J. (2007). Effect of intermittent normobaric hypoxic exposure at rest on haematological, physiological, and performance parameters in multi-sport athletes. *Journal of sports sciences, 25*(4), 431-441.

Hemmingsson, T., & Linnarsson, D. (2009). Lower exhaled nitric oxide in hypobaric than in normobaric acute hypoxia. *Respiratory physiology & neurobiology, 169*(1), 74-77.

Hendriksen, I. J., & Meeuwsen, T. (2003). The effect of intermittent training in hypobaric hypoxia on sea-level exercise: a cross-over study in humans. *European journal of applied physiology, 88*(4-5), 396-403.

Henning, P. C., Park, B.-S., & Kim, J.-S. (2011). Physiological decrements during sustained military operational stress. *Military medicine, 176*(9), 991-997.

Hennis, P. J., O'Doherty, A. F., Levett, D. Z., Grocott, M. P., & Montgomery, H. M. (2015). Genetic Factors Associated with Exercise Performance in Atmospheric Hypoxia. *Sports medicine, 45*(5), 745-761.

Holliss, B. A., Burden, R. J., Jones, A. M., & Pedlar, C. R. (2014). Eight weeks of intermittent hypoxic training improves submaximal physiological variables in highly trained runners. *The Journal of Strength & Conditioning Research, 28*(8), 2195-2203.

Hoppeler, H., Klossner, S., & Vogt, M. (2008). Training in hypoxia and its effects on skeletal muscle tissue. *Scandinavian journal of medicine & science in sports, 18*(s1), 38-49.

Humberstone-Gough, C. E., Saunders, P. U., Bonetti, D. L., Stephens, S., Bullock, N., Anson, J. M., & Gore, C. J. (2013). Comparison of live high: train low altitude and intermittent hypoxic exposure. *Journal of sports science & medicine, 12*(3), 394.

Igor, R., Vladimir, I., Milos, M., & Goran, B. (2011). New tendencies in the application of altitude training in sport preparation. *Journal of Physical Education and Sport, 11*(2), 200.

Katayama, K., Sato, Y., Ishida, K., Mori, S., & Miyamura, M. (1998). The effects of intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. *European journal of applied physiology and occupational physiology, 78*(3), 189-194.

Katayama, K., Sato, Y., Morotome, Y., Shima, N., Ishida, K., Mori, S., & Miyamura, M. (1999). Ventilatory chemosensitive adaptations to intermittent hypoxic exposure with endurance training and detraining. *Journal of applied physiology, 86*(6), 1805-1811.

Katayama, K., Sato, Y., Morotome, Y., Shima, N., Ishida, K., Mori, S., & Miyamura, M. (2000). Cardiovascular response to hypoxia after endurance training at altitude and sea level and after detraining. *Journal of applied physiology, 88*(4), 1221-1227.

Katayama, K., Sato, Y., Morotome, Y., Shima, N., Ishida, K., Mori, S., & Miyamura, M. (2001). Intermittent hypoxia increases ventilation and SaO2 during hypoxic

exercise and hypoxic chemosensitivity. *Journal of applied physiology*, *90*(4), 1431-1440.

Kato, T., Matsumura, Y., Tsukanaka, A., Harada, T., Kosaka, M., & Matsui, N. (2004). Effect of low oxygen inhalation on changes in blood pH, lactate, and ammonia due to exercise. *European journal of applied physiology*, *91*(2-3), 296-302.

Kolb, J. C., Ainslie, P. N., Ide, K., & Poulin, M. J. (2004). Effects of five consecutive nocturnal hypoxic exposures on the cerebrovascular responses to acute hypoxia and hypercapnia in humans. *Journal of applied physiology*, *96*(5), 1745-1754.

Krueger, G. P. (1993). Environmental medicine research to sustain health and performance during military deployment: desert, arctic high altitude stressors. *Journal of Thermal Biology*, *18*(5), 687-690.

Laird, R. F., Timperlake, E. T., & Delaporte, M. (2014). Forging a 21st-century Military Strategy. *JFQ*, *72*(1st Quarter).

Lawler, J., Powers, S. K., & Thompson, D. (1988). Linear relationship between VO2max and VO2max decrement during exposure to acute hypoxia. *Journal of applied physiology*, *64*(4), 1486-1492.

Lecoultre, V., Boss, A., Tappy, L., Borrani, F., Tran, C., Schneiter, P., & Schutz, Y. (2010). Training in hypoxia fails to further enhance endurance performance and lactate clearance in well-trained men and impairs glucose metabolism during prolonged exercise. *Experimental physiology*, *95*(2), 315-330.

Levine, B., & Stray-Gundersen, J. (1992). A practical approach to altitude training: where to live and train for optimal performance enhancement. *International journal of sports medicine*, *13*, S209-212.

Levine, B. D. (2002). Intermittent hypoxic training: fact and fancy. *High altitude medicine & biology*, *3*(2), 177-193.

Levine, B. D., & Stray-Gundersen, J. (1997). "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *Journal of applied physiology*, *83*(1), 102-112.

Levine, B. D., & Stray-Gundersen, J. (2005). Point: positive effects of intermittent hypoxia (live high: train low) on exercise performance are mediated primarily by augmented red cell volume. *Journal of applied physiology*, *99*(5), 2053-2055.

Loeppky, J., Icenogle, M., Scotto, P., Robergs, R., Hinghofer-Szalkay, H., & Roach, R. (1997). Ventilation during simulated altitude, normobaric hypoxia and normoxic hypobaria1. *Respiration physiology*, *107*(3), 231-239.

Lundby, C., Araoz, M., & Van Hall, G. (2001). Peak heart rate decreases with increasing severity of acute hypoxia. *High altitude medicine & biology, 2*(3), 369-376.

Mackenzie, R. W., Watt, P. W., & Maxwell, N. S. (2008). Acute normobaric hypoxia stimulates erythropoietin release. *High altitude medicine & biology, 9*(1), 28-37.

Mateika, J. H., & Duffin, J. (1994). The ventilation, lactate and electromyographic thresholds during incremental exercise tests in normoxia, hypoxia and hyperoxia. *European journal of applied physiology and occupational physiology, 69*(2), 110-118.

McLean, B. D., Gore, C. J., & Kemp, J. (2014). Application of 'live low-train high'for enhancing normoxic exercise performance in team sport athletes. *Sports medicine, 44*(9), 1275-1287.

Mekjavic, I. B., Debevec, T., Amon, M., Keramidas, M. E., & Kounalakis, S. N. (2012). Intermittent normobaric hypoxic exposures at rest: effects on performance in normoxia and hypoxia. *Aviation, space, and environmental medicine, 83*(10), 942-950.

Millet, G. P., Faiss, R., & Pialoux, V. (2012). Point: Counterpoint: Hypobaric hypoxia induces/does not induce different responses from normobaric hypoxia. *Journal of applied physiology, 112*(10), 1783-1784.

Millet, G. P., Roels, B., Schmitt, L., Woorons, X., & Richalet, J. (2010). Combining hypoxic methods for peak performance. *Sports medicine, 40*(1), 1-25.

Mizuno, M., Savard, G. K., Areskog, N.-H., Lundby, C., & Saltin, B. (2008). Skeletal muscle adaptations to prolonged exposure to extreme altitude: a role of physical activity? *High altitude medicine & biology, 9*(4), 311-317.

Mollard, P., Woorons, X., Antoine-Jonville, S., Jutand, L., Richalet, J. P., Favret, F., & Pichon, A. (2008). 'Oxygen uptake efficiency slope'in trained and untrained subjects exposed to hypoxia. *Respiratory physiology & neurobiology, 161*(2), 167-173.

Mollard, P., Woorons, X., Letournel, M., Cornolo, J., Lamberto, C., Beaudry, M., & Richalet, J. (2007). Role of maximal heart rate and arterial o2 saturation on the decrement of v. o2max in moderate acute hypoxia in trained and untrained men. *International journal of sports medicine, 28*(3), 186.

Mollard, P., Woorons, X., Letournel, M., Lamberto, C., Favret, F., Pichon, A., . . . Richalet, J.-P. (2007). Determinants of maximal oxygen uptake in moderate acute hypoxia in endurance athletes. *European journal of applied physiology, 100*(6), 663-673.

Morton, J. P., & Cable, N. T. (2005). The effects of intermittent hypoxic training on aerobic and anaerobic performance. *Ergonomics, 48*(11-14), 1535-1546.

Muza, S. R. (2007). Military applications of hypoxic training for high-altitude operations: DTIC Document.

Muza, S. R., Beidleman, B. A., & Fulco, C. S. (2010). Altitude preexposure recommendations for inducing acclimatization. *High altitude medicine & biology, 11*(2), 87-92.

Muza, S. R., Fulco, C. S., & Beidleman, B. A. (2009). Comparison of an Intermittent Hypoxic Exposure Acclimatization Program to Staging at Moderate Altitude on Endurance Performance at 4300 m: DTIC Document.

Naeije, R. (2010). Physiological adaptation of the cardiovascular system to high altitude. *Progress in cardiovascular diseases, 52*(6), 456-466.

Neya, M., Enoki, T., Kumai, Y., Sugoh, T., & Kawahara, T. (2007). The effects of nightly normobaric hypoxia and high intensity training under intermittent normobaric hypoxia on running economy and hemoglobin mass. *Journal of applied physiology, 103*(3), 828-834.

Nindl, B. C., Castellani, J. W., Warr, B. J., Sharp, M. A., Henning, P. C., Spiering, B. A., & Scofield, D. E. (2013). Physiological Employment Standards III: physiological challenges and consequences encountered during international military deployments. *European journal of applied physiology, 113*(11), 2655-2672.

Norris, J. N., Viirre, E., Aralis, H., Sracic, M. K., Thomas, D., & Gertsch, J. H. (2012). High altitude headache and acute mountain sickness at moderate elevations in a military population during battalion-level training exercises. *Military medicine, 177*(8), 917-923.

Nummela, A., & Rusko, H. (2000). Acclimatization to altitude and normoxic training improve 400-m running performance at sea level. *Journal of sports sciences, 18*(6), 411-419.

Ofner, M., Wonisch, M., Frei, M., Tschakert, G., Domej, W., Kröpfl, J. M., & Peter, H. (2014). Influence of Acute Normobaric Hypoxia on Physiological Variables and Lactate Turn Point Determination in Trained Men. *Journal of sports science & medicine, 13*(4), 774.

Ostadal, B., & Kolar, F. (2007). Cardiac adaptation to chronic high-altitude hypoxia: beneficial and adverse effects. *Respiratory physiology & neurobiology, 158*(2), 224-236.

Ponsot, E., Dufour, S. P., Zoll, J., Doutrelau, S., N'Guessan, B., Geny, B., . . . Ventura-Clapier, R. (2006). Exercise training in normobaric hypoxia in endurance runners.

II. Improvement of mitochondrial properties in skeletal muscle. *Journal of applied physiology, 100*(4), 1249-1257.

Powell, F. L., & Garcia, N. (2000). Physiological effects of intermittent hypoxia. *High altitude medicine & biology, 1*(2), 125-136.

Rasmussen, P., Siebenmann, C., Diaz Molina, V., & Lundby, C. (2013). Red cell volume expansion at altitude: a meta-analysis and Monte Carlo simulation. *Medicine & Science in Sports & Exercise., 45*(9), 1767-1775.

Reis, V. M., Van den Tillaar, R., & Marques, M. C. (2011). Higher precision of heart rate compared with VO2 to predict exercise intensity in endurance-trained runners. *Journal of sports science & medicine, 10*(1), 164.

Ricart, A., Casas, H., Casas, M., Pagés, T., Palacios, L., Rama, R., . . . Ventura, J. L. (2000). Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness & environmental medicine, 11*(2), 84-88.

Richard, N. A., & Koehle, M. S. (2012). Differences in cardio-ventilatory responses to hypobaric and normobaric hypoxia: a review. *Aviation, space, and environmental medicine, 83*(7), 677-684.

Richard, N. A., Sahota, I. S., Widmer, N., Ferguson, S., Sheel, A. W., & Koehle, M. S. (2014). Acute mountain sickness, chemosensitivity, and cardiorespiratory responses in humans exposed to hypobaric and normobaric hypoxia. *Journal of applied physiology, 116*(7), 945-952.

Roach, R., Maes, D., Sandoval, D., Robergs, R., Icenogle, M., Hinghofer-Szalkay, H., . . . Loeppky, J. (2000). Exercise exacerbates acute mountain sickness at simulated high altitude. *Journal of applied physiology, 88*(2), 581-585.

Roach, R. C., Loeppky, J. A., & Icenogle, M. V. (1996). Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. *Journal of applied physiology, 81*(5), 1908-1910.

Robach, P., Siebenmann, C., Jacobs, R. A., Rasmussen, P., Nordsborg, N., Pesta, D., . . . Fiedler, J. (2012). The role of haemoglobin mass on VO2max following normobaric 'live high–train low'in endurance-trained athletes. *British Journal of Sports Medicine*, bjsports-2012-091078.

Rodriguez, F. A., Truijens, M. J., Townsend, N. E., Stray-Gundersen, J., Gore, C. J., & Levine, B. D. (2007). Performance of runners and swimmers after four weeks of intermittent hypobaric hypoxic exposure plus sea level training. *Journal of applied physiology, 103*(5), 1523-1535.

Rodríguez, F. A., Ventura, J. L., Casas, M., Casas, H., Pagés, T., Rama, R., . . . Viscor, G. (2000). Erythropoietin acute reaction and haematological adaptations to short, intermittent hypobaric hypoxia. *European journal of applied physiology, 82*(3), 170-177.

Roels, B., Bentley, D. J., Coste, O., Mercier, J., & Millet, G. P. (2007). Effects of intermittent hypoxic training on cycling performance in well-trained athletes. *European journal of applied physiology, 101*(3), 359-368.

Roels, B., Millet, G. P., Marcoux, C., Coste, O., Bentley, D. J., & Candau, R. B. (2005). Effects of hypoxic interval training on cycling performance. *Med Sci Sports Exerc, 37*(1), 138-146.

Roskamm, H., Landry, F., Samek, L., Schlager, M., Weidemann, H., & Reindell, H. (1969). Effects of a standardized ergometer training program at three different altitudes. *Journal of applied physiology, 27*(6), 840-847.

Rusko, H., Tikkanen, H., & Peltonen, J. (2004). Altitude and endurance training. *Journal of sports sciences, 22*(10), 928-945.

Sargent, C., Schmidt, W. F., Aughey, R. J., Bourdon, P. C., Soria, R., Claros, J. C. J., . . . Hammond, K. (2013). The impact of altitude on the sleep of young elite soccer players (ISA3600). *British Journal of Sports Medicine, 47*(Suppl 1), i86-i92.

Saunders, P. U., Garvican-Lewis, L. A., Schmidt, W. F., & Gore, C. J. (2013). Relationship between changes in haemoglobin mass and maximal oxygen uptake after hypoxic exposure. *British Journal of Sports Medicine, 47*(Suppl 1), i26-i30.

Saunders, P. U., Telford, R. D., Pyne, D. B., Cunningham, R., Gore, C. J., Hahn, A. G., & Hawley, J. A. (2004). Improved running economy in elite runners after 20 days of simulated moderate-altitude exposure. *Journal of applied physiology, 96*(3), 931-937.

Savourey, G., Launay, J.-C., Besnard, Y., Guinet, A., & Travers, S. (2003). Normo-and hypobaric hypoxia: are there any physiological differences? *European journal of applied physiology, 89*(2), 122-126.

Schmidt, W., & Prommer, N. (2010). Impact of Alterations in Total Hemoglobin Mass on V˙ O2max. *Exercise and sport sciences reviews, 38*(2), 68-75.

Schommer, K., Menold, E., Subudhi, A. W., & Bärtsch, P. (2012). Health risk for athletes at moderate altitude and normobaric hypoxia. *British Journal of Sports Medicine, 46*(11), 828-832. doi: 10.1136/bjsports-2012-091270

Schommer, K., Wiesegart, N., Menold, E., Haas, U., Lahr, K., Buhl, H., . . . Dehnert, C. (2010). Training in normobaric hypoxia and its effects on acute mountain sickness after rapid ascent to 4559 m. *High altitude medicine & biology, 11*(1), 19-25.

Schuler, B., Thomsen, J., Gassmann, M., & Lundby, C. (2007). Timing the arrival at 2340 m altitude for aerobic performance. *Scandinavian journal of medicine & science in sports, 17*(5), 588-594.

Semenza, G. L. (2000). HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *Journal of applied physiology, 88*(4), 1474-1480.

Sharma, S., & Brown, B. (2007). Spirometry and respiratory muscle function during ascent to higher altitudes. *Lung, 185*(2), 113-121.

Sheel, A. W., & MacNutt, M. J. (2003). Control of ventilation in humans following intermittent hypoxia. *Applied Physiology, Nutrition, and Metabolism, 33*(3), 573-581.

Sherwood, L. (2011). *Essentials of Physiology* (4th ed.): Cengage Learning.

Siebenmann, C., & Lundby, C. (2015). Regulation of cardiac output in hypoxia. *Scandinavian journal of medicine & science in sports, 25*(S4), 53-59.

Siebenmann, C., Robach, P., Jacobs, R. A., Rasmussen, P., Nordsborg, N., Diaz, V., . . . Lundby, C. (2012). "Live high–train low" using normobaric hypoxia: a double-blinded, placebo-controlled study. *Journal of applied physiology, 112*(1), 106-117.

Stang, J., Bråten, V., Caspersen, C., Thorsen, E., & Stensrud, T. (2014). Exhaled nitric oxide after high-intensity exercise at 2800 m altitude. *Clinical physiology and functional imaging*.

Stickney, J. C., & Van Liere, E. J. (1953). Acclimatization to low oxygen tension. *Physiol. Rev, 33*(1), 13-34.

Tannheimer, M., Albertini, N., Ulmer, H.-V., Thomas, A., Engelhardt, M., & Schmidt, R. (2009). Testing individual risk of acute mountain sickness at greater altitudes. *Military medicine, 174*(4), 363-369.

Terrados, N., Melichna, J., Sylvén, C., Jansson, E., & Kaijser, L. (1988). Effects of training at simulated altitude on performance and muscle metabolic capacity in competitive road cyclists. *European journal of applied physiology and occupational physiology, 57*(2), 203-209.

Terrados, N., Mizuno, M., & Andersen, H. (1985). Reduction in maximal oxygen uptake at low altitudes; role of training status and lung function. *Clinical Physiology, 5*(s3), 75-79.

Thompson, W. (2010). In W. Thompson (Ed.), *ACSM's Guidelines for Exercise Testing and Prescription* (8th ed.). Baltimore, MD: Wolters Kluwer.

Townsend, N. E., Gore, C. J., Hahn, A. G., McKenna, M. J., Aughey, R. J., Clark, S. A., . . . Chow, C.-M. (2002). Living high-training low increases hypoxic ventilatory response of well-trained endurance athletes. *Journal of applied physiology, 93*(4), 1498-1505.

Truijens, M. J., Rodriguez, F. A., Townsend, N. E., Stray-Gundersen, J., Gore, C. J., & Levine, B. D. (2008). The effect of intermittent hypobaric hypoxic exposure and sea level training on submaximal economy in well-trained swimmers and runners. *Journal of applied physiology, 104*(2), 328-337.

Truijens, M. J., Toussaint, H. M., Dow, J., & Levine, B. D. (2003). Effect of high-intensity hypoxic training on sea-level swimming performances. *Journal of applied physiology, 94*(2), 733-743.

Tucker, A., Reeves, J. T., Robertshaw, D., & Grover, R. F. (1983). Cardiopulmonary response to acute altitude exposure: water loading and denitrogenation. *Respiration physiology, 54*(3), 363-380.

Vallier, J., Chateau, P., & Guezennec, C. (1996). Effects of physical training in a hypobaric chamber on the physical performance of competitive triathletes. *European journal of applied physiology and occupational physiology, 73*(5), 471-478.

Van Liere, E. J. (1943). ANOXIA. ITS EFFECT ON THE BODY. *The American Journal of the Medical Sciences, 205*(3), 433.

VENTURA, M., JORDI, I., & FERRAN, A. (2000). Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviation, space, and environmental medicine, 71*(2), 125-130.

Ventura, N., Hoppeler, H., Seiler, R., Binggeli, A., Mullis, P., & Vogt, M. (2003). The response of trained athletes to six weeks of endurance training in hypoxia or normoxia. *International journal of sports medicine, 24*(3), 166-172.

Vogt, M., Puntschart, A., Geiser, J., Zuleger, C., Billeter, R., & Hoppeler, H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. *Journal of applied physiology, 91*(1), 173-182.

Wagner, P. D. (2000). Reduced maximal cardiac output at altitude—mechanisms and significance. *Respiration physiology, 120*(1), 1-11.

Wilber, R. L. (2001). Current trends in altitude training. *Sports medicine, 31*(4), 249-265.

Wilber, R. L. (2007a). Application of altitude/hypoxic training by elite athletes. *Medicine and science in sports and exercise, 39*(9), 1610-1624.

Wilber, R. L. (2007b). Introduction to altitude/hypoxic training symposium. *Medicine and science in sports and exercise, 39*(9), 1587-1589.

Wilber, R. L., Stray-Gundersen, J., & Levine, B. D. (2007). Effect of hypoxic" dose" on physiological responses and sea-level performance. *Medicine and science in sports and exercise, 39*(9), 1590-1599.

Wolfarth, B. (2005). A three-week traditional altitude training increases hemoglobin mass and red cell volume in elite biathlon athletes. *Int J Sports Med, 26*, 350-355.

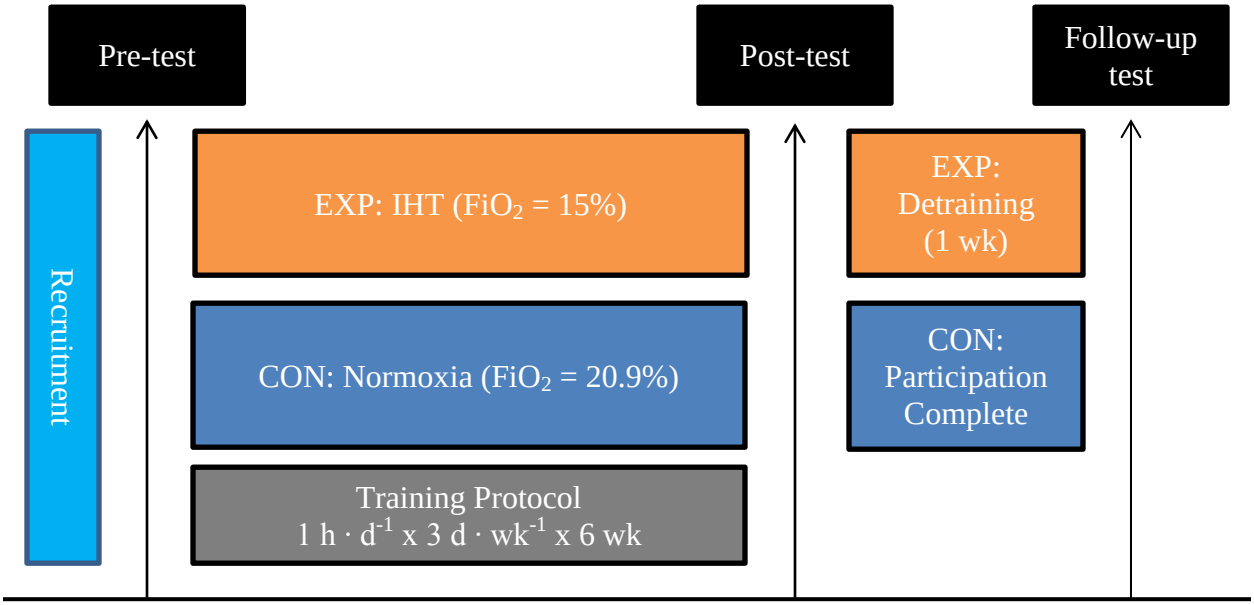
Wyatt, F. B. (2014). Physiological Responses to Altitude: A Brief Review. *Journal Of Exercise Physiology Online, 17*(1), 90-96.

Zaccagni, L., Barbieri, D., Cogo, A., & Gualdi-Russo, E. (2014). Anthropometric and Body Composition Changes during Expeditions at High Altitude. *High altitude medicine & biology, 15*(2), 176-182.

APPENDICES

APPENDIX A

RESEARCH DESIGN



APPENDIX B

NORMOBARIC NORMOXIA VO_{2max} TESTING SETUP

APPENDIX C

HYPOBARIC HYPOXIA VO_{2max} TESTING SETUP

APPENDIX D

PRE-EXERCISE TESTING HEALTH & EXERCISE STATUS QUESTIONNAIRE

RECRUITMENT NO._____

OKLAHOMA STATE UNIVERSITY

Name _____ Date_____

Work Phone _____ Home Phone (Cell)_____

E-mail address_____ Preferred method of contact: Call, email, or text

Person to contact in case of emergency_____

Emergency Contact Phone _____

Gender_____ Age _____(yrs) Height _____ (ft)_____(in) Weight_____(lbs)

Does the above weight indicate: a gain____ a loss____ no change____ in the past year?

If a change, how many pounds?_____(lbs)

A. JOINT-MUSCLE STATUS (✓Check areas where you currently have problems)

Joint Areas	Muscle Areas
( ) Wrists	( ) Arms
( ) Elbows	( ) Shoulders
( ) Shoulders	( ) Chest
( ) Upper Spine & Neck	( ) Upper Back & Neck
( ) Lower Spine	( ) Abdominal Regions
( ) Hips	( ) Lower Back
( ) Knees	( ) Buttocks
( ) Ankles	( ) Thighs
( ) Feet	( ) Lower Leg
( ) Other_____	( ) Feet
	( )Other_____

B. HEALTH STATUS (✓Check if you currently have any of the following conditions)

( ) High Blood Pressure	( ) Acute Infection
( ) Heart Disease or Dysfunction Abnormality	( ) Diabetes or Blood Sugar Level
( ) Peripheral Circulatory Disorder	( ) Anemia
( ) Lung Disease or Dysfunction	( ) Hernias
( ) Arthritis or Gout	( ) Thyroid Dysfunction
( ) Edema	( ) Pancreas Dysfunction

( ) Epilepsy
( ) Multiply Sclerosis
( ) High Blood Cholesterol or
( ) Triglyceride Levels
( ) Allergic reactions to rubbing alcohol
( ) Liver Dysfunction
( ) Kidney Dysfunction
( ) Phenylketonuria (PKU)
( ) Loss of Consciousness

C. PHYSICAL EXAMINATION HISTORY

Approximate date of your last physical examination _____

Physical problems noted at that time _____

Has a physician ever made any recommendations relative to limiting your level of physical exertion? _____YES _____NO
If YES, what limitations were recommended?
_____

D. CURRENT MEDICATION USAGE (List the drug name and the condition being managed)

MEDICATION	CONDITION
_____	_____
_____	_____
_____	_____

E. PHYSICAL PERCEPTIONS (Indicate any unusual sensations or perceptions. ✓Check if you have recently experienced any of the following during or soon after *physical activity* (PA); or during *sedentary periods* (SED))

PA	SED		PA	SED	
( )	( )	Chest Pain	( )	( )	Nausea
( )	( )	Heart Palpitations	( )	( )	Light Headedness
( )	( )	Unusually Rapid Breathing	( )	( )	Loss of Consciousness
( )	( )	Overheating	( )	( )	Loss of Balance
( )	( )	Muscle Cramping	( )	( )	Loss of Coordination
( )	( )	Muscle Pain	( )	( )	Extreme Weakness
( )	( )	Joint Pain	( )	( )	Numbness
( )	( )	Other_____	( )	( )	Mental Confusion

F. FAMILY HISTORY (✓Check if any of your blood relatives . . . parents, brothers, sisters, aunts, uncles, and/or grandparents . . . have or had any of the following)

( ) Heart Disease
( ) Heart Attacks or Strokes (prior to age 50)
( ) Elevated Blood Cholesterol or Triglyceride Levels
( ) High Blood Pressure
( ) Diabetes
( ) Sudden Death (other than accidental)

G. EXERCISE STATUS

Do you regularly engage in aerobic forms of exercise (i.e., jogging, cycling, walking, etc.)?

YES NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly lift weights?

YES NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

Do you regularly play recreational sports (i.e., basketball, racquetball, volleyball, etc.)?

YES NO

How long have you engaged in this form of exercise? _____ years _____ months

How many hours per week do you spend for this type of exercise? _____ hours

APPENDIX E

IRB APPROVAL

Oklahoma State University Institutional Review Board

Date:	Monday, July 20, 2015
IRB Application No	ED15101
Proposal Title:	The effects of normobaric hypoxic training on hypobaric performance
Reviewed and Processed as:	Expedited

Status Recommended by Reviewer(s): Approved Protocol Expires: 7/19/2016

Principal Investigator(s):

John Sellers
226 Hartford Street
Stillwater, OK 74078

Taylor Monaghan
1001 W Will Rogers Dr
Stillwater, OK 74075

Bert Jacobson
180 CRC
Stillwater, OK 74078

The IRB application referenced above has been approved. It is the judgment of the reviewers that the rights and welfare of individuals who may be asked to participate in this study will be respected, and that the research will be conducted in a manner consistent with the IRB requirements as outlined in section 45 CFR 46.

☑ The final versions of any printed recruitment, consent and assent documents bearing the IRB approval stamp are attached to this letter. These are the versions that must be used during the study.

As Principal Investigator, it is your responsibility to do the following:

1.Conduct this study exactly as it has been approved. Any modifications to the research protocol must be submitted with the appropriate signatures for IRB approval. Protocol modifications requiring approval may include changes to the title, PI advisor, funding status or sponsor, subject population composition or size, recruitment, inclusion/exclusion criteria, research site, research procedures and consent/assent process or forms
2.Submit a request for continuation if the study extends beyond the approval period. This continuation must receive IRB review and approval before the research can continue.
3.Report any adverse events to the IRB Chair promptly. Adverse events are those which are unanticipated and impact the subjects during the course of the research; and
4.Notify the IRB office in writing when your research project is complete.

Please note that approved protocols are subject to monitoring by the IRB and that the IRB office has the authority to inspect research records associated with this protocol at any time. If you have questions about the IRB procedures or need any assistance from the Board, please contact Dawnett Watkins 219 Scott Hall (phone: 405-744-5700, dawnett.watkins@okstate.edu).

Sincerely,

Hugh Crethar, Chair
Institutional Review Board

APPENDIX F

INFORMED CONSENT FORM

RESEARCH PARTICIPANT CONSENT FORM

Project Title: The effects of normobaric hypoxic training on hypobaric performance.

Investigators: John Sellers, Health & Human Performance, Oklahoma State University
Taylor Monaghan, Health & Human Performance, Oklahoma State University
Dr. Bert Jacobson, Health & Human Performance, Oklahoma State University

Purpose:
The primary aim of the research project will be to determine the efficacy to improve maximal aerobic capacity in well-trained individuals in a hypobaric hypoxia setting using normobaric hypoxia intermittent hypoxia training (IHT). A secondary aim of this investigation will be to determine if the proposed intervention protocol (6 wk x 1 hr x 3 d per week) is sufficient to elicit significant changes in the oxygen carrying capacity measures in the blood. Another purpose of this study will be to determine if significant changes in body composition as evaluated through skinfold measurements occur as a result of IHT when compared to the control group.

Procedures:
The tasks required if you volunteer for this study are to:

- Once you have read through and sign this informed consent document you will be scheduled to participate.

Upon granting consent to participate in this study, you will perform the initial base-line testing. Testing will take place in either the Applied Musculoskeletal and Human Physiology Research Laboratory in 192 Colvin Recreation Center at Oklahoma State University or the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine. As part of the pre-screening process, you will complete the following:

- Height and weight measurements
- A 7-site skinfold measurement test to analyze body composition
- A blood draw performed by an Oklahoma State University Health Sciences Center medical professional
- Complete a maximal oxygen uptake treadmill test (aka VO2 max test). This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test
    - In order to be considered for continued participation in the study, participants will have achieved a VO2 max of at least 55 ml/kg/min. As there is a minimum fitness standard that must be met prior to participation in the training intervention, it is possible that you will complete the first day of pre-testing at the Applied Musculoskeletal and Human Physiology Research Laboratory and will not meet the minimum standards and will thus no further participation will be asked of you. If you meet the VO2 max requirement from the initial pre-tests, you will then perform the same VO2 treadmill test in an altitude chamber at the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine. If selected for participation, you will be asked to maintain

your current dietary and sleeping habits as well as complete weekly physical activity logs.

Upon selection to this study, you will then perform a treadmill ergometer training protocol, with the control group performing the training sessions in a normoxic (normal partial pressure of Oxygen in the air) setting and the experimental group will perform all training sessions in normobaric hypoxia (simulated altitude of 3,000 m). The training intervention will be 6 weeks in duration, with 3 1-hr training sessions per week. Each training session for all participants will consist of a 10-min warm-up at approximately 50% of the participant's pre-screening VO2 max, a 40-min interval workout between 60-80% of the participant's pre-screening VO2 max, and a 10-min cool-down at approximately 40-50% of the participant's pre-screening VO2 max. There will be a 24-48 hr recovery period between each training session. All training sessions will take place in the Oklahoma State University Applied Musculoskeletal and Human Physiology Research Laboratory in 192 Colvin Recreation Center under the supervision of the primary investigator or other OSU Health & Human Performance graduate assistants who have completed the necessary CITI Responsible Conduct of Research Training.

Upon the completion of the 6-wk intervention period, you will perform post-testing assessments. Post-testing will take place in either the Applied Musculoskeletal and Human Physiology Research Laboratory in 192 Colvin Recreation Center at Oklahoma State University or the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine. As part of the post-testing process, you will complete the following:

- Weight measurement
- A 7-site skinfold measurement test to analyze body composition
- A blood draw performed by an Oklahoma State University Health Sciences Center medical professional
- Complete a maximal oxygen uptake treadmill test (aka VO2 max test) in both the Oklahoma State University Applied Musculoskeletal and Human Physiology Research Laboratory in 192 Colvin Recreation Center and the altitude chamber at the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine. This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test.

If you are selected to participate in the experimental training group, you will be asked to return approximately two weeks after the completion of the post-testing sessions. During this fifth and final testing day, you will be asked to complete the following:

- A blood draw performed by an Oklahoma State University Health Sciences Center medical professional
- Complete a maximal oxygen uptake treadmill test (aka VO2 max test) in the altitude chamber at the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine. This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test.

Risks of Participation:

As this study will be utilizing highly-trained individuals, the risks associated with the study are minimal and with no greater physical demands than your current exercise program. In case of

injury or illness resulting from this study, emergency medical treatment will be available; responders are CPR – 1st responder certified along with access to 911 will be available. No funds have been set aside by Oklahoma State University to compensate you in the event of illness or injury.

Benefits:
Participants will benefit from being able to see if increases in aerobic capacity occur as a result of completing 6 weeks of intermittent hypoxic training. Participants will also be compensated in the amount of $100 if they complete all phases of this study.

Confidentiality:
Due to multiple testing sessions to be completed during various times over more than 2 months, all testing results will be tracked by a random subject ID number issued to each participant. The subject ID number will only be known by the primary investigator and the respective participant. Upon completion of the testing period subject ID numbers will be destroyed immediately. Only aggregate data will be reported. Aside from the original data all references will only contain subject ID number references as each participant will be assigned an ID number. We are interested in reporting data reflective of how the group(s) as a whole responded to the intervention program. Only aggregate data will be published. No individual data will be published. Testing results will not be shared with supervisors of any nature. Research records will be stored securely for 3 years and only researchers and individuals responsible for research oversight will have access to the records. These forms will be kept in a locked file cabinet in the Applied Musculoskeletal and Human Physiology Laboratory which only the researchers will have access to. The signed consent forms will be kept for 3 years after the research is complete per federal guidelines.

Compensation:
Financial compensation in the amount of $100.00 will be provided to each participant that completes all phases of this research study; further, individual results of the study can be obtained by all participants following analysis by contacting John Sellers at john.sellers@okstate.edu.

Contacts:
If you need additional information concerning the study contact advisor Dr. Bert Jacobson, 101 CRC, Oklahoma State University, Stillwater, OK 74078, 405-744-2025, bert.jacobson@okstate.edu, or John Sellers, 192 CRC, Oklahoma State University, Stillwater, OK 74078, 405-744-9373, john.sellers@okstate.edu.
If you should have questions about your rights as a research volunteer, you may contact Dr. Hugh Crethar, IRB Chair, 223 Scott Hall, Oklahoma State University, Stillwater, OK 74078, 405-744-3377 or irb@okstate.edu.

Participant Rights:
Participation in this research is voluntary and there is no penalty for your refusal to participate. You are free to withdraw from the study at any time and revoke your consent to participate at any time without penalty.

Signatures:

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy of this form has been given to me.

_____ _____

Signature of Participant Date

I certify that I have personally explained this document before requesting that the participant sign it.

_____ _____

Signature of Researcher Date

APPENDIX G

RECRUITMENT SCRIPT

Dear Potential Participant,

My colleagues and I are currently interested in investigating the effects of intermittent hypoxic training on hypobaric performance. In other words, we are interested in learning about the efficacy of simulated altitude exercise training on aerobic performance at altitude. We are doing so with the hope of gaining more insight in this area in order to assist those responsible for the physical training programs in the U.S. Armed Forces.

This study will involve the completion of the following testing procedures:

- Once you have read through and signed the informed consent document you will be asked to schedule a day to begin the study. Once you provide your consent you will be scheduled to participate.

- Depending on the group you are randomly selected to participate in, you will be asked to attend testing on either four or five separate days, the pre-assessment testing days, the

- post-assessment testing days approximately 6 weeks following the initial testing day, and if you are selected to participate in the experimental group, the final testing day approximately 2 weeks following the post-assessment testing day.

On the first day of both the pre- and post-assessment testing days you will be asked to complete the following at the OSU Health & Human Performance Laboratory located in the Colvin Recreation Center:

- Complete height, weight, and body composition (7-site skinfold) testing
- Complete a 5 minute warm-up on a stationary bicycle
- Complete a maximal oxygen uptake (VO2 max) treadmill test. This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test.
- Complete a blood draw performed by an Oklahoma State University Health Sciences Center medical professional

On the second day of both the pre- and post-assessment testing days you will be asked to complete the following at the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine:

- Complete a 5 minute warm-up on a stationary bicycle
- Complete a maximal oxygen uptake (VO2 max) treadmill test in a simulated altitude chamber. This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test.

On the fifth testing day, which will only apply if you are selected to participate in the experimental training group, you will be asked to complete the following at the Oklahoma State University Center for Health Sciences Center for Aerospace and Hyperbaric Medicine:

- Complete a blood draw performed by an Oklahoma State University Health Sciences Center medical professional
- Complete a 5 minute warm-up on a stationary bicycle

- Complete a maximal oxygen uptake (VO2 max) treadmill test in a simulated altitude chamber. This test consist of 3-minute stages with increases in intensity every stage until exhaustion is reached and the participant ends the test.

If you decide to participate, and you complete all phases of this research study, you will be compensated in the amount of $100. If you are willing to participate in the aforementioned study, please email me indicating your willingness to participate.

Thank you in advance for your time.

Sincerely,

John Sellers
(918) 625-9945
john.sellers@okstate.edu

APPENDIX H

UNIVERSITY HEALTH SERVICES BLOOD DRAW LETTER

Health and Human Performance

192 Colvin Recreation Center
Stillwater, Oklahoma 74078
P 405.744.9573

Dear University Health Services,

This individual is a research participant for the study titled: The effects of normobaric hypoxic training on hypobaric performance. Please direct billing to account: 1-559826. If you have any questions do not hesitate to contact me. Or you may speak with the laboratory manager, Patricia Elsener.

Thank you,

John Sellers
Graduate Research Assistant
Oklahoma State University
Health & Human Performance
192 Colvin Recreation Center
(918) 625-9945
john.sellers@okstate.edu

VITA

John H. Sellers

Candidate for the Degree of

Doctor of Philosophy

Dissertation: THE EFFECTS OF NORMOBARIC INTERMITTENT HYPOXIC TRAINING ON HYPOBARIC PERFORMANCE

Major Field: Health, Leisure, & Human Performance

Biographical:

I was born and raised in Oklahoma and am the oldest of four children. I spent the majority of my youth and early adulthood involved with competitive sports and spent a good majority of my free time from athletics doing chores with and for my parents. It was through sports and chores that my parents instilled in me the work ethic that has allowed me to be in this position today and I look forward to my future in the United States Army.

Education:

Completed the requirements for the Doctor of Philosophy in Health & Human Performance at Oklahoma State University, Stillwater, Oklahoma in May 2016.

Completed the requirements for the Master of Science in Health & Human Performance at Oklahoma City University, Oklahoma City, Oklahoma in July 2010.

Completed the requirements for the Bachelor of Science in Business Administration at Oklahoma State University, Stillwater, Oklahoma in May 2008.

Experience:
Graduate Assistant, Oklahoma State University
August 2013-May 2016
Lecturer, University of Central Oklahoma
August 2011-May 2012
Worked as a personal trainer and fitness specialists at various gyms and wellness centers

Professional Memberships:
National Strength & Conditioning Association (2010 – Present)
American College of Sports Medicine (2015 – Present)