SEX DIFFERENCES IN PHYSIOLOGICAL RESPONSES TO ACUTE HYPOXIA IN HUMANS: CURRENT EVIDENCE AND DIRECTIONS FOR FUTURE RESEARCH

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Abstract

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Acute exposure (<48 hours) to hypoxic environments poses physiological challenges which are amplified during periods of exercise or physical activity. This is particularly important for military personnel, athletes, and researchers sojourning to higher elevations (>2,500m) due to the potential risk of developing acute mountain sickness and implications for health and performance. Physiological responses to hypoxia have been extensively described, yet important knowledge gaps exist concerning sex differences in these physiological responses. Direct comparison of studies is challenging due to differing durations and magnitudes of altitude, hypobaric versus normobaric hypoxia, passive versus exercise conditions, and differing exercise intensities. The present review aims to critically evaluate current literature regarding cardiovascular and thermoregulatory responses to acute hypoxia at rest and during exercise, while highlighting areas for future research related to sex differences. Acute hypoxic exposure is characterized by a decreased arterial oxygen saturation with a concomitant increase in ventilation and heart rate via stimulation of the autonomic nervous system. Despite similar heart rate and oxygen saturations between sexes, men demonstrate a higher sympathetic response to hypoxia compared to women.

Cardiovascular alterations in cardiac output, stroke volume, and blood pressure occur upon exposure to hypoxia, however, comparisons between sexes are sparse. Thermoregulatory responses to hypoxic exposure, in combination with cold, should be considered, due to potential implications for predicting risk for acute mountain sickness. Research remains limited and inconsistent, highlighting the need to prioritizing sex-related comparisons during passive and exercise responses to hypoxic exposure, with implications for performance and acute mountain sickness risk.

Keywords: altitude; women; hypobaric; cardiovascular; thermoregulatory

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Foreword

This thesis will be submitted to *The American Journal of Physiology: Regulatory, Integrative, and Comparative Physiology*, an international peer-reviewed journal published by The American Physiological Society; it has been formatted according to the style guide for that journal.

Chapter 1

Author Contributions

This thesis represents a collaborative effort amongst Seaver Wait, Nisha Charkoudian, Ph.D., Jared Skinner, Ph.D., and Caroline Smith, Ph.D. Seaver Wait assumes primary authorship of this work and was responsible for literature review and drafting of the manuscript. All authors contributed to manuscript conceptualization, editing, and review for submission.

Chapter 2

Introduction

SEX DIFFERENCES IN PHYSIOLOGICAL RESPONSES TO ACUTE HYPOXIA IN HUMANS: CURRENT EVIDENCE AND DIRECTIONS FOR FUTURE RESEARCH

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Hypoxia is defined as low tissue oxygenation which usually accompanies exposure to hypobaric environments (i.e., altitude), where barometric pressure is reduced below that of sea level (760 mmHg) [1]. Acute exposure to hypoxia poses many physiological challenges, which are amplified during exercise or physical exertion [2]. Acute physiological responses are elicited in response to the low partial pressure of oxygen, subsequent hypoxemia and insufficiency of oxygen available for bodily tissues [3, 4]. However, many of these responses have been researched in isolated settings with a small sample size that is unrepresentative and thus not generalizable to the normal population [5]. Specifically, there is an underrepresentation of women in current literature, despite important physiological differences compared to men [6]. Limited research is available regarding potential sex-related differences in physiological responses to hypobaric or normobaric hypoxia, and data currently available provides conflicting results. This presents an important knowledge gap as both men and women sojourn to high altitudes for research, athletic, military, and work-related purposes, and may present differing risk of developing acute mountain sickness (AMS) [5, 7]. Preliminary data suggests women may be more vulnerable to both AMS development and worsening symptom severity compared with men, yet data are variable [6]. If sex differences do exist, investigating the physiological basis for those differences will help inform future research directions and safety guidelines. As such, our goal in the present review is to critically evaluate current knowledge regarding cardiovascular and thermoregulatory responses to acute hypoxia with an emphasis on sex-differences and to highlight current gaps in knowledge as potential areas for future research.

Acute Mountain Sickness and Hypoxic Environments. Low and moderate altitude are commonly defined to begin at elevations equivalent to 0 and 1,500m, with a fraction of inspired air (FiO_2) equal to 21% and 18%, respectively [8]. Progression to high altitude (≥2,500m, FiO_2 = 15%) elicits physiological responses with important health and performance implications [8]. Specifically, the development of AMS and potential progression to more serious high-altitude illness becomes of greater concern. The Lake Louise Consensus Group defines AMS as the presence of headache in an unacclimatized person who recently arrived at an altitude above 2500 meters, plus the presence of one or more of the following: anorexia, nausea, vomiting, insomnia, dizziness, or fatigue [9]. To understand and combat these potential complications, research has focused on the underlying cardiovascular and thermoregulatory responses to hypoxia that accompanies acute exposure to hypobaria [5, 10, 11]. This is important to note, as much of the current research produces conflicting results making it difficult to establish the relative risk of AMS development between men and women [6, 12]. For example, a recent meta-analysis by Hou et al. (2019) found women to be 1.24 times more likely to develop AMS as a result of hypoxic exposure (RR = 1.24, CI 1.09, 1.41) compared to men. However, the differing experimental conditions between studies makes the characterization of AMS between men and women difficult. While research has provided insight regarding human tolerance to hypoxic stress, the conclusions are to be viewed with caution, as the variables accompanying differing testing methodologies and conditions can produce conflicting results.

It is widely recognized that the physiological responses to high altitude are influenced by the change in ambient barometric pressure from sea level, making the

simulation of terrestrial high altitude difficult in a laboratory setting [14]. This potentially compromises the applicability of results collected from environmental chambers that mimic high altitude utilizing normobaric hypoxia [14]. Thus, efforts have been made to establish whether there are meaningful differences between varying methods of simulated hypoxic exposure. These methods primarily differ in either ambient oxygen saturation (normoxia vs. hypoxia), barometric pressure (normobaric vs. hypobaric), or a combination of the two. Boos et al. [14] aimed to clarify inconsistencies in the literature by completing a four-way comparison between normobaric normoxia (NN), normobaric hypoxia (NH), hypobaric hypoxia (HH), and terrestrial altitude (TA) in relation to cardiovascular function during physical exertion. It is worth noting these data identified significant differences amongst heart rate ($HR_{[bpm]}$) and arterial oxygen saturation ($SpO_{2[\%]}$) at both two hours and 15 minutes post-exercise (120 minutes at 55%W_{max}), dependent upon exposure condition. HR responses two hours after initial exposure were significantly higher in TA compared to NH (89.4 ± 10.0bpm vs. 76.6 ± 15.3bpm, $p < .05$) [14]. Additionally, SpO_2 values reflected significant differences between TA, NH, and HH conditions when recorded within 15 minutes of initial exposure (89.3 ± 2.2% vs. 93.6 ± 2.5% vs. 89.8 ± 5.0%, $p < .01$) [14]. Based on these findings, Boos et al. [14] suggest both the environmental conditions and experimental protocol (passive vs. exercise) are capable of influencing physiological response to high altitude, whilst recognizing only cardiovascular responses were assessed. These conclusions are supported by Fulco et al. [15] who found that NH exposure could not be used interchangeably with HH as a preacclimatization strategy to reduce AMS, further suggesting environmental conditions impact physiological responses. As such, we

recognize the inherent challenges of comparing similar studies with the understanding that different experimental designs and environmental control may impact the results. Conclusions drawn from other research in this review will be analyzed in recognition of the fact that limited data are currently available to support the valid application of other physiological variables between environmental and simulated conditions.

Chapter 3

Cardiovascular Responses

Arterial Oxygen Saturation. Acute exposure to high altitude results in hypoxemia (low PaO_2), and potential widespread tissue hypoxia [16]. A decrement in PaO_2 often results in a subsequent decline in SpO_2 which is important to consider due to considerable research indicating an association with the risk of developing AMS [17]. Faulhaber et al. [17] recruited 55 healthy male adults to complete a 30-minute passive exposure protocol in NH (4,500m, FiO_2 =12.5%) to assess acute SpO_2 response and identify potential links to AMS development. AMS symptom development was determined by the Lake Louise Score (LLS) administered at 3-hour intervals post-exposure, with scores ≥ 3 reflecting the presence of AMS. Direct comparison between those with AMS (n=34) versus those without (n = 21) indicated a significantly lower SpO_2 in individuals with AMS (79.8 ± 3.6% vs. 83.9 ± 3.9%, $p < .01$) [17]. Similar results were noted in research completed by Karinen et al. (2010), in which 74 healthy adults (64M, 10F) were monitored during physical exertion on their ascent to varying levels of TA (2,400m – 5,300m). At 4,300m, both resting (R-SpO_2) and exercise (Ex-SpO_2) were lower in individuals with AMS (n = 17) as opposed to those without (n = 66) (88 ± 2% vs. 91 ± 3%, $p < .05$, and 80 ± 2% vs. 85 ± 4%, $p < .01$ respectively) [18].

Based on these findings, researchers suggest that both reduced R-SpO_2 and Ex-SpO_2 may be plausible predictors in identifying AMS susceptibility [18].

The potential impact that the SpO_2 response may have on predicting AMS is well established in the literature, yet research investigating potential sex differences of this response is limited and has produced conflicting results. Previous research has shown women to have a significantly, albeit only slightly higher, resting SpO_2 in NN than men but analyzing respective changes in hypoxic conditions are less well characterized [14]. Shen et al. [19] recruited 99 healthy, young adults (67M, 32F) to complete an abbreviated submaximal exercise protocol (9 minutes at 50W) at low altitude (500m) while collecting data for comparison after ascent to TA (4,100m). After exercise at low altitude, women recorded a higher SpO_2 as opposed to men (97.6 ± 0.8% vs. 96.8 ± 1.3%, $p < .001$) [19]. Upon arrival to 4,100m, women had a lower R-SpO_2 (85.9 ± 4.3% vs. 87.8 ± 3.5%, $p < .05$) and greater RSpO_2 reduction (-11.6 ± 4.2% vs. -9.1 ± 3.9%, $p = .005$) in contrast to men [19]. Researchers also noted a higher rate of AMS in women compared to men (75.0% vs. 34.3%, $p < .001$), and further regression analysis indicated a correlation in AMS presence with the decrement in SpO_2 upon arrival to 4,100m in women, but not in men (adjusted $OR = 1.47$, 95% CI 1.01 to 2.12, $p = 0.042$) [19]. While limitations to the research included large age differences between women and men (23.3 ± 3.7 vs. 28.5 ± 9.3, $p < .001$), a small female sample size ($n = 32$), and a low intensity exercise protocol, the authors do speculate their preliminary findings point to major sex differences in physiological responses to high altitude and development of AMS.

Conflicting results are reported by Horiuchi et al. [20] who observed similar reductions in SpO_2 between the sexes. Twenty young, healthy adults (10M, 10F)

completed a low intensity exercise protocol in NN and NH (3,200m, FiO_2 = 13%) conditions, each completed on separate days in a randomized order. Despite greater SpO_2 decrements in NH compared to NN (~10% in men and ~14% in women) the results indicated no significant interaction between sex and oxygen condition in NN [$F(7, 126) = 1.65$, $p = 0.127$] and NH [$F(7, 126) = 1.34$, $p = 0.236$] [20]. However, further bivariate analyses' revealed contributions of other breathing and circulatory responses (i.e., energy expenditure (EE), ventilation (V_E), and HR) which, when combined, could be used to generate a model to predict changes in SpO_2 in both men ($r^2 = .900$, $p < .001$) and women ($r^2 = .957$, $p < .001$) [20]. Despite being preliminary findings, this suggests more complex underlying mechanisms responsible for sex-related hypoxemia in high altitude. This alone supports the need for future investigations to confirm if arterial oxygen saturation can be used as reliable tool to predict and assess the development of AMS.

Cardiac Function. Cardiac function also plays an important role at high altitude. Changes in common measures of cardiac function (i.e., HR, cardiac output ($\dot{Q}$), stroke volume (SV), etc.) are well established both at rest and during exercise upon exposure to acute hypoxic conditions, and often implicates them in the development of AMS symptoms [9, 21]. Fukuda et al. [21] designed a study where nine healthy male adults completed a maximal exercise test in NN and NH (3,000m, FiO_2 = 14.4%) conditions to analyze various measures of cardiac function. At rest, HR and SpO_2 were the only variables found to be significantly higher during NH as opposed to NN exposure (73 ± 4bpm vs. 70 ± 4bpm, $p < .01$, and 90 ± 1% vs. 98 ± 0%, $p < .001$ respectively) [21]. However, the maximal exercise protocol appeared to elicit a more marked cardiac

response. $\dot{V}O_2$, $\dot{Q}$, and SV all demonstrated a significant decrease in NH compared to NN (2761 ± 99mL/min vs. 3039 ± 133mL/min, $p < .005$; 26.7 ± 2.1L/min vs. 30.2 ± 1.8L/min, $p < .05$; 145 ± 11mL vs. 163 ± 11mL, $p < .05$)
[21]. Interestingly, no significant changes were recorded in HR during maximal exercise in NN and NH (182 ± 3bpm vs. 181 ± 2bpm) [21]. This is worth noting, as it indicates that the overall decrease in $\dot{Q}$ during exercise in NH cannot be attributed to a decrease in HR, but primarily from an attenuated SV response [21]. Several limitations should be noted, including a small sample size and potentially ineffective washout period between testing sessions (3 days). Although, the results do offer some insight into the underlying mechanisms regulating cardiac function at high altitude. Whilst speculative, Fukuda et al. (2010) suggest indices of potential ventricular impairment preceded by disruptions in the electrical activity of cardiomyocytes during acute NH [21]. Further investigation regarding potential electrical activity disruption of cardiomyocytes at high altitude was conducted by Coustet et al. [10] via electrocardiographic (ECG) analysis of 456 healthy adults (262M ,194F) in NH prior to an ascent to TA (4,000m) collected from 2010 to 2012. Data were collected throughout a 20-minute exercise protocol in NN and NH (4,800m, $FiO_2 = 11.5\%$) and subsequently compared to results indicating the presence of severe high-altitude illness (SHAI). SHAI is an encompassing term used to describe more serious, life-threatening altitude pathologies including high altitude pulmonary and cerebral edema (HAPE and HACE respectively) in comparison to AMS. When comparing ECG data at moderate exercise in NN and NH at the same HR, the results identified no hypoxia-induced conduction disorders, arrhythmia, or changes in the QRS axis (vector of ventricular activation) [10]. However, the amplitude of the P-waves (atrial

depolarization) in lead V_1 was significantly lower in NH compared to NN (1.44 ± 0.54mm vs. 1.52 ± 0.55mm, $p < .05$) [10]. The amplitude of the R, S (ventricular depolarization), and T-waves (ventricular repolarization) were also significantly higher in NN compared to NH respectively (15.26 ± 5.97mm vs. 14.26 ± 5.63mm, $p < .05$; 8.41 ± 3.58mm vs. 7.83 ± 3.44mm, $p < .05$; 3.01 ± 1.75mm vs. 2.77 ± 1.66mm, $p < .05$) [10]. While no standard ECG component was found to have a correlation with the individuals who developed SHAI this research does support the theory regarding potential electrical changes facilitating ventricular dysfunction at high altitude. Although compelling, the research by Coustet et al. [10] failed to analyze if differences in ECG characteristics were present between men and women. This is important to consider, as 15 of the 22 of the individuals (68%) who developed SHAI were female. Furthermore, AMS is often considered to be a predecessor and predictor to SHAI, a much more serious form of altitude illness. This potentially explains why no correlations were made between ECG characteristics and SHAI, due to the very high standard defining the presence of altitude illness in this study. Future research should employ objective measures of AMS to determine if correlations to ECG characteristics are present at high altitude. This has potential utility if ECG data can be used to predict individuals at increased risk of developing SHAI.

Adaptations in cardiac function have been observed at rest and during exercise upon exposure to acute hypoxic conditions, yet research investigating potential sex differences is minimal. Boos et al. [14] recruited 14 young, healthy adults (7M, 7F) who were well-matched for age (25.9 ± 3.2 vs. 27.3 ± 4.4, $p = .51$) to investigate cardiac function variables similar to Fukuda et al. (2010), in addition to AMS measures. Data

were collected during rest in NN, during rest immediately after a 5-minute exercise step test in NH (4,800m, FiO_2 = 11.4%), and again in NN after 180 minutes of total NH exposure. The results did not identify baseline differences between men and women when assessing HR, systolic and diastolic blood pressure (SBP/DBP), and SpO_2 [14]. However, expected baseline differences were noticed between sex for SV and $\dot{Q}$. Men recorded significantly higher SV and $\dot{Q}$ values compared to women (85.3 ± 19.0mL vs. 62.3 ± 12.7mL, $p < .05$; 5.4 ± 1.6L/min vs. 4.0 ± 0.9L/min, $p < .05$) [14]. While these findings are not novel, it prevents potential differences noted during NH exposure from being attributed to a population sample uncharacteristic of what would be normally seen between sex. The main effect of time and NH exposure was a significant increase in HR and, as expected, in LLS as an index of AMS ($F = 9.9$, $p = .0006$; $F = 15.0$, $p = .002$), and a significant decrease in SBP, DBP, and SV ($F = 7.0$, $p = .02$; $F = 4.1$, $p = .07$; $F = 2.8$, $p = .09$) [14]. A main effect of sex indicated a higher SV and $\dot{Q}$ in men ($F = 11.9$, $p = .005$; $F = 4.6$, $p = .049$) despite a higher HR in women during NH (80.3 ± 10.2bpm vs. 69.7 ± 10.7bpm, $p < .05$) [14]. Finally, there was no observed interaction between NH exposure and sex, leading to the conclusion there was no sex dependent effect of NH on the measured variables [14]. Though no significant differences were noted between sex, a small sample size and lack of experimental control regarding the female menstrual cycle limit the conclusions drawn from this study. Researchers acknowledge that the female participants were all at different phases of their menstrual cycle, and 4 were on oral contraceptives. These are important variables to consider as potential confounding factors impacting the role of sex hormones in the physiological responses observed. Lahm et al. [22] observed menstrual cycle to be a determinant cause in the attenuation of

acute hypoxic pulmonary vasoconstriction based on endogenous estrogen. This suggests sex hormones have overlapping chemical and physiological properties which might impact cardiovascular function and prove beneficial in mitigating AMS development [14]. Future investigations are necessary to elucidate the putative effects of female sex hormones on AMS susceptibility.

Autonomic Control. Autonomic nervous system (ANS) modulation of cardiovascular function is well characterized at sea level in healthy adults, both at rest and during exercise. The arterial chemoreflex response to systemic hypoxia results in increased sympathetic nerve activity, which increases heart rate and peripheral vascular resistance among other variables. Many of the aforementioned cardiovascular responses seen at high altitude are typically mediated by the function of the ANS, and prevailing hypotheses' point to the role of the ANS in facilitating AMS via the cardiovascular system [23]. Particularly, much of the current research attempts to focus on the balance between parasympathetic and sympathetic outflow observed during hypoxic conditions. The presence of arterial hypoxemia stimulates the carotid bodies, which, through autonomic innervation, leads to the activation of the adrenergic system and subsequent increased level of circulating catecholamines [10]. However, the extent to which this impacts cardiac function at high altitude is poorly characterized. Botek et al. [16] attempted to establish this link by gathering 29 healthy, young adult men to monitor SpO_2 and heart rate variability (HRV) in a resting supine position during NH (6,200m, FiO_2 = 9.6%). Spectral analysis of HRV was used to quantify autonomic cardiac activity via low frequency (LF, representing sympathetic activity) (0.05-0.15Hz) and high frequency (HF, representing vagal activity) (0.15-0.50 Hz) power transformed by

natural logarithm (Ln) [16]. Based on SpO_2 response in NH, participants were retrospectively divided into two groups, resistant (RG, SpO_2 = 80.8 ± 7.0%) and sensitive (SG, SpO_2 = 67.2 ± 2.9%) [16]. SpO_2 decreased significantly in both RG and SG ($p < .001$) whilst HR significantly increased ($p < .001$) during hypoxic exposure [16]. In SG, the LnLF variable decreased significantly during NH compared to NN (5.0 ± 1.7ms^2 vs. 7.2 ± 1.3ms^2, $p = .002$) [16]. In both the RG and SG, the LnHF significantly decreased during NH compared to NN (6.5 ± 1.4ms^2 vs. 7.2 ± 1.3ms^2, $p = 0.013$; 5.0 ± 1.7ms^2 vs. 7.2 ± 1.3ms^2, $p < .001$) respectively [16]. In the RG, no changes in what is often regarded as sympathetic modulation (Ln LF/HF) were significant between rest, hypoxia, and recovery [16]. However, in the SG, the Ln LF/HF ratio was significantly increased during the hypoxia phase compared to rest (0.2 ± 1.0 vs. -1.1 ± 1.0, $p < .001$) [16]. Accordingly, the Ln LF/HF of the SG was significantly higher than that of the RG during hypoxia (0.2 ± 1.0 vs. -1.2 ± 0.9, $p < .001$) [16]. Based on these results, researchers concluded that basal vagal activity is not a suitable marker to predict SpO_2 during NH. However, further correlational analysis revealed a moderately positive association between ΔLnHF and ΔSpO_2 ($r = 0.595$, $p < .001$), and a moderately negative association between ΔLnLF/HF and ΔSpO_2 ($r = -0.461$, $p = 0.012$) during NH [16]. While this research did note NH induced an individual desaturation response associated with changes in sympathovagal balance, the introduction of sex adds a layer of complexity which prevents these findings from being viewed decisively. It is also worth mentioning the limitations regarding spectral analysis of HRV as an indicator of autonomic function. Several studies have outlined discrepancies among indices of HRV (i.e., LF, HF, etc.), impacting the validity and reliability of these measures. For example,

administration of atropine during resting conditions elicits a bradycardic effect via a decreased R-R interval, yet HRV indices do not demonstrate a consistent correlation with bradycardia [24]. This suggests HF variability may not be an exclusive index of vagal tone. Similar inconsistencies were found in a similar study, where the onset of exercise would be expected to facilitate an increase in cardiac sympathetic activity, yet LF power decreased [25].

Botek et al. [7] expanded on their previous research by investigating potential sex differences in autonomic cardiac function and SpO_2 responses during simulated NH. HRV, $\dot{V}O_{2max}$ and SpO_2 were assessed among 58 healthy, young adults (28 men) in a resting supine position during NN, NH (6,800m, FiO_2 = 9.6%) and recovery in NN. Researchers opted to implement $\dot{V}O_{2max}$ as former literature had previously noted a higher AMS incidence with higher VO_{2max}. This speculation is commonly explained as a result of relative hypoventilation mediated by blunted chemoreceptor sensitivity in individuals with higher $\dot{V}O_{2max}$ [7]. Thus, both men and women with a high $\dot{V}O_{max}$ are likely to experience decrements in SpO_2, potentially putting them at higher risk for AMS [7]. Results indicated no significant differences in SpO_2 between men and women during NH exposure (71.9 ± 7.5% vs. 70.8 ± 7.1%, p = .376) [7]. No significant differences in vagal activity (LnHF) were observed between sexes across any of the three phases. However, the index of sympathovagal balance (LnLF/HF) showed men to have significantly higher sympathetic activity compared to women during NH (0.5 ± 1.3 vs. -0.6 ± 1.4, p < .001) [7]. $\dot{V}O_{2max}$ data during NH were used to create four groups based on aerobic capacity with regard to sex. Women with the lowest $\dot{V}O_{2max}$ (FL, N = 7, 36.2 ± 3.9 mL/kg/min^{-1}) were analyzed separately from those with the highest $\dot{V}$

O_{2max} (FH, $N = 7$, 57.0 ± 8.3 mL/kg/min^{-1}); men were divided into the same categories (ML, $N = 7$, 49.5 ± 4.9 mL/kg/min^{-1}; MH, $N = 7$, 68.4 ± 5.2 mL/kg/min^{-1}) [7]. No significant difference was noted in ΔSpO_2 between the FL and FH groups (-27.9 ± 5.7% vs. -29.4 ± 6.7%, $p = .659$, $d = .24$, small effect) [7]. Notably, the ΔSpO_2 slope between the male groups showed the MH group to have significantly steeper decline in SpO_2 during NH compared to the ML group (-28.4 ± 3.6% vs. -20.0 ± 8.0%, $p = .019$, $d = 1.34$, large effect) [7]. In relation to sex differences, ΔSpO_2 between the ML and FL groups showed the ML group to exhibit significantly less change compared to FL ($p = .027$, $d = 1.26$, large effect) [7]. However, no differences were noted between the MH and FH groups. This suggest that despite similar SaO_2, men exhibit a higher sympathetic response to NH compared to women, bearing in mind the limitations of HRV analysis. Results also imply a correlation between aerobic capacity and SpO_2 desaturation in men, but such a relationship did not exist between women. This is a relevant conclusion, as it leads to speculation that differences in autonomic control between men and women are present in hypoxic conditions. If autonomic control is directly related to hemodynamics and cardiac function variables, which are then subsequently used to predict and monitor responses to hypoxic environments, then identification and function of the different underlying mechanisms modulating the ANS response to altitude between sexes will be important in future research.

Research investigating autonomic control on vascular responses during hypoxic exposure are also relevant, but conclusions remain unclear. Specifically, the potential relationship between AMS and changes in systemic BP has received little attention and produced conflicting results, despite the known association between autonomic

cardiovascular dysfunction and AMS. Winkler et al. [26] claim that while hypoxic exposure is shown to directly induce vasodilation at the peripheral level and vasoconstriction at the pulmonary level, systemic BP should remain stable through the activity of arterial baroreceptors [26]. In response to systemic vasodilation, baroreceptors decrease firing rate to allow the vasomotor center to uninhibit sympathetic activity, leading to systemic vasoconstriction [26]. This response is theorized to be a positive physiological adjustment due to competition between local vasodilator reflexes attempting to secure adequate blood flow to match metabolic demand, and neural vasoconstrictor reflexes attempting to maintain arterial pressure [27]. However, these conclusions are not uniform amongst all investigations. Niebauer et al. [28] attempted to identify systemic blood pressure responses to acute NH in 77 healthy, young adults (43 men) over a 12-hour period. Participants were exposed to NH (4,500m, FiO_2 = 12.6%) during a passive protocol, where BP and LLS were collected at 30 min., 3-, 6-, 9-, and 12-hour intervals. Results indicated 73% of participants developed AMS (N = 56, LLS ≥ 3), with a higher prevalence noted in women compared to men (83% vs. 65%) although it did not reach statistical significance [28]. Within 30 minutes of NH exposure, SBP, DBP, and mean arterial blood pressure (MABP) all demonstrated a significant decrease in comparison to baseline values (112 vs. 128.5mmHg, $p < .05$; 66.0 vs. 73.5mmHg, $p < .05$; 81.3 vs. 90.5mmHg, $p < .05$) [28]. It should be noted SBP remained significantly lower at all time intervals in comparison to baseline, however, this was not the case with DBP. Beginning at 6 hours of NH exposure, DBP values were no longer significantly different to baseline. Significant between group differences in SBP were observed in those with AMS as opposed to those without when comparing baseline to the 30-minute

interval (-17.5 vs. 11.0mmHg, $p < .01$) [28]. These results further indicate a degree of autonomic dysfunction is present in those suffering from AMS, and even directly contradicts the prevailing theory proposed by Winkler et al. [26].

Chapter 4

Thermoregulatory Responses

Core and Skin Temperature. Despite the widely recognized compensatory physiology responses to acute hypoxia, thermoregulatory responses have received limited attention and available data provide conflicting results. Thermoregulatory responses are often heavily integrated via the hypoxic effect on fluid balance, cardiovascular responses, and blood flow redistribution, making the current literature difficult to compare [29]. Nevertheless, current theories regarding the impact of hypoxia on thermoregulatory responses has given rise to the idea of hypoxia-induced anapyrexia (decreased core body temperature), which has been well established in animal models, but has yet to be fully elucidated in humans [30]. This mechanism is thought to be protective in nature by reducing oxygen demand in the body due to reduced ambient PO_2 and subsequent hypoxemia. This is accomplished through a leftward shift in the oxyhemoglobin dissociation curve, increasing the affinity of hemoglobin to bind oxygen, allowing for increased oxygen loading at the lungs and subsequent delivery to bodily tissues, thereby reducing overall $\dot{V}_E$ [4, 30]. Although this avenue has yet to be fully explored, studies attempting to standardize core and skin temperature responses in hypoxic conditions produce conflicting results, preventing clear conclusions from being formed. Dipasquale et al. [11] recruited 10 healthy, young adults (6 men) to identify if

NH induced anapyrexia in association with hypoxemia. Participants were seated and exposed, in order, to the following environmental conditions: NN (FiO_2 = 21%), NH (FiO_2 = 14%), and NH (FiO_2 = 12%) for 30 minutes each in a single day. Core temperature was monitored via a rectal thermometer (Tre). Results showed a significant decrease ($p < .0001$) in average SpO_2 by 6.1% in NH14 and 16.0% in NH12 compared to 97.1% baseline in NN [11]. Tre was also reduced during NH, with a graded effect noted based on severity of exposure. Average Tre was 0.13°C lower during NH14 ($p = .014$) and 0.25°C during NH12 ($p = .0001$) compared to NN [11]. Researchers subsequently found SpO_2 to be a significant predictor of Tre ($p = .0001$), therefore suggesting the change in Tre to be a direct result of hypoxemia.

Conflicting results were observed by Seo et al. [4] in 10 young, healthy adults with a similar study design to Dipasquale et al. [11] Participants were seated in both NN and NH conditions with FiO_2 percentages equivalent to 21% (NN), 17% (NH), and 13% (NH) for 60 minutes in a counterbalanced manner. As expected, there was a significant condition by time interaction for SpO_2 ($F = 18.924$, $p < .001$) with SpO_2 reduced during exposure to hypoxia in NH17 (6%) and NH13 (13%), but not in NN21, indicating a clear dose-response relationship to NH severity ($p < .001$) [4]. However, no significant interaction was noted for Tre ($F = 1.658$, $p < .124$), demonstrating a decreasing trend across NN21, NH17, and NH13 respectively (0.2 ± 0.1°C, 0.3 ± 0.1°C, 0.3 ± 0.2°C) [4]. Tsk was also unchanged from baseline in NN21, NH17, and NH13, thus indicating no significant change in thermal gradient (Tre – Tsk). As a result, no meaningful association was identified between SpO_2 and Tre; NN21 ($R^2 = .352$, $p = .071$), NH17 ($R^2 = .021$, $p = .693$), and NH13 ($R^2 = .155$, $p = .260$) [4]. These findings provided no

indication of hypoxia-induced anapyrexia. The results and discrepancies between Seo et al. [4] and Dipasquale et al. (2015), although marginally different, can be largely attributed to methodology. In both cases, researchers elected to have participants in a passive state, ultimately reducing metabolic demand and subsequent heat production, potentially explaining the lacking presence of a thermal gradient in the research conducted by Seo and colleagues [4]. This passive state, in conjunction with ambient temperatures controlled at 25°C in both studies, are not necessarily indicative of the true environmental and physical demands placed on individuals sojourning to terrestrial high altitude, reducing generalizability of the results. Additionally, the findings by Dipasquale et al. [11] are viewed with caution owing to the absence of an effective washout period, making it difficult to characterize Tre responses between conditions. This provides a potential explanation for the opposing results.

Research by Coombs et al. [29] was also unable to identify alterations in thermoregulatory responses due to acute hypoxia at fixed rates of heat production. In this study, eight healthy male participants completed a 45-minute cycling protocol, once in NN (FiO_2 =21%) and twice in NH (FiO_2 = 13%). Trials were designed to 1) elicit two different %$\dot{V}O_{2peak}$ at the same heat production; and to 2) elicit different heat production at the same %$\dot{V}O_{2peak}$. Results indicated that at a fixed %$\dot{V}O_{2peak}$, changes in rectal (ΔTre) and esophageal (ΔTes) temperature were significantly higher at the end of the exercise protocol in NN compared with NH (ΔTre: 0.76°C; ΔTes: 0.64°C vs. ΔTre: 0.56°C; ΔTes: 0.42°C, $p < .01$) [29]. However, at fixed heat production, ΔTre (0.75°C, $p = .77$) and ΔTes (0.63°C, $p = .69$) were not significantly different in NN

compared to NH [29]. These data demonstrate, using a within-subjects design, that hypoxia did not independently influence thermoregulatory responses.

It is also important to note that several studies involve confounding influences such as AMS development, further complicating the interpretation of results. One study in particular was able to find a significant correlation between changes in core body temperature (T_{core}) with changes in SpO_2 and AMS scores [31]. Researchers assessed T_{core} and SpO_2 in 40 alpinists at 1,000m TA and again after ascent to 3,100m TA along with AMS scores. Three alpinists developed AMS (LLS ≥ 3), demonstrating a 0.87 ± 0.12°C rise in T_{core} in conjunction with 10.67 ± 1.15% reduction in SpO_2 [31]. In those without signs of AMS, temperature did not change significantly (0.02 ± 0.14°C) and SpO_2 decreased by 4.59 ± 0.82% [31]. Further analysis indicated a significant correlation with T_{core} and SpO_2 change between the two altitudes ($r^2 = .408$, $p < .01$) and with AMS scores ($r^2 = .814$, $p < .01$) [31]. In addition, when ascending to high altitude individuals are often carrying load during physical exertion. This factor, in conjunction with decreases in ambient temperature and humidity, all contribute to a 'multi-stressor' environment making the interpretation of thermoregulatory responses difficult to characterize.

The influence of hypoxia on thermoregulation during exercise yields interesting results. Hypoxia is a well-established stimulator of pulmonary ventilation, where the low partial pressure of inspired oxygen is detected by peripheral chemoreceptors to stimulate ventilation [32]. Exercise or physical exertion is recognized to be an amplifier of the hypoxic ventilatory response (HVR). However, elevated T_{core} has also been suggested as a modulator of the HVR [32]. Chu et al. [32] recruited 11 healthy male adults

to assess whether the elevated sensitivity of ventilation ($\dot{V}_E$) to hypoxia during exercise was accounted for by an elevation in esophageal temperature (T_{es}). Participants completed two 10-minute exercise sessions, separated by one week and randomized, at a steady-state rate of $\dot{V}O_2$ in both normothermic and hyperthermic conditions. Immediately after exercise, participants inhaled a normoxic ($FiO_2 = 21\%$) and hypoxic ($FiO_2 = 12\%$) gas mixture in random order. During the normothermic condition, $\dot{V}_E$ significantly increased from 22.8 ± 2.7L/min immediately after exercise, to 34.5 ± 4.1L/min in the hypoxic condition [32]. During the hyperthermic condition, $\dot{V}_E$ significantly increased from 24.9 ± 2.8L/min immediately after exercise, to 44.6 ± 10.6L/min in the hypoxic condition ($p < .05$) [32]. Further analysis found hyperthermic hypoxia had elicited a significant increase in $\dot{V}_E$ in relation to normothermic hypoxia (44.6 ± 10.6L/min vs. 34.5 ± 4.1L/min, $p = .017$) [32]. Baseline T_{es} prior to exercise was found to be between 37.2 and 37.3°C [32]. In the normothermic exercise condition, participants' average T_{es} was maintained at ~37.1°C during both normoxia and hypoxia [32]. However, during the hyperthermic scenario, researchers found T_{es} to increase significantly ($p < .01$) from baseline before gradually reaching a plateau at ~38.5°C during both normoxia and hypoxia [32]. Researchers ultimately found a significant T_{es} and gas-type interaction evident for $\dot{V}_E$ ($F = 5.8$, $p = .012$), indicating the elevated sensitivity of exercise $\dot{V}_E$ to hypoxia may be modulated by elevations in T_{es}.

Overall, research investigating sex differences regarding thermoregulatory responses to high altitude is scarce, making it challenging to draw definitive conclusions. This is especially concerning given that differences in thermoregulatory response between men and women even at sea level have been debated, often due to

study design exacerbating putative sex-related differences. For example, research failing to match men and women based on individual characteristics and utilizing relative (%VO_{2max}) workloads between unmatched groups prevent the direct analysis of true sex comparisons. Research by Gagnon and Kenny [33] demonstrates these limitations through results showing the rate of metabolic heat production (MHP) to be greater in men compared to women during exercise at 50% $\dot{V}O_{2max}$ ($p < .001$) at sea level, which was paralleled by a greater rate of whole-body evaporative heat loss (EHL) ($p < .001$). Limited conclusions can be drawn from this research, as it is well understood that at 50% $\dot{V}O_{2max}$ men are typically exercising at a greater absolute intensity compared to women. As such, future studies examining sex difference per se, should utilize workloads normalized to watts per kilogram body weight and will need to be conducted with respect to the multitude of additional confounding variables impacting thermoregulation at altitude.

Chapter 5

Conclusions

Acute exposure to high altitude generally results in systemic hypoxia as a result of hypoxemia. While the physiological responses to high altitude are well characterized, research investigating sex differences is limited, and the available data provide conflicting results. This is concerning, as preliminary research suggests the risk for the development of altitude illnesses (i.e., AMS) is different between men and women. With much of the research focusing on high altitude and AMS centered on understanding cardiovascular and thermoregulatory responses, the goal of this review was to critically evaluate the current literature with an emphasis on sex differences and

to highlight current gaps in knowledge as potential areas for future research. Current evidence indicates conflicting results between sexes in regard to arterial oxygen saturation and cardiac function, suggesting complex underlying autonomic mechanisms may be responsible for sex-related differences in the magnitude of hypoxemia at high altitude. While significant increases in sympathetic activity are noted during hypoxia via both direct and indirect measures, some studies suggest the modulation of sympathetic activity is different between sexes. Although sex differences in cardiovascular and autonomic responses to hypoxia have been studied more extensively, in addition to the prevalence of AMS, sex differences in thermoregulatory responses remain understudied. The inherent complexity of thermoregulation at altitude is generally multifactorial, but studies often isolate associated variables, making the characterization of responses difficult. While thermoregulatory theories such as hypoxia-induced anapyrexia are well established in animal models, conflicting results are observed in humans. Moreover, the information relating to sex differences at altitude are scare. With sex-based differences even at sea-level debated due to study design, drawing definitive conclusions that might be observed at altitude is difficult. Future research will need to (1) standardize physiological responses between environmental conditions and testing protocols, (2) identify sex-related differences, and (3) determine if correlations to AMS exist based on sex differences.

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Vita

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