RELATIONSHIP BETWEEN ORTHOSTATIC STRESS RESPONSE
AND ACUTE MOUNTAIN SICKNESS SUSCEPTIBILITY AT HIGH
ALTITUDE: A PILOT STUDY

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ACUTE MOUNTAIN SICKNESS SUSCEPTIBILITY AT HIGH ALTITUDE: A
PILOT STUDY

by

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B.S. IN SPORTS SCIENCE
M.S. IN EXERCISE SCIENCE

DISSERTATION

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RELATIONSHIP BETWEEN ORTHOSTATIC STRESS RESPONSE AND DEVELOPMENT OF ACUTE MOUNTAIN SICKNESS AT HIGH ALTITUDE: A PILOT STUDY

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ABSTRACT

The purpose of this study was to determine whether there is a difference in hemodynamic responses to head-up tilt (HUT) in subjects who do, and do not, experience acute mountain sickness (AMS) during exposure to hypobaric hypoxia. Secondarily, we aimed to determine if those hemodynamic variables altered during HUT correlated with AMS severity. Fifteen participants completed three testing sessions: 1) VO₂max test to determine workload at 50% VO₂max for hypoxia exposure; 2) HUT test consisting of supine rest for 20 min followed by 70° upright tilting for ≤ 40 min; and 3) six hours of hypobaric hypoxic exposure simulating 4572 m where participants performed two, 30 min cycling bouts and rested when not exercising. During HUT, continuous blood pressure monitoring was used to assess systolic and diastolic blood pressure (SBP & DBP), mean arterial pressure (MAP), variability in SBP, DBP, and MAP, and heart rate. AMS scores were determined before and after six hours of hypoxic exposure. Statistical analysis included mixed effects ANOVA to determine changes between supine rest and end of HUT and between selected AMS positive (AMS+) and AMS negative (AMS-) groups. Correlations by linear regression determined associations between HUT...
hemodynamic responses and AMS scores. Statistical significance was set to $p < 0.05$. Those with higher AMS scores tended to have a greater magnitude of change in SBP, DBP, and MAP variability during the HUT test ($r = 0.65$, 0.64, & 0.60, respectively).

Increased blood pressure variability (BPV) indicated a disruption in blood pressure regulation, suggesting that AMS+ individuals may have a disruption in their blood pressure regulation. This increases their susceptibility which could be observed during a postural change prior to hypoxic exposure. In conclusion, BPV during HUT may be a promising predictive variable for AMS but further research is needed. In the future, researchers should consider using sea-level living participants and a range of simulated elevations to determine the predictability of AMS-susceptibility by BPV.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>CHAPTER 1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Study Objectives</td>
<td>4</td>
</tr>
<tr>
<td>Limitations</td>
<td>5</td>
</tr>
<tr>
<td>Assumptions</td>
<td>5</td>
</tr>
<tr>
<td>Hypotheses</td>
<td>6</td>
</tr>
<tr>
<td>Significance of Study</td>
<td>6</td>
</tr>
<tr>
<td>CHAPTER 2 REVIEW OF THE LITERATURE</td>
<td>8</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>8</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td>10</td>
</tr>
<tr>
<td>Search Strategy</td>
<td>10</td>
</tr>
<tr>
<td>Inclusion and Exclusion Criteria</td>
<td>11</td>
</tr>
<tr>
<td>Quality Assessment and Data Extraction</td>
<td>12</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>13</td>
</tr>
<tr>
<td>RESULTS</td>
<td>15</td>
</tr>
<tr>
<td>Search Results</td>
<td>15</td>
</tr>
<tr>
<td>Publication Bias Analysis</td>
<td>15</td>
</tr>
<tr>
<td>Outlier Analysis</td>
<td>15</td>
</tr>
<tr>
<td>Meta-Analysis Results</td>
<td>16</td>
</tr>
<tr>
<td>Meta-Regression Analysis</td>
<td>16</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>24</td>
</tr>
<tr>
<td>Limitations</td>
<td>26</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>27</td>
</tr>
<tr>
<td>CHAPTER 3 MANUSCRIPT</td>
<td>30</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>30</td>
</tr>
<tr>
<td>MATERIALS &amp; METHODS</td>
<td>32</td>
</tr>
<tr>
<td>Participants</td>
<td>32</td>
</tr>
<tr>
<td>Experimental Design</td>
<td>34</td>
</tr>
<tr>
<td>Procedures</td>
<td>35</td>
</tr>
</tbody>
</table>
Statistical Analysis ......................................................................................................................... 39
RESULTS ........................................................................................................................................ 40
Selection of AMS+ and AMS- Groups ............................................................................................. 40
Baseline Participant Descriptors ................................................................................................... 40
Physiological Responses to Head-up Tilt Test ............................................................................... 41
DISCUSSION .................................................................................................................................. 43
Limitations ...................................................................................................................................... 45
CONCLUSION ................................................................................................................................. 46
CHAPTER 4 SUMMARY, RECOMMENDATIONS, & FUTURE DIRECTIONS .................. 48
SUMMARY ...................................................................................................................................... 48
RECOMMENDATIONS .................................................................................................................... 51
FUTURE DIRECTIONS ...................................................................................................................... 51
APPENDICES ................................................................................................................................. 53
APPENDIX A: DISCUSSION OF ADDITIONAL FINDINGS FROM CHAPTER 2 .... 53
APPENDIX B: DISCUSSION OF ADDITIONAL FINDINGS FROM CHAPTER 3 .... 54
APPENDIX C: AMS SCREENING QUESTIONNAIRE ................................................................. 55
REFERENCES ................................................................................................................................. 61
LIST OF FIGURES

Figure 1. Flow chart of study inclusion. AMS+ = acute mountain sickness positive. AMS- = acute mountain sickness negative. LLS = Lake Louise Scale questionnaire…..19

Figure 2. Funnel plot showing standardized mean difference against standard error to demonstrate possible publication bias…………………………………………………………..20

Figure 3. Forest plot showing standardized mean differences (SMD) for 13 studies and 95% confidence intervals (CI) associated with each data point. Some studies used more than one physiological measurement and/or more than one elevation. Red diamonds are the SMDs for the respective groupings. Negative SMDs favor lower values for AMS+ compared to AMS-. Positive SMDs favor higher values for AMS+ compared to AMS-……………………………………………………………………………………………………21

Figure 4. The regression analysis with 95% confidence interval between Environmental Symptoms Questionnaire and Lake Louise Scale scores to determine an adjusted Lake Louise Scale score………………………………………………………………………………..40
LIST OF TABLES

Table 1. Characteristics of 13 included studies………………………………………………22
Table 2. Meta-regression modeling results for each physiological measurement……23
Table 3. Baseline participant descriptors………………………………………………………33
Table 4. Comparisons between AMS+ (n = 8) and AMS- (n = 7) groups during the head-up tilt test and correlations with physiological responses to acute mountain sickness scores……………………………………………………………………………42
Table 5. Physiological measurement in hypobaric hypoxia after six hours of exposure for AMS+ and AMS- groups………………………………………………………………………43
CHAPTER 1 INTRODUCTION

INTRODUCTION

Orthostatic intolerance is defined by Freeman et al. [1,2] as a decrease in systolic blood pressure (SBP) ≥ 20 mmHg and/or diastolic blood pressure (DBP) ≥ 10 mmHg within the first three minutes of standing up or head-up tilt (HUT) to ≥ 60°. Symptoms of orthostatic intolerance include dizziness, lightheadedness, weakness, fatigue, headache, presyncope (feeling faint), and syncope (fainting) [2]. These symptoms are more pronounced when individuals are moved from supine to an upright position on a tilt table (HUT) as opposed to active standing [3]. When transitioning from supine to upright posture there is a blood volume redistribution, with 300 – 800 ml of blood pooling in the lower extremities due to gravitational forces [2]. Subsequently, venous return and ventricular filling pressure decrease, resulting in reduced stroke volume (SV), SBP, and DBP. This decrease in SBP and DBP can occur immediately upon or ≥ three minutes after postural changes [1,2]. During posture change, the autonomic nervous system (ANS) acts to maintain homeostasis by increasing heart rate (HR), cardiac contractility, and vasoconstriction to prevent orthostatic hypotension via increased sympathetic outflow [1,2]. A mismatch between peripheral vascular resistance and cardiac output or a form of sympathetic adrenergic failure may be responsible for the drop in BP from postural change [2].

Exposure to additional simultaneous stressors, such as hypoxia, can affect an individual’s response to orthostatic stress [4]. An individual’s level of orthostatic tolerance as measured by HUT is reduced when exposed to hypoxia [5–8]. Blaber et al. [5] found reduced orthostatic tolerance in healthy individuals after 60 min at a simulated
altitude of 3660 m, observing a shorter time to presyncope. The authors [5] attributed this to increased ventilation from hypoxic exposure and reduced end-tidal carbon dioxide. The increase in ventilation and reduction in end-tidal carbon dioxide could cause insufficient cerebral oxygen perfusion compared to exposure to hypoxia alone [5]. The reduced orthostatic tolerance in hypoxic environments is further supported by Mytton et al. [7], who observed a greater fall in SBP at 5200m compared to sea level (an average 24.5 mmHg decrease at three different altitudes vs. a 11.9 mmHg decrease at sea level) when participants stood upright from a supine position.

A possible reason for a greater decrease in SBP could be that severe hypoxia (fractional inspired oxygen [FiO₂] = 12%) causes vasodilation of the lower extremities at rest [6]. Huang et al. [6] found that when participants changed posture from supine to standing, lower extremity SBP decreased whereas upper extremity SBP stayed the same. They reasoned that since upper and lower extremities share the same cardiac output (CO), peripheral vascular resistance must be reduced in the lower body compared to the upper body [6]. Another reason for the greater decrease in blood pressure (BP) at high altitude could be the effect that postural changes have on hypoxia’s ability to influence HR. Huang et al. [6] observed a blunted increase in HR upon sitting up from supine when inhaling hypoxic gas (FiO₂ = 12%, 4500 m) compared to mild hypoxia (FiO₂ = 15%, 3000 m) and normoxia.

Mytton et al. [7] found individuals who reported dizziness on their acute mountain sickness (AMS) questionnaire at 5200 m consistently had a greater decrease in SBP (mean 21.0 mmHg reduction) compared to sea level (mean 11.9 mmHg reduction). The reduction in SBP was not significantly different compared to individuals who did not
experience dizziness (averaged 20.6 mmHg reduction). There were also no differences between individuals who were AMS positive (AMS+) and AMS negative (AMS-) for changes in SBP upon postural changes at 5200 m and sea level. This could be because the participants stood upright from a supine position engaging lower extremity muscles to assist venous return. Using passive HUT minimizes the use of those muscles [7]. Other hemodynamic variables are affected by postural changes (i.e., HR, CO, SV, and peripheral vascular resistance) and no analyses were conducted between AMS+ and AMS- individuals when postural changes were conducted at sea level [7]. Therefore, it is of interest to know whether individuals who are AMS+ have different hemodynamic responses to postural changes (i.e., HUT) in normoxia compared to AMS- individuals. This question could have merit as Loeppky et al. [9] suggested there may be similar pathophysiological mechanisms common to orthostatic stress and the development of AMS.

While orthostatic tolerance was not assessed in Loeppky’s [9] study, they did differentiate between AMS+ and AMS- individuals. Heart rate and the low frequency to high frequency ratio (LF:HF ratio, indicator of heart rate variability), a measure of sympathetic to parasympathetic influence on the heart, respectively, increased in AMS+ individuals during a postural change when breathing 12% O₂ (4300 m) [6,9]. Loeppky et al. [9] also noticed that individuals with AMS had increased peripheral blood flow related to greater vasodilation in the extremities. Upon postural changes, orthostatic intolerant individuals have more vasodilation because of a blunted increase in muscle sympathetic nerve activity [10,11]. Though researchers have suggested there may be some pathophysiological overlap between the development of AMS and enhanced orthostatic
stress responses, this has yet to be verified. This is surprising considering the number of possible mechanisms (e.g., changes in LF:HF ratio, HR, and peripheral vascular resistance [12–16]) and symptoms (e.g., dizziness, lightheadedness, headache, nausea, weakness, and fatigue [17–19]) that are common responses to orthostatic stress and hypoxic exposure leading to the development of AMS. Because of the possible common mechanisms for the development of AMS and orthostatic stress responses, the exaggerated response to HUT at a lower elevation may correlate with the development of AMS.

**Study Objectives**

An objective of the study was to determine the strength and direction of association between orthostatic stress responses to HUT (e.g., BP, HR, LF:HF ratio, CO, SV, total peripheral resistance [TPR]) and AMS scores after six hours of hypobaric hypoxia. Another objective was to determine whether there were differences in orthostatic stress responses from HUT between individuals who are AMS+ (Lake Louise Scale [LLS] score ≥ 3 or AMS- (LLS score < 3) [20].

*Specifically, we investigated:*

**Objective 1:** To identify the strength and direction of the association between AMS scores after 6 hours of hypoxia and hemodynamic orthostatic stress responses during HUT.

**Objective 2:** To identify the strength and direction of the association between AMS scores after 6 hours of hypoxia and time to presyncope from HUT.
Objective 3: To assess differences between the AMS+ and AMS- participants for the change in SBP, HR, HRV, cardiac output, and stroke volume, during HUT.

Limitations

1: Some, but not all, participants had BP, HR, and SpO₂, continuously monitored during hypobaric hypoxic exposure due to having only one continuous noninvasive blood pressure monitor.

2: We recruited a smaller sample size than intended because of the research shutdown due to COVID-19. This reduced the power of the study to find statistical significance. The sample size was 15 when it should have been 26 according to an a priori power analysis.

3: All individuals in this study lived at moderate altitude (1610 – 1620 m) which limits generalizability to individuals living at lower or higher altitudes.

Assumptions

This study was conducted based on the following assumptions:

1: Participants answered the Pre-Testing Guidelines Questionnaire honestly and maintained the same lifestyle routine throughout the duration of their participation.

2: Subjects put forth a maximal effort during the maximal oxygen consumption test.

3: Subjects did not contract their lower extremity muscles during HUT.

4: Subjects accurately reported their health and exercise history.

5: Subjects accurately reported their AMS scores on the Lake Louise Scale and Environmental Symptoms Questionnaire.
6: All equipment used in the study was correctly calibrated and in good working order.

**Hypotheses**

This study tested the following null hypotheses:

1: There will be weak associations \( (r < 0.20) \) between orthostatic stress responses as measured from baseline to end of HUT and AMS scores.

2: There will be a weak association \( (r < 0.20) \) between time to presyncope during HUT and AMS scores.

3: There will be no significant differences in orthostatic stress responses between AMS+ and AMS- groups.

**Significance of Study**

Orthostatic stress testing holds promise as a predictor of AMS. Loeppky et al. [9] suggested that there may be similar pathophysiological mechanisms related to orthostatic stress responses and AMS. This included changes in HRV and HR from both stressors, postural change and hypoxia [6,9]. Loeppky et al. [9] also observed that individuals with AMS had increased peripheral blood flow related to greater vasodilation of the extremities. A tendency toward vasodilation and inability for the sympathetic system to increase peripheral resistance could result in greater decreases in SBP and DBP during HUT, thereby causing orthostatic hypotension [1].

The HUT test is a simple protocol to induce orthostatic stress with non-invasive, easy to assess measurements that can be conducted by medical professionals at the individual’s base elevation prior to traveling. This is the first study to assess the association of orthostatic stress responses with the development of AMS. If responses to
orthostatic stress testing demonstrate strong relationships with AMS scores, HUT could be used by medical personnel as a prediction tool for the development of AMS for those planning travel to high altitude (> 2500 m [17]) . This is important, especially for people who would be deployed quickly, such as military personnel and wildland firefighters, but also low-altitude residents going on a high-altitude ski or hiking trip. Therefore, if an individual’s responses to a HUT test indicated that they were more AMS-susceptible, they could alter their itinerary to ascend more slowly, allowing for additional acclimatization periods during the climb. If changing the ascent itinerary is not possible in the case of military personnel or firefighters, individuals who were identified as more likely to develop altitude sickness could be grounded or prescribed AMS prophylaxis.

Changing the ascent speed and/or prescription of prophylaxis to those in need could increase the chance of successful travel to and work at high altitude without AMS incidence.
CHAPTER 2 REVIEW OF THE LITERATURE

INTRODUCTION

A decrease in the partial pressure of oxygen (PO$_2$) occurs as elevation increases to high altitude (HA, >2500m [17]) and results in the need for individuals to adapt and acclimatize [13,18,21]. An ascent faster than recommended (i.e., 300-600 m per day with an non-climbing acclimatization day for every 600-1200 m elevation gain) can result in a failure to adapt and acclimatize properly, leading to an increased risk for developing acute mountain sickness (AMS) [13,18,22–25]. Typically, AMS occurs above elevations of 2500 m; however, incidence of AMS has been reported at lower elevations [16]. At elevations of 1850-2750 m AMS has been shown to affect ~25% of individuals. At 3000 m this increases to ~42%, and for those attempting Mount Kilimanjaro (5895m), the incidence can be as high as ~75% of individuals making the ascent [13,18,26,27]. Acute mountain sickness is usually characterized by headache with the addition of one or more of the following symptoms: gastrointestinal distress (e.g., loss of appetite, nausea, vomiting), dizziness, lightheadedness, or fatigue [16–19,23,28–31]. If ascent continues and symptoms are allowed to progress, the more severe (though less common) illnesses such as high-altitude pulmonary or cerebral edema could occur [13,17,21,23,24,28–30,32–34]. However, if AMS symptoms are not severe, individuals can descend 300 – 1000 m and rest to alleviate symptoms [35].

Though the symptoms of AMS are well understood, the physiological responses differentiating those individuals with and without AMS during hypoxic exposure remains less clear. The impact of hypoxia on the body is commonly observed by a decrease in the percentage of blood oxygen saturation (SpO$_2$) [30]. If arterial PO$_2$ decreases from
70mmHg to 60mmHg, SpO\textsubscript{2} could drop from about 98% to 95% in whole blood. An SpO\textsubscript{2} \geq 95% would still be considered normal [36,37]. A fall in PO\textsubscript{2} from 40mmHg to 30mmHg could result in SpO\textsubscript{2} dropping from 80% to 60% both which are considered severely hypoxic [38]. With a decrease in SpO\textsubscript{2} related to increased elevation, heart rate (HR) tends to increase because of a decrease in vagal tone and increase in sympathetic activity [12,39–41]. In a hypoxic environment an increase in sympathetic activity also leads to an increase in norepinephrine release which causes arterial vasoconstriction. The decreased diameter of the blood vessels results in an increase in blood pressure (BP), which includes increases in both systolic and diastolic BP (SBP and DBP, respectively) [31,42–44]. Because these four cardiovascular variables (i.e., SpO\textsubscript{2}, HR, SBP, & DBP) change based on the magnitude of hypoxic stress, researchers have explored their possible connection to AMS.

Since the risk of developing AMS is associated with increasing elevation, this suggests a concurrent decreasing SpO\textsubscript{2} with corresponding increases in HR, SBP, and DBP, along with diagnosed AMS (most often defined as a Lake Louise Scale [LLS] score \geq 3 [20]). Karinen et al. [13] reported that SpO\textsubscript{2} during exercise yielded a stronger negative correlation (\(r = -0.62, p < 0.01\)) to AMS scores than resting SpO\textsubscript{2} at 4300 m (\(r = -0.48, p < 0.05\)). They suggested that individuals who maintained their SpO\textsubscript{2} during rest and during exercise as elevation increased were less likely to develop AMS [13]. However, these were not strong correlations and while research studies have shown SpO\textsubscript{2} is lower in AMS positive (AMS+) compared to AMS negative (AMS-) individuals [15,23,30], this is not always the case [16]. There is evidence suggesting AMS+ individuals have higher resting HRs compared to AMS- individuals, but the results are
inconsistent [12–15,23,28,45]. Karinen et al. [13] found that resting HR weakly correlated with increases in AMS scores ($r \leq 0.32$) as elevation increased from 3500 – 5300m. In contrast, the differences for SBP and DBP between individuals who are AMS+ and AMS- are equivocal even though a weak but significant correlation was found between DBP and AMS scores ($r = 0.10$) [31,43,44]. Due to discrepancies in the literature for the determination of cardiovascular differences between AMS+ and AMS- individuals, there is a need to collectively assess the studies that report SpO$_2$, HR, SBP, and DBP, in relation to AMS.

Therefore, due to discrepancies in the literature the purpose of this meta-analysis was to identify whether SpO$_2$, HR, SBP, and DBP, when measured in AMS+ individuals during acute HA exposure is higher or lower compared to AMS- individuals. Understanding the differences between AMS+ and AMS- individuals and how aspects of study design (ascent time, measurement timing, participants’ age, height, weight, and LLS cut-offs) affect these outcomes, could allow for a better understanding of the physiological differences between AMS+ and AMS- during acute HA exposure. This study aimed to determine which measurements have significant effect sizes when differentiating between AMS+ and AMS- individuals. It was expected that AMS+ individuals would have significantly different (higher or lower) physiological values (SpO$_2$, HR, SBP, and DBP) compared to AMS- individuals during exposure to hypoxia.

**MATERIALS AND METHODS**

**Search Strategy**

This meta-analysis was conducted according to PRISMA guidelines [46]. Articles were found using Google Scholar and PubMed database searches from January 2008 to
February 2020 to build on the previous systematic review by Burtscher et al. [47]. Only articles written in English were examined. Articles that were only abstracts were excluded as were unpublished reports. Further, if a full text article could not be retrieved through the databases, the University of New Mexico’s interlibrary loan system was used. The following search terms and phrases were used in varying order: “AMS,” “predicting AMS,” “reliable predictor of AMS susceptibility,” “AMS susceptibility,” “predictive value of AMS,” “hypoxia,” “oxygen saturation,” “heart rate,” “blood pressure,” “hypertension,” and “arterial stiffness.” Boolean operators (“and” and “or”) were used to connect search terms. Articles referenced in selected articles and review articles were also examined. Duplicates were identified and excluded. Final decision for inclusion or exclusion was based on the following criteria.

**Inclusion and Exclusion Criteria**

Inclusion criteria:

1. Studies in which individual AMS scores using the Lake Louise Scale (LLS) from 0 – 12 [19,20] were determined from acute HA exposure [>2500 m [17] or equivalent normobaric hypoxia] were entered. Though some researchers used LLS ≥ 3 or ≥ 4 in the presence of a headache as a cutoff for diagnosis of AMS, all studies were included.

2. Studies using acute HA exposure that report recruitment of adult participants (>18 years old) below elevations of 1000m.

3. Studies using physiological assessment methodology that included noninvasive (measures that do not require instrument insertion into the body),
easily portable devices capable of being used quickly on many individuals during a screening process. This included SpO₂, HR, SBP, and DBP monitors.

4. Studies using acute HA exposure to compare physiological variables between groups who were AMS+ and AMS-.

Exclusion criteria:

1. Studies using animal or cell models exclusively.

2. Methodology used was invasive (i.e., blood draws or biopsy for the determination of biomarkers or gene polymorphism) and did not include noninvasive measurements.

3. Studies that focused only on the determination of HA cerebral or pulmonary edema.

4. Studies that did not differentiate between AMS+ and AMS-.

5. Studies that did not report base elevation of participants recruited.

Quality Assessment and Data Extraction

The methodological quality of each study was determined using an 8-point scale created by Loney et al. [48]. This tool critically appraises the prevalence or incidence of a health problem and was recently used in a 2019 AMS meta-analysis [49]. Two authors (BNB and ADW) independently assessed the quality of the selected research articles and disagreements were resolved by verbal consensus. There are three parts to this scale: methodological validity (0 – 6 points), interpretation of results (0 – 1 points), and applicability of results (0 – 1 points). A score of ≤ 3 is low quality, 4 – 5 is adequate quality, and ≥ 6 is high quality [49]. Studies with a score of ≤ 3 were excluded from analysis [48].
Two researchers (BNB and ADW) independently extracted data from the studies. Any disagreements were reconciled through verbal consensus. For each study, the following information was extracted: the first author, year of publication, sample size, participants’ living elevation, age, height, body weight (BW), time for measurement of physiological variables after reaching desired elevation in hours (measurement timing), ascent time to desired elevation in days (AT), altitude or simulated altitude used in meters, the exposure type (natural, hypobaric, or normobaric), number of AMS+ and AMS- participants, the physiological measurement(s) used, the means and standard deviations found from the physiological measurement(s) determined at HA, and the LLS cut-off used. The outcome variables were resting SpO₂, HR, SBP, and DBP measurements that were dependent on whether individuals were considered AMS+ or AMS- in their respective studies. If multiple altitudes were used, all measurements were recorded for each altitude ≥ 2500 m prior to descent, if reported.

**Statistical Analysis**

This meta-analysis was performed using the “metaphor” and “meta” packages [50,51] in R (version 3.6.3, R Core Team, Vienna, Austria). The means, standard deviations, and sample sizes for AMS+ and AMS- groups were used to conduct a standardized mean difference (SMD) meta-analysis. The SMDs (with 95% confidence intervals [CI]) could be either negative or positive. For SMD, the adjusted Hedges’ g equation (Equation 1) was used where \( m_{1i} \) was the physiological measurement for the AMS+ group and \( m_{2i} \) was the same physiological measurement for the AMS- group, divided by the pooled standard deviation (\( s_i \)). The adjusted Hedges’ g equation was used to account for sample size bias (\( n_1 = \text{AMS+ sample size, } n_2 = \text{AMS- sample size} \)). The
analyses were done in subgroups based on the physiological measurement (SpO₂, HR, SBP, and DBP). The negative direction of the SMD suggests the mean difference between AMS+ and AMS- is negative.

A random effects model with a restricted maximum-likelihood estimator was used, and the heterogeneity assumption was assessed by chi-squared (Q) test and $I^2$. Outliers were determined using residual estimates to identify z-scores greater than 2, influence and leave-one-out analysis, and Cook’s distance [51]. Forest plots were created for each group or physiological measurement (SpO₂, HR, SBP, DBP). Cohen recommends the SMD be classified as follows: an SMD of 0 – 0.19 is a negligible effect, 0.20 – 0.49 is a small effect, SMD = 0.5 – 0.79 is a moderate effect, and an SMD ≥ 0.8 is a large effect [52]. Publication bias was investigated using a funnel plot with each study’s SMD plotted against standard error. An asymmetric plot suggests possible publication bias. Funnel plot asymmetry was assessed using Egger’s regression test.

Within each outcome (i.e., physiological measurement), meta-regression was conducted to examine the effects of moderator variables to explain possible heterogeneity and their effect on the SMDs. The multi-variable meta-regression moderator variables were age, BW, elevation, measurement timing, and AT, combined to provide the most appropriate model. The LSS cut-off was used as a single-variable meta-regression to determine its influence on the SMDs.

$$SMD = \frac{m_{1i} - m_{2i}}{s_i} \left(1 - \frac{3}{4(n_1 + n_2) - 9}\right)$$  \text{Equation 1}
RESULTS

Search Results

Of the 328 full-text articles retrieved, 13 were selected for use in this meta-analysis based on selection criteria (Figure 1). The quality of the included studies was adequate with a score of 5.2 ± 0.9 out of 8. A total of four measurements: SpO\textsubscript{2}, HR, SBP, and DBP, were assessed for AMS+ and AMS- individuals. Most studies reported measurement of more than one of these physiological variables [13,29,43,53–61]. Researchers conducted physiological assessments during resting conditions while participants were exposed to normobaric [29,55,56] or hypobaric hypoxia [13,23,43,53,54,57–61] (mean ± SD altitude: 3986 ± 834 m). These measurements were made on 435 AMS+ and 520 AMS- individuals aged 19.8 – 49.3 years. Sample sizes ranged from 16 – 204 individuals. Table 1 presents the characteristics of the included studies.

Publication Bias Analysis

Publication bias was assessed using a funnel plot (Figure 2) and Egger’s test. The funnel plot suggests symmetry on sight. This suggests a lack of publication bias because of an even spread of the data based on sight. The Egger’s test confirms the funnel plot results as this test was not significant (Egger’s test coefficient = -0.63, \( p = 0.53 \)).

Outlier Analysis

The Huang et al. [53] data point for HR at 3440 m was determined to be an outlier and removed from further statistical analyses. The z-score from the standardized residuals was 4.6 and had the greatest influence on the HR SMD when using the leave-one-out
analysis. This data point also had the largest Cook’s distance, 0.23, when using the leave-one-out analysis.

**Meta-Analysis Results**

The forest plot is shown with the heterogeneity analysis and the $I^2$ statistic for each physiological measurement in Figure 2. AMS+ individuals had lower SpO$_2$ levels than AMS+ individuals as indicated by a significant and moderate effect size (13 studies, SMD = -0.74, 95% CI: -0.94 – -0.54, $p < 0.001$). AMS+ individuals had higher HRs than AMS- individuals as indicated by a significant and moderate effect size (11 studies, SMD = 0.52, 95% CI: 0.29 – 0.75, $p < 0.001$). Since the effect size is negligible for SBP and DBP, the results are equivocal to determine whether SBP and DBP are higher or lower in AMS+ groups compared to AMS- groups (8 studies for both, SMD = -0.14, 95% CI: -0.37 – 0.09, $p = 0.24$ and SMD = -0.19, 95% CI: -0.47 – 0.09, $p = 0.18$, respectively).

However, an analysis with <10 studies should be interpreted with caution [51]. Heterogeneity for these physiological measurements ranged from 48.3 – 65.5% and could be explained by differences in age, body weight (BW), elevation, measurement timing, and ascent time (AT) (i.e., moderators), between included studies. A meta-regression model using a combination of the previously mentioned moderators would discern the reasons for heterogeneity.

**Meta-Regression Analysis**

A summary of the meta-regression analyses separated by variable (SpO$_2$, HR, SBP, and DBP) can be found in Table 2. The measurement timing did not influence the effect size for SpO$_2$ between AMS+ and AMS- ($p = 0.40$). Only BW significantly influenced effects sizes between AMS+ and AMS- for SpO$_2$ ($p = 0.01$). The SpO$_2$ effect
size is significantly reduced by 0.13 for every 1kg increase in BW (Appendix A). The AT still contributed to the model for SpO₂ (p = 0.08). For every day added to AT, the effect size increased by 0.09. The model for SpO₂ studies accounted for 100% of the heterogeneity. The residual heterogeneity was not significant (QM(3) = 0.78, p = 0.86, I² = 0.0%).

Both AT and measurement timing significantly influenced the effect size for HR between AMS+ and AMS- groups (p = 0.004 and 0.03, respectively). BW also contributed to changes in the effect size for HR (p = 0.09). The HR effect size significantly increased by 0.15 for every day added to AT. For every hour after reaching the desired elevation before HR was measured, the effect size significantly increased by 0.04. For every 1 kg increase in BW, the HR effect size was significantly reduced by -0.09. This model for HR studies accounted for 100% of the heterogeneity resulting in nonsignificant residual heterogeneity (QM(3) = 2.8, p = 0.43, I² = 0.0%).

AT significantly influenced the effect size for SBP between AMS+ and AMS- groups (p = 0.001). Elevation reached was not significant in the SBP model (p = 0.35). For every day added to AT, the SBP effect size was significantly reduced by 0.09. The heterogeneity was 100% accounted for when using these moderating variables, resulting in nonsignificant residual heterogeneity (QM(4) = 1.60, p = 0.81, I² = 0.0%). For DBP, AT and age were used to create the model, and both significantly influenced the effect size (p = 0.04 and 0.002, respectively). The DBP effect size between AMS+ and AMS- groups was reduced by 0.17, for every day added to AT. For every 10-year increase in age, the effect size for DBP increased by -0.57. This model accounted for 100% of the
heterogeneity, the model did not contain significant residual heterogeneity \((Q_{M(3)} = 0.29, \ p = 0.96, I^2 = 0.0\%\).

The single-variable meta-regression was conducted to determine if studies using a different LLS cut-off from the traditional \(\geq 3\) score impacted the effect sizes of \(\text{SpO}_2\), HR, SBP, and DBP. Differences in LLS cut-offs yielded significance for \(\text{SpO}_2\) \((p = 0.03)\). For every 1-point increase in the LLS cut-off, the \(\text{SpO}_2\) effect size increases by -0.51.

Increasing the LLS cut-off also accounted for 27.1\% of the heterogeneity on its own with significant heterogeneity remaining \((Q_{M(15)} = 30.40, \ p = 0.01, I^2 = 46.1\%\). Increasing the LLS cut-off also accounted for 47.2\% of the heterogeneity of the DBP data and the residual heterogeneity was not significant \((Q_{M(6)} = 12.08, \ p = 0.06, I^2 = 50.1\%\). For every increase in LLS cut-off by 1 point, the DBP effect size is decreased by 0.45 \((p = 0.08)\). No heterogeneity was accounted for when analyzing HR and SBP data.
Figure 1. Flow chart of study inclusion. AMS+ = acute mountain sickness positive. AMS- = acute mountain sickness negative. LLS = Lake Louise Scale questionnaire.
Figure 2. Funnel plot showing standardized mean difference against standard error to demonstrate possible publication bias.
Figure 3. Forest plot showing standardized mean differences (SMD) for 13 studies and 95% confidence intervals (CI) associated with each data point. Some studies used more than one physiological measurement and/or more than one elevation. Red diamonds are the SMDs for the respective groupings. Negative SMDs favor lower values for AMS+ compared to AMS-. Positive SMDs favor higher values for AMS+ compared to AMS-.
Table 1. Characteristics of 13 included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Destination</th>
<th>Altitude</th>
<th>Sample Size</th>
<th>Sex</th>
<th>Relationship with AMS scores (p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. 2010 [53]</td>
<td>Namche, Bazaar, Nepal</td>
<td>3440m</td>
<td>32</td>
<td>Male &amp; Female</td>
<td>Higher HR &amp; LF:HF in AMS+; No difference in SpO₂</td>
<td></td>
</tr>
<tr>
<td>Karinen et al. 2010 [13]</td>
<td>Denali, Tibet, &amp; Nepal</td>
<td>2400m – 5300m</td>
<td>74</td>
<td>Male &amp; Female</td>
<td>Lower resting &amp; exercise SpO₂ = higher AMS scores; No HR correlation</td>
<td></td>
</tr>
<tr>
<td>Modesti et al. 2011 [54]</td>
<td>Mt. Everest Base Camp</td>
<td>5400m</td>
<td>47</td>
<td>Male &amp; Female</td>
<td>Lower SpO₂ = higher AMS scores</td>
<td></td>
</tr>
<tr>
<td>MacInnis et al. 2012 [55]</td>
<td>Normobaric Chamber</td>
<td>FiO₂ = 12.0% (4550m)</td>
<td>17</td>
<td>Male</td>
<td>No difference in SpO₂ or HR</td>
<td></td>
</tr>
<tr>
<td>Mairer et al. 2013 [56]</td>
<td>Normobaric Chamber</td>
<td>FiO₂ = 11.0% (5500m)</td>
<td>20</td>
<td>Male</td>
<td>Negative relationship between increasing LF:HF ratio and GI symptom severity (protective)</td>
<td></td>
</tr>
<tr>
<td>Faulhaber et al. 2014 [29]</td>
<td>Normobaric Chamber</td>
<td>FiO₂ = 12.5% (4500m)</td>
<td>55</td>
<td>Male &amp; Female</td>
<td>SpO₂ correctly predicted 69% of AMS cases, but including breathing frequency improved it to 78%</td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2014 [43]</td>
<td>Lhasa, China</td>
<td>3700m</td>
<td>931</td>
<td>Male</td>
<td>SBP &amp; MAP higher in severe AMS+ compared to mild &amp; moderate AMS+ on initial exposure</td>
<td></td>
</tr>
<tr>
<td>Hsu et al. 2015 [23]</td>
<td>Jiaming Lake, Taiwan</td>
<td>3350m</td>
<td>91</td>
<td>Male &amp; Female</td>
<td>AMS associated with initial decrease in SpO₂; lower SpO₂ = higher AMS score</td>
<td></td>
</tr>
<tr>
<td>Ren et al. 2015 [57]</td>
<td>Tibet</td>
<td>4300m</td>
<td>80</td>
<td>Male &amp; Female</td>
<td>Higher HR, lower DBP in AMS+</td>
<td></td>
</tr>
<tr>
<td>Qiu et al. 2017 [58]</td>
<td>Lhasa, China</td>
<td>3700m</td>
<td>123</td>
<td>Male</td>
<td>Lower SpO₂ &amp; higher HR in AMS+; No difference in SBP &amp; DBP; HR ≥ 85 bpm &amp; SpO₂ ≤ 88% with predictive value of 82.3% and 85.2%, respectively</td>
<td></td>
</tr>
<tr>
<td>Boos et al. 2018 [59]</td>
<td>Himalayas</td>
<td>5140m – 5360m</td>
<td>80</td>
<td>Male &amp; Female</td>
<td>Higher HR &amp; lower SpO₂ = higher AMS scores</td>
<td></td>
</tr>
<tr>
<td>Burscher et al. 2019 [60]</td>
<td>Plateau Rosa, Testa Grigia, Italy</td>
<td>3489m</td>
<td>40</td>
<td>Male &amp; Female</td>
<td>SpO₂ of &lt;87% was the best predictor of AMS+; Higher HR &amp; lower SpO₂ &amp; DBP in AMS+</td>
<td></td>
</tr>
<tr>
<td>Liu et al. 2019 [61]</td>
<td>NR</td>
<td>4000m</td>
<td>84</td>
<td>Male</td>
<td>Lower SpO₂ in AMS+; Lower SpO₂ = higher AMS scores</td>
<td></td>
</tr>
</tbody>
</table>

Note: AMS+ = acute mountain sickness positive, AMS- = acute mountain sickness negative, SpO₂ = oxygen saturation, HR = heart rate, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, AMS = acute mountain sickness, HRV = heart rate variability, LF = low frequency HRV, HF = high frequency HRV, GI = gastrointestinal, MAP = mean arterial pressure.
Table 2. Meta-regression modeling results for each physiological measurement.

<table>
<thead>
<tr>
<th>Moderator</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxygen Saturation, R² = 100%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-9.80</td>
<td>-2.62</td>
<td>0.009*</td>
<td>-17.13 – -2.48</td>
</tr>
<tr>
<td>Measurement Time</td>
<td>0.02</td>
<td>0.02</td>
<td>0.40</td>
<td>-0.20 – 0.06</td>
</tr>
<tr>
<td>Ascent Time</td>
<td>-0.09</td>
<td>0.05</td>
<td>0.08</td>
<td>-0.20 – 0.01</td>
</tr>
<tr>
<td>Body Weight</td>
<td>0.13</td>
<td>0.05</td>
<td>0.01*</td>
<td>-0.02 – 0.06</td>
</tr>
<tr>
<td><strong>Heart Rate, R² = 100%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>5.86</td>
<td>1.59</td>
<td>0.11</td>
<td>-1.35 – 13.06</td>
</tr>
<tr>
<td>Measurement Time</td>
<td>0.04</td>
<td>0.02</td>
<td>0.03*</td>
<td>0.005 – 0.08</td>
</tr>
<tr>
<td>Ascent Time</td>
<td>0.15</td>
<td>0.05</td>
<td>0.004*</td>
<td>0.05 – 0.25</td>
</tr>
<tr>
<td>Body Weight</td>
<td>-0.09</td>
<td>0.05</td>
<td>0.09</td>
<td>-0.19 – 0.01</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure, R² = 100%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.57</td>
<td>-0.81</td>
<td>0.42</td>
<td>-1.96 – 0.81</td>
</tr>
<tr>
<td>Elevation</td>
<td>0.0001</td>
<td>0.0002</td>
<td>0.73</td>
<td>-0.003 – 0.0004</td>
</tr>
<tr>
<td>Ascent Time</td>
<td>0.09</td>
<td>0.03</td>
<td>0.001*</td>
<td>0.04 – 0.15</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure, R² = 100%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.29</td>
<td>0.50</td>
<td>0.01*</td>
<td>0.30 – 2.27</td>
</tr>
<tr>
<td>Age</td>
<td>-0.057</td>
<td>0.02</td>
<td>0.002*</td>
<td>-0.09 – -0.02</td>
</tr>
<tr>
<td>Ascent Time</td>
<td>0.17</td>
<td>0.08</td>
<td>0.04*</td>
<td>0.009 – 0.33</td>
</tr>
</tbody>
</table>

*Note: CI = confidence interval, R² = Amount of heterogeneity accounted for. Alpha level is < 0.05. * denotes moderators that had significant influence on the effect size for the physiological variable between those with and without acute mountain sickness.*
DISCUSSION

The purpose of this meta-analysis was to determine which of the non-invasive physiological measurements (SpO₂, HR, SBP, DBP) best differentiated between AMS+ and AMS- individuals. The screening criteria resulted in 13 studies being included in this systematic meta-analysis. The measurements with the greatest SMDs were SpO₂ and HR. AMS+ individuals have a lower SpO₂ levels and higher HRs compared to AMS- individuals at HA. Blood pressure does not seem to be an acceptable measure to differentiate AMS+ and AMS- individuals.

The SpO₂ displayed by a pulse oximeter indicates the percent oxygen saturation of arterial blood with oxygen. As elevation increases, SpO₂ decreases because of the decreasing oxygen pressure gradient between alveoli and pulmonary capillaries [30,47]. A lower SpO₂ in AMS+ individuals is consistent with a previous meta-analysis by Guo et al. [30]. Supporting these findings, a faster AT can result in increased prevalence of AMS [62–64]. Having a staging period during the ascent (staying at a lower elevation prior to continuing ascent) prevents further decreases in SpO₂ compared to a continuous ascent [64].

As SpO₂ decreases with increasing elevation, HR increases to circulate blood faster in response to an increased oxygen demand by systemic tissue [12,39–41,65,66]. The magnitude of the increase in HR is influenced by the AT [66]. If AT is a day faster or if measuring HR was delayed an hour, there will be a greater difference in HR between AMS+ and AMS- with AMS+ individuals having a higher HR. However, the current literature contrasts with these findings [66,67]. Faster ascents have resulted in greater increase in HR, regardless of being AMS+ or AMS-, compared to slower ascents [66].
Hence, if all individuals experience an elevated HR on faster ascents, this could reduce potential differences observed between AMS+ and AMS- groups. Similarly, Niebauer et al. [67] did not observe differences in resting HR between AMS+ and AMS- groups after 30 min and every 3 hours after exposure to normobaric hypoxia (FiO<sub>2</sub> = 12.5%, about 4500 m). However, heart rate variability (indicating changes in autonomic activity) are different in AMS+ and AMS- individuals when exposed to hypoxia [68,69]. Though speculative, there could be changes in sympathetic influence over the sinoatrial node during the first hours of hypoxic exposure that would mediate differences in resting HR between AMS+ and AMS- groups. An analysis of heart rate variability over time during acute hypoxic exposure could provide insight for the measurement timing meta-regression HR results and should be included in future analyses. Supporting evidence that AMS+ individuals have higher HRs compared to AMS- individuals is that hypoxia induces an increase in sympathetic activity and catecholamine release [9]. Loeppky et al. [9] observed an increase in sympathoadrenergic tone related to higher catecholamine levels in AMS+ individuals.

SBP and DBP show negligible differences between AMS+ and AMS- individuals. The studies used in this meta-analysis did not demonstrate a trend for AMS+ individuals to have higher or lower SBP and DBP compared to AMS- individuals. Equivocal results may be due to measurement timing after initial exposure. Niebauer et al. [67] found resting SBP and DBP varied based on the duration from initial exposure to FiO<sub>2</sub> = 12.6% (or about 4500 m). SBP and DBP decreased through the first three hours and rose back toward initial exposure values after being hypoxic for six hours. Between AMS+ and AMS- individuals, SBP had a more pronounced decrease for AMS+ individuals within
the first 3 hours of exposure, but the differences ceased after 3 hours. These differences were attributed to differences in the autonomic nervous system (ANS) and baroreflex responses in AMS+ and AMS- individuals [67]. However, for the current study measurement timing did not influence the regression models. Future researchers should control for measurement timing to determine if SBP and DBP could be used to differentiate AMS+ and AMS- individuals at HA. Differences in ANS and baroreflex responses could explain why AT influences the between-group effect size for SBP and DBP, but the literature is not clear on hypoxia’s impact on BP prior to reaching the desired elevation.

An increase in participants’ age can reduce the difference in DBP between AMS+ and AMS- groups. As individuals age, arterial stiffness increases through a thickening of the blood vessel walls, the loss of elastin, and addition of collagen [70]. These physiological changes resulted in DBP increases until about the fifth to sixth decade after which DBP decreases [71]. Researchers should consider controlling for age when determining differences in DBP between AMS+ and AMS- groups due to physiological differences in arterial wall structures between younger and older individuals.

Limitations

Though some studies were not included because they used the Environmental Symptoms Questionnaire – III [72,73], there was no publication bias when only using studies assessing AMS by the LLS. Since some studies used different LLS cut-offs to determine individuals who were AMS+ [54,56,57], a regression analysis was applied to determine if the cut-offs impacted the results. An increase in the LLS cut-off by 1 point significantly increased the difference in SpO₂ between AMS+ and AMS- individuals and
decreased the difference in DBP between the two groups. These findings should be interpreted with caution because <10 studies used LLS cut-offs of ≥ 4 so the statistical power was hindered [74]. For the studies that used LLS cut-offs ≥ 4 [54,56,57], it was not clear why this change was made. We do not recommend changing the current cut-off criteria for the LLS of ≥ 3 as it has been shown to be reliable and valid [19,20]. An LLS cut-off ≥ 4 may miss individuals experiencing mild AMS and in need of rest before continuing their ascent. Changing the LLS cut-offs can also contribute to disparate findings between AMS+ and AMS- groups for SpO₂ and DBP which could then lead to conflicting results.

A second limitation of this meta-analysis is that prophylactic drug use, smoking status, and sex were not considered when searching for studies to include. Prophylactic drug use is meant to reduce the symptoms of AMS [75], potentially decreasing self-reported LLS scores. A meta-analysis by Vinnikov et al. [76] determined smoking status likely does not have a positive nor negative effect on AMS. Hou et al. [49] conducted a meta-analysis on sex differences and AMS-susceptibility and found that females were more susceptible compared to males. It is possible that these remaining variables could account for heterogeneity in this meta-analysis.

CONCLUSION

According to this study, SpO₂ and HR yielded the largest differences (SMD = -0.71 and 0.45, respectively) between AMS+ and AMS- groups compared to SBP and DBP, which were both negligible. AMS+ individuals tended to have lower SpO₂ levels and higher HRs compared to AMS- individuals. A faster AT alters differences for SpO₂, HR, SBP, and DBP between AMS+ and AMS- individuals by increasing the difference
for SpO₂ and HR and reducing the between-group differences in SBP and DBP.

Measurement timing after arriving at the desired elevation should be considered as it can affect the difference between AMS+ and AMS- for HR. The longer time before measurement after arrival (by 1 hr), the greater the difference in HR between the two groups. The participants’ age should be considered when measuring DBP as physiological differences in arterial wall composition alters DBP in older compared to younger individuals. The LLS cut-offs used also influenced difference in SpO₂ and DBP’s between AMS+ and AMS- individuals, but the authors did not recommend increasing the cut-off from ≥ 3 with a headache as this criteria is considered reliable and valid [19,20].

As demonstrated in this meta-analysis and meta-regression, there are many factors that can contribute to effects sizes for differences in SpO₂, HR, SBP, and DBP, between AMS+ and AMS- groups after exposure to hypoxia. By indicating that SpO₂ and HR have moderate effect sizes, these two variables could be used by future researchers to create a predictive model based on initial hypoxic exposure (first 20-30 min of exposure to 2300-4200 m, [47]) to determine AMS-susceptibility. Burtscher et al. [47] originally suggested SpO₂ as a possible predictive variable for identifying AMS-susceptibility, but based on the results of the present meta-analysis, researchers should also consider HR. The inclusion of HR could strengthen the prediction of AMS-susceptibility because SpO₂ and HR are related; as SpO₂ goes down, HR goes up [12,39–41,65,66]. Since this study only assessed non-invasive measurements, researchers creating predictive models using Burtscher’s method [47], should also consider invasive measurements (e.g., hemoglobin,
hematocrit) and additional laboratory measurements (e.g., fractional expired nitric oxide, end-tidal carbon dioxide).
CHAPTER 3 MANUSCRIPT

INTRODUCTION

Upon standing, an individual’s cardiovascular homeostasis is challenged where an increase in sympathetic activity acts to prevent a decrease in blood pressure (BP) caused by blood pooling in the lower extremities [1,2]. This is referred to as the orthostatic stress response. Tolerance to an orthostatic challenge is reduced at high altitude (HA, > 2500 m), potentially resulting in syncope in healthy, young individuals [5,8,77–80]. This reduction in orthostatic tolerance has been observed as a shorter time to presyncope (e.g., a feeling of fainting) at 3660 m and a greater fall in systolic blood pressure (SBP) at 5200 m compared to sea level (about 24.5 mmHg and 11.9 mmHg, respectively) [5,7]. This decrease in tolerance may be related to hypoxia-induced vasodilation in the lower extremities at rest [6]. At sea level and HA [17], an inability to overcome an orthostatic challenge can result in feelings of dizziness, lightheadedness, weakness, fatigue, headache, presyncope, and syncope [2]. These symptoms are also similar for those who develop acute mountain sickness (AMS) at HA.

Literature is sparse in terms of determining responses to and symptoms of orthostatic stress assessed at HA between AMS positive (AMS+) and AMS negative (AMS-) individuals. Mytton et al. [7] assessed auscultated changes in SBP within 15 seconds of standing after lying supine at 5200 m and reported dizziness on the Lake Louise scale (LLS). They found that individuals who reported dizziness consistently had a greater decrease in SBP at HA (about 21.0 mmHg) compared to sea level (about 11.9 mmHg decrease), but this was not significantly different than in individuals who did not experience dizziness (about 20.6 mmHg). Of the studies that assessed orthostatic
challenges in hypoxic environments [4–8], Mytton et al. [7] were the only ones to assess
differences between AMS+ as measured by the LLS [20] (LLS ≥ 3) and AMS- (LLS < 3)
individuals for changes in SBP within 15 seconds of standing. There were no differences
in SBP reductions between the two groups. This could be because they had participants
stand upright after lying supine for two minutes, such that the lower extremity muscles
contracted and assisted with venous return, compared to using head-up tilt (HUT) [7],
which minimizes or eliminates the use of these muscles. While comparisons were made
between AMS+ and AMS- individuals at HA (5200 m) for differences in SBP from
orthostatic stress, there was no attempt to determine if orthostatic stress at sea level
correlated with AMS scores. There are also other hemodynamic variables (stroke volume
[SV], cardiac output [CO], diastolic blood pressure [DBP], mean arterial pressure [MAP],
total peripheral resistance [TPR], and heart rate variability [HRV]) and perhaps others,
affected by orthostatic challenges and HA [1,81]. Therefore, it may be possible to
differentiate AMS-sensitive individuals from those who are not when using variables
other than SBP.

If responses to HUT demonstrate strong relationships with AMS scores, HUT
could be used by medical personnel who perform pre-trek health assessments of those
traveling to HA for work or exercise. If HUT responses differ significantly, then changes
in variables during HUT observed in the AMS-sensitive group may be useful to predict
AMS-susceptibility and provide an individualized AMS mitigation plan in future
scenarios where HA exposure is imminent. The primary purpose of this study was to
determine whether exaggerated responses to HUT (e.g. greater change in BP, HR, HRV,
SV, CO, TPR) occurred in those individuals that were susceptible to AMS during HA
exposure. If so, this could assess whether orthostatic stress responses at low altitude could predict which individuals are more susceptible to the development of AMS when exposed to hypoxia.

MATERIALS & METHODS

Participants

Fifteen (10 males, 5 females) participants aged 20 – 29 years volunteered to participate in this study (Table 3). A screening questionnaire (Appendix C) was used to determine if participants met the inclusion criteria and were in good health. Inclusion criteria for participants consisted of answering “no” to all PARQ+ questions and having no known cardiovascular, pulmonary, renal, or metabolic diseases or symptoms thereof in accordance with the American College of Sports Medicine pre-participation screening guidelines [82]. Participants lived in the Albuquerque, NM area (1610-1620 m, moderate altitude) for the past year, were not smokers, and were not pregnant. Blood pressure was measured via auscultation prior to starting the study. If the participant’s blood pressure was either ≥ 130 mmHg for SBP or ≥ 80 mmHg for DBP after a five-minute seated rest, the person re-tested at a later, rescheduled lab visit. Blood pressure was also auscultated prior to each testing session. No participants had blood pressure ≥ 130 mmHg for SBP or ≥ 80 mmHg for DBP. Each participant provided written informed consent approved by the University of New Mexico’s Office of the Institutional Reviews Board for human subject research.
<table>
<thead>
<tr>
<th></th>
<th>Age (yrs.)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>VO$_2$max (mL·kg$^{-1}$·min$^{-1}$)</th>
<th>50% VO$_2$max (mL·kg$^{-1}$·min$^{-1}$)</th>
<th>PPO (W)</th>
<th>50% PO (W)</th>
<th>%BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS+ (n = 8)</td>
<td>23.5 ± 3.1</td>
<td>1.7 ± 0.1</td>
<td>66.0 ± 10.7</td>
<td>41.0 ± 12.3</td>
<td>20.5 ± 6.1</td>
<td>238 ± 103</td>
<td>86 ± 56</td>
<td>19.1 ± 9.7</td>
</tr>
<tr>
<td>AMS- (n = 7)</td>
<td>22.6 ± 2.0</td>
<td>1.8 ± 0.1</td>
<td>75.8 ± 16.5</td>
<td>45.2 ± 7.2</td>
<td>22.6 ± 3.6</td>
<td>274 ± 63</td>
<td>99 ± 31</td>
<td>12.6 ± 7.9</td>
</tr>
<tr>
<td>p</td>
<td>0.51</td>
<td>0.06</td>
<td>0.19</td>
<td>0.45</td>
<td>0.45</td>
<td>0.43</td>
<td>0.59</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Note: AMS+ = acute mountain sickness (AMS) score ≥ 3, AMS scores for AMS+ group = 5.3 ± 1.4, AMS- = AMS score < 3, AMS scores for AMS- group = 1.7 ± 0.6, VO$_2$max = maximal oxygen consumption, PPO = peak power output, 50% PO = workload at 50% of VO$_2$max, %BF = percent body fat, yrs. = years, m = meters, kg = kilogram, ml·kg$^{-1}$·min$^{-1}$ = milliliters per kilogram per minute, W = watts. There were no significant differences between groups (p > 0.05).
**Experimental Design**

All participants completed three testing sessions. The first visit was the baseline testing and familiarization day. Participants completed a maximal oxygen consumption test (VO$_2$max) on an electronically braked cycle ergometer (Excalibur Sport, Lode B.V., Lode Medical Technology, Groningen, Netherlands). Afterward, participants were shown the tilt table and what a 70° tilt looked like for familiarization. On the second visit, participants performed the head-up tilt test (HUT) to determine their orthostatic stress response and time to presyncope, if applicable. On the third visit, participants were exposed to hypobaric hypoxia for a total of six hours, at 429 mmHg equivalent to 4572 m. In the altitude chamber, participants performed two, 30-minute cycling bouts at 50% VO$_2$max on a mechanically braked cycle ergometer (Monark 828E, Sweden). The cycling bouts were completed within the first 3 hours of the exposure with at least 1 hour separating the bouts. Exercise bouts were performed to increase the likelihood of AMS as six hours is the minimum duration of hypoxic exposure needed to cause AMS [20,83]. Participants could read or work on their computers during the resting periods but were required to stay seated. They were also permitted to eat a light snack and drink water *ad libitum*. Nine participants were randomized to have hemodynamic responses to hypoxic exposure during exercise and rest recorded continuously (if they agreed to those procedures in the informed consent); otherwise, HR, BP, and SpO$_2$ were recorded at regular intervals. Acute mountain sickness scores were recorded pre-exposure and six hours into hypobaric hypoxic exposure. These scores were then correlated with hemodynamic changes measured during HUT.
There were at least 48 hours between testing sessions. Participants were instructed to refrain from alcohol for 24 hours, strenuous exercise for 12 hours, and caffeine for 4 hours before each session. They were instructed to maintain similar daily living activities throughout the duration of their participation.

**Procedures**

*Maximal Oxygen Consumption Test*

Prior to the maximal oxygen consumption (VO\textsubscript{2max}) test, the participants’ heights and body weights were measured without shoes using a stadiometer (Seca Heavy Plastic Measuring Rod 216, Hamburg, Germany) and weight scale (Seca Floor scale 884, Hamburg, Germany), respectively. The participants’ body composition was estimated using the Jackson-Pollock three-site, sex-specific skinfold method [84,85] for participant description. A VO\textsubscript{2max} test to volitional fatigue was performed on an electronically braked cycle ergometer. The test was terminated when the pedal cadence was < 60 rpm. Participants performed an individualized ramped protocol, based on sex, body weight, and self-reported fitness level, designed to result in exhaustion in 8 – 12 minutes [86]. A metabolic cart (TrueOne 2400 Metabolic System, ParvoMedics, Sandy UT), calibrated using manufacturer guidelines, collected breath-by-breath expired gas. Data collected during the VO\textsubscript{2max} test included VO\textsubscript{2max} (mL·kg\textsuperscript{-1}·min\textsuperscript{-1}) using 11-breath averaging and peak power output (W).

*Head-up Tilt Test*

Participants were strapped across the chest and above the knee to and rested supine on the tilt table for 20 minutes. The strappings held them in place to reduce contact with the foot plate when the table was tilted to limit contraction of the leg.
muscles. After 20 minutes of rest, participants were quickly tilted to 70° and remained there for up to 40 minutes [87]. Participants were instructed to stay as still as possible and to refrain from voluntarily contracting their muscles at any point during HUT. They were returned to horizontal supine position if they fainted, stated they felt faint, the 40 minutes expired, or they asked to return to the horizontal position.

**Hemodynamic Measurements**

A noninvasive continuous blood pressure monitor [(NCBPM) Caretaker 4, Empirical Technologies Corporation, Charlottesville, VA] was used to record beat-to-beat blood pressure (BP) using an automated finger BP cuff positioned on the index or middle finger of the right or left hand. The NCBPM was manually calibrated before each trial using a sphygmomanometer and stethoscope. The NCBPM also measured HR using the finger blood pressure cuff. SpO₂, by finger pulse oximetry, was wirelessly recorded using the NCBPM.

A noninvasive hemodynamic monitor (PhysioFlow, NeuMeDex, Bristol, PA) was used to measure stroke volume during HUT. Technicians prepared the skin using prep gel prior to electrode placement. The six electrodes were configured according to manufacturer guidelines for exercising placement. The exercising electrode placement was used because pilot testing found the resting electrode configuration resulted in missing data during the tilt. This was not the case with the exercising electrode placements. Total peripheral resistance was calculated using MAP and CO determined by the NCBPM and noninvasive hemodynamic monitor, respectively [88].

\[
Total \text{ peripheral resistance} = \frac{\text{Mean Arterial Pressure}}{\text{Cardiac Output}}
\]
Autonomic Nervous System Measurements

Heart rate variability was measured using a chest strap HR transmitter (H1, Polar USA) which wirelessly recorded HR to a Polar receiver (V800, Polar USA). The data were downloaded and analyzed using Kubios software (HRV standard, Kubios version 3.3.1) [89,90]. A low threshold was set to remove artifact. If any samples required correction of > 5% of the data, those samples were excluded from analysis. The Kubios software indicates the HRV sample may be inaccurate due to low quality data when samples require correction of > 5%. Frequency domains were used to calculate the low frequency to high frequency (LF:HF) ratio for HRV measurements.

Blood pressure variability (BPV) was defined as the standard deviation of the continuous BP data from the start of supine rest to the end of the HUT. The SBP, DBP, and MAP data was averaged over 5-minute intervals [91–93]. Therefore, if the HUT test lasted the entire 60 minutes (supine rest = 20 min, tilt = 40 min), there would be a total of 12 mean values. The standard deviation of the first four mean values was calculated to yield the variability of SBP, DBP, and MAP during supine rest (20-min interval). The following eight mean values (if the tilt lasted 40 min) yielded the standard deviation indicating the variability of SBP, DBP, and MAP during the tilted portion of the HUT test (40-min interval). A greater standard deviation value would indicate a great variation in the BP during their respective time points [91,92].

High Altitude Protocol

Participants were exposed to hypoxia simulating 4572 m during cycling exercise (two 30-min bouts) and rest (5 hrs.) in a hypobaric chamber (Special Devices Center, Office of Naval Research, Guardite Corporation, Chicago, IL). Simulated altitude
increased by ≤ 305 m per minute to prevent confounding symptoms related to a rapidly simulated ascent (e.g., ear pain, dizziness, lightheadedness). Upon reaching 429 mmHg (4572 m, as previously used in our laboratory when studying AMS [83]), participants remained at that pressure for six hours. During the first 3 hours of exposure, participants performed two, 30-min cycling bouts at a workload corresponding to 50% VO$_2$max at 75 rpm [83]. The cycling bouts were separated by at least one hour. When the participants were not cycling, they rested. Participants could interact with their digital device or read during resting periods but could not sleep.

During the hypoxic exposure, a subset of the sample (nine participants) were randomized to have their hemodynamic variables measured continuously using the NCBPM as done during HUT. This was due to limited equipment. Those who were not continuously monitored wore a Polar HR monitor (H1, Polar USA) and finger pulse oximeter (GO$_2$ Achieve, Nonin, Plymouth, MN). HR and SpO$_2$ were recorded every five minutes during exercise and at 1 hour, 3 hours, and 6 hours into exposure. Blood pressure was measured manually using a sphygmomanometer and stethoscope immediately post-exercise, at 1 hour, 3 hours, and 6 hours into exposure by the same technician for those participants. Heart rate variability was measured continuously for all participants as described above (HUT protocol).

**Acute Mountain Sickness Assessment**

Acute mountain sickness (AMS) was assessed using the modified Lake Louise scale (LLS) [20] and the Environmental Symptoms Questionnaire – III (ESQ) [72,73]. The AMS scores were recorded pre-exposure and six hours into hypoxic exposure. The score at baseline was subtracted from that at hour six. The scores from both
questionnaires were combined to create an adjusted LLS score (AMS score) for a less subjective assessment of AMS. Classifications of AMS was a score ≥ 3 [20] to determine the AMS+ group and an AMS score of < 3 for AMS- group.

**Statistical Analysis**

All statistical analyses were performed using SPSS (version 26.0, IBM SPSS Statistics). Mean and SD were used to characterize the participants, the hemodynamic changes to orthostatic stress and hypobaric hypoxia, and the AMS scores in response to hypobaric hypoxia. Independent t-tests were performed to determine if there were differences in participant characteristics, time to presyncope during HUT, and physiological responses to hypobaric hypoxic exposure (e.g., BP, HR, SpO₂, HRV) between AMS+ (AMS score ≥ 3) and AMS- (AMS score < 3) groups. Mixed effects ANOVA was used to determine differences between AMS+ and AMS- groups for changes from supine rest (BP, BPVs, HR, HRV, SpO₂, SV, CO, ejection fraction [EF], and TPR) prior to HUT to end of HUT. LLS scores were correlated with ESQ scores by linear regression. The regression equation was used to predict the LLS equivalent to the ESQ. These predicted scores were averaged with the measured LLS scores to obtain the adjusted LLS that was used as the AMS score to select AMS+ and AMS- groups. Correlations were also conducted between mean difference of end of tilt from baseline supine rest values (BP, BPV, HR, HRV, SpO₂, SV, CO, EF, TPR) and AMS scores. The *a priori* alpha level was set to *p* < 0.05.
RESULTS

Selection of AMS+ and AMS- Groups

The LLS scores strongly and positively correlated with the ESQ scores ($r = 0.80, p < 0.001$). The regression equation determined from LLS and ESQ scores was $LLS = 1.61 + 2.63 \times ESQ$, $R^2 = 0.63$, $p = 0.0004$ (Figure 4). Mean and standard deviations for physiological responses to hypobaric hypoxia can be found in Table 5. All AMS+ individuals also experienced at least a mild headache in addition to other self-reported symptoms. None of the physiological responses were significantly different between AMS+ and AMS- individuals.

![Regression analysis](image)

**Figure 4.** Regression analysis with 95% confidence interval between Environmental Symptoms Questionnaire and Lake Louise Scale scores to determine an adjusted Lake Louise Scale score. *Note:* 2 data points at (x,y = 0.18, 2).

Baseline Participant Descriptors

The baseline group descriptors (Table 3) were not significantly different between those who developed AMS and those who did not. None of the participants had an SBP ≥
130 mmHg or a DBP ≥ 80 mmHg prior to all trials. When assessing LF:HF ratios, the corrected portions of the HRV data was > 5% for four data points during supine rest prior to HUT (AMS+ n = 6, AMS- n = 5), five data points at the end of HUT (AMS+ n = 6, AMS- n = 4), and one data point during hypoxic exposure (AMS+ n = 7, AMS- n = 7), and these were excluded from the statistical analyses as recommended by the Kubios software instructions.

**Physiological Responses to Head-up Tilt Test**

Mean differences in SBP, DBP, and MAP variability all positively correlated with AMS scores ($r = 0.65, 0.64, and 0.60, p = 0.008, 0.01, and 0.02$, respectively). Variability in SBP, DBP, and MAP significantly increased from supine rest to end of tilt during the HUT test for both groups ($p = 0.004, 0.004, and 0.006$, respectively; Table 4). Oxygen saturation was significantly lower for AMS+ compared to AMS- individuals ($p = 0.03$) at baseline and when tilted. Stroke volume was significantly higher for AMS- compared to AMS+ individuals ($p = 0.04$) at baseline and when tilted (Appendix B). Six participants ended the HUT test before 40 min due to feeling faint. Table 4 shows that SBP, DBP, MAP, and TPR decreased, HR, LF:HF ratio, and CO increased, and SpO2, SV, and EF did not change during HUT. No interactions were observed for any of the previously mentioned variables (Table 4).
**Table 4.** Comparisons between AMS+ (n = 8) and AMS- (n = 7) groups during the head-up tilt test and correlations with physiological responses to acute mountain sickness scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (supine rest)</th>
<th>End of Tilt</th>
<th>Mean Difference</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMS+</td>
<td>AMS-</td>
<td>AMS+</td>
<td>AMS-</td>
<td>AMS+</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114 ± 7</td>
<td>117 ± 13</td>
<td>95 ± 7</td>
<td>102 ± 16</td>
<td>-19.0 ± 5.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 ± 9</td>
<td>73 ± 8</td>
<td>61 ± 8</td>
<td>66 ± 10</td>
<td>-9.6 ± 2.9</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87 ± 8</td>
<td>89 ± 8</td>
<td>71 ± 6</td>
<td>78 ± 12</td>
<td>-15.8 ± 6.0</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71 ± 10</td>
<td>62 ± 14</td>
<td>96 ± 12</td>
<td>91 ± 13</td>
<td>25.6 ± 9.1</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>96 ± 3</td>
<td>98 ± 1</td>
<td>95 ± 2</td>
<td>97 ± 1</td>
<td>-0.6 ± 3.8</td>
</tr>
<tr>
<td>LF:HF ratio</td>
<td>2.2 ± 1.2</td>
<td>1.1 ± 0.9</td>
<td>5.7 ± 2.8</td>
<td>6.0 ± 5.0</td>
<td>3.5 ± 3.7</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>83.4 ± 15.9</td>
<td>99.0 ± 20.2</td>
<td>80.2 ± 11.4</td>
<td>96.0 ± 8.2</td>
<td>-3.2 ± 9.1</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5.7 ± 1.1</td>
<td>6.4 ± 1.6</td>
<td>7.6 ± 1.2</td>
<td>9.1 ± 2.0</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>70.6 ± 10.4</td>
<td>68.6 ± 8.6</td>
<td>70.5 ± 8.3</td>
<td>69.0 ± 9.0</td>
<td>-0.1 ± 4.0</td>
</tr>
<tr>
<td>TPR</td>
<td>16.1 ± 4.6</td>
<td>14.4 ± 2.9</td>
<td>9.6 ± 1.8</td>
<td>8.9 ± 2.0</td>
<td>-6.5 ± 3.1</td>
</tr>
<tr>
<td>SBP variability</td>
<td>1.7 ± 1.5</td>
<td>1.7 ± 0.4</td>
<td>5.2 ± 2.5</td>
<td>2.9 ± 2.1</td>
<td>3.5 ± 3.0</td>
</tr>
<tr>
<td>DBP variability</td>
<td>0.9 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>2.6 ± 1.2</td>
<td>1.4 ± 1.0</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>MAP variability</td>
<td>1.9 ± 1.6</td>
<td>1.4 ± 0.8</td>
<td>4.7 ± 2.3</td>
<td>2.5 ± 1.7</td>
<td>2.8 ± 2.9</td>
</tr>
<tr>
<td>Time to Presyncope (min)</td>
<td>36.4 ± 6.9</td>
<td>26.8 ± 16.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** AMS+ = acute mountain sickness (AMS) score ≥ 3, AMS scores for AMS+ group = 5.3 ± 1.4, AMS- = AMS score < 3, AMS scores for AMS- group = 1.7 ± 0.6, Mean Difference = end of tilt minus baseline. All variables were assessed for significance using a mixed effect ANOVA except for Time to Presyncope which was done using an independent t-test. Correlation (Pearson’s r) determined the relationship between mean difference values and AMS scores. p Within = differences between baseline and end of tilt for all subjects, p Between = differences between AMS+ and AMS- groups for each variable, Interact = interaction, indicates a greater difference in the change from baseline to end of tilt between AMS+ and AMS- groups. Blood pressure variability is the standard deviation of the respective blood pressure over continuous measurements in time. * denotes significant differences (p < 0.05). † denotes a significant correlation to AMS scores (p = 0.008 mean difference of SBP variability, 0.01 mean difference of DBP variability, and 0.02 mean difference of MAP variability). SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, SpO₂ = oxygen saturation, LF:HF ratio = low frequency to high frequency ratio used for heart rate variability, SV = stroke volume, CO = cardiac output, EF = ejection fraction, TPR = total peripheral resistance in mmHg-min/mL, mmHg = millimeters of mercury, bpm = beats per minute, % = percent, mL = milliliters, L/min = liters per minute, min = minutes.
Table 5. Physiological measurements in hypobaric hypoxia after six hours of exposure for AMS+ and AMS- groups.

<table>
<thead>
<tr>
<th></th>
<th>AMS scores</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>HR (mmHg)</th>
<th>SpO₂ (%)</th>
<th>LF:HF ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS+ (n = 8)</td>
<td>5.3 ± 1.4</td>
<td>113 ± 9</td>
<td>71 ± 9</td>
<td>86 ± 9</td>
<td>93 ± 19</td>
<td>77 ± 2</td>
<td>5.6 ± 2.2</td>
</tr>
<tr>
<td>AMS- (n = 7)</td>
<td>1.7 ± 0.6</td>
<td>111 ± 9</td>
<td>69 ± 9</td>
<td>84 ± 8</td>
<td>101 ± 11</td>
<td>78 ± 4</td>
<td>6.5 ± 2.4</td>
</tr>
</tbody>
</table>

*p < 0.001* 0.66 0.63 0.64 0.38 0.31 0.51

Note: AMS+ = acute mountain sickness (AMS) score ≥ 3, AMS- = AMS score < 3, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, SpO₂ = oxygen saturation, LF:HF ratio = low frequency to high frequency ratio used to determine heart rate variability. mmHg = millimeter of mercury, % = percent. * denotes significant differences between AMS+ and AMS- (p < 0.05).

DISCUSSION

The purpose of this study was to determine if BP, BPV, HR, HRV, SpO₂, SV, CO, EF, and TPR can be used to identify AMS-susceptible individuals and whether these responses correlate with AMS scores during exposure to hypobaric hypoxia simulating 4572 m. The major finding was that those with higher AMS scores tended to have a greater change in variability in SBP, DBP, and MAP from supine rest to end of tilt.

An increase in BPV is an indicator of sympathetic activity on the vascular system [68,94]. In the present study, all participants had increased SBP, DBP, and MAP variability at the end of tilt compared to supine rest. This is consistent with the findings of Burke et al. [95] who found that postural changes result in increasing sympathetic bursts when BP decreases. This suggests that participants in the present study and those in the study from Burke et al. [95] demonstrated greater oscillations in BP due to a postural shift. This is observed as an increase in sympathetic activity causing BP to
briefly increase. As BP increases, the frequency of sympathetic bursts decrease causing BP to subsequently decrease [95]. This oscillation continues due to feedback from the changing BP even as average SBP, DBP, and MAP decrease during the duration of a postural change, as observed in the present study [95].

In the current study, those with higher AMS scores correlated with having a greater change from supine rest to end of tilt in SBP, DBP, and MAP variability during HUT. This was consistent with findings by Lanfranchi et al. [68] who observed greater SBP variability in AMS+ individuals compared to AMS- individuals at 4559 m. The present study also supported findings by Niebauer et al. [67]. They found AMS+ individuals had lower SBP within the first three hours of normobaric hypoxic exposure ($\text{FiO}_2 = 12.6\%, 4500 \text{ m}$) compared to AMS- individuals. Niebauer et al. [67] suggested the greater decrease in SBP for their AMS+ group may be related to a disruption in BP control that resulted in insufficient vasoconstriction due to blunted baroreflex sensitivity. Lanfranchi et al. [68] suggested the increase in SBP variability in AMS+ individuals was the result of an exaggerated sympathetic chemoreflex response. Our study demonstrates that those with higher AMS scores possibly had a disruption in BP control during HUT because of their association with a greater change in BPV. Since this occurred without hypoxic exposure, we speculate that assessing BPV via a postural change (using HUT) may help predict AMS-susceptibility. However, a multitude of factors can influence changes in BPV: baroreflex, neural vasoconstrictive mechanisms, adrenergic vasodilatory mechanisms, and nitric oxide production [96–99]. Determining a causal mechanistic reasoning for these changes requires additional investigation to determine if BPV changes during HUT could predict the likelihood of developing AMS at high
altitude. This should be done using sea-level and moderate-altitude living participants exposed to a range of simulated elevations.

Though increasing BPV indicates increasing sympathetic activity, SBP, DBP, MAP, and TPR all decreased during HUT in the present study. This suggests a vasodilatory effect. Though not measured, a possible explanation is an increase in epinephrine to a level that resulted in peripheral vasodilation which would oppose the sympathetic neural vasoconstrictive effect [94,100]. Previous researchers have observed an elevated catecholamine response from HUT and in AMS+ individuals at HA [9,101]. This increase in catecholamines could also promote peripheral vasodilation, along with localized muscle metabolites acting on the endothelium, to cause vascular smooth muscle relaxation which will assist with directing blood flow tissues in need of oxygen as SpO₂ falls due to hypoxia [30,100,102].

Oxygen saturation was lower in AMS+ compared to AMS- individuals at baseline during supine resting and HUT. The results of the current study are in contrast to Niedermeier et al. [103]. They found AMS+ individuals had higher seated SpO₂ at baseline elevation (570 m) [103], but the present study found the opposite during supine resting at baseline elevation (1610-1620 m). We speculate that though the difference in SpO₂ between groups was found to be statistically significant in both the present study and in Niedermeier’s [103] study, the measurements could be within the margin of error of the pulse oximeters (± 2%) [15].

**Limitations**

Though variability in SBP, DBP, and MAP during HUT moderately correlated with LLS scores, results of the study were unable to demonstrate that variability in SBP,
DBP, and MAP from HUT correlate with variability in SBP, DBP, and MAP during hypoxic exposure. This is because HUT and hypoxia result in increased sympathetic responses which impacts BPV [9,68,94,100]. A time constraint to complete the study meant two participants were in the hypobaric chamber with one NCBPM machine limiting the number of participants with continuous measurements.

Another limitation of this study is the small sample size which occurred due to the 2020 COVID-19 pandemic. This means the statistical results are under-powered and should be interpreted with caution. An a priori power analysis to determine the sample size determined that 26 participants were required, but only 15 participants completed the protocol (no withdrawals). After data from more participants are analyzed, it is hoped we will be able to gain insights into whether HUT responses could predict AMS-susceptibility. If so, this could then provide a tool for medical professionals to help counsel individuals prior to going to HA. Additional research should be done using sea-level living participants to ensure generalizability to this population.

**CONCLUSION**

In conclusion, BPV during HUT could be a promising measurement to determine individuals at risk of developing AMS at high altitude. AMS+ individuals tended to have higher variability in their SBP, DBP, and MAP, and there were moderate correlations between variability in SBP, DBP, and MAP with AMS scores. Based on the results of this study, in the future, researchers should determine detailed mechanisms related to changes in BPV during HUT and hypoxic exposure that could better link variability in SBP, DBP, and MAP during HUT and hypoxic exposure. This should be done using sea-level living participants and a range of simulated hypoxic exposures. This could better
determine if HUT responses, specific to BPV, could predict AMS-susceptibility prior to hypoxic exposure.
CHAPTER 4 SUMMARY, RECOMMENDATIONS, & FUTURE DIRECTIONS

SUMMARY

Researchers have attempted to determine physiological differences between individuals who develop acute mountain sickness (AMS+) and those who do not (AMS-) when exposed to high altitude (>2500 m [17]). The meta-analysis (Chapter 2) demonstrated that AMS+ individuals have lower oxygen saturation (SpO\textsubscript{2}) levels and higher heart rates (HR) compared to AMS- individuals in hypoxia. A decrease in SpO\textsubscript{2} is the result of increasing elevation [30]. As SpO\textsubscript{2} decreases with increasing elevation, HR increases to circulate the blood faster in response to hypoxic tissue [12,39–41,65,66]. The Chapter 2 meta-analysis demonstrated that an increase in ascent rate could create a more homogenous SpO\textsubscript{2} and HR response. Previous literature shows that SpO\textsubscript{2} is lower and HR is higher when ascending quickly [64,66]. Measurement timing for physiological variables after reaching the desired elevation should also be controlled for as AMS+ individuals’ autonomic nervous systems respond differently from those who do not develop AMS [68,69]. This can affect HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) due to autonomic influence over the sinoatrial node and vascular smooth muscle. A confounding variable that decreased the effect sizes for differences between AMS+ and AMS- for SpO\textsubscript{2} could be the participants’ body weight (BW). A greater BW with increased fat distribution around the trunk and total body mass correlated with higher AMS scores at 4100m [104]. However, only collecting BW does not give researchers an idea of fat mass distribution. Age is also a variable to control for when assessing BP in hypoxic environments because older individuals have stiffer arteries due to structural changes that increase BP [70,71]. Finally, Lake Louise Scale
(LLS) cut-offs differed among the selected studies included in the meta-analysis and influenced the effect size concerning the differences between individuals who are AMS+ and AMS- for both SpO$_2$ and DBP. However, it is not recommended to change the current LLS cut-off as it is currently considered valid and reliable [19,20]. Many of the studies used in the Chapter 2 meta-analysis assessed differences between AMS+ and AMS- individuals after exposing them to hypoxia. This indirectly led to the research question addressed in Chapter 3 – assessing individuals prior to hypoxic exposure to differentiate people who become AMS+ or remain AMS- at high altitude.

An orthostatic challenge involves a postural change (i.e., head-up tilt [HUT]) that results in a fall in SBP and DBP, respectively, by tilting individuals from a supine position to 70° without contraction of the lower extremities. The fall in SBP and DBP is greater (about 21 mmHg) when an orthostatic challenge occurs at 5200 m compared to sea level [7]. Since dizziness is a symptom of both HUT and AMS, Mytton et al. [7] assessed whether individuals who reported dizziness on their LLS had greater decreases in SBP compared to those who did not. There were no significant differences in the SBP reduction when standing from a supine position. This was also the case when this research group compared AMS+ and AMS- individuals [7]. Again, the researchers’ [7] designed the study to only assess differences between AMS+ and AMS- individuals during hypoxic exposure as opposed to also including sea-level measurements. In addition, there are other hemodynamic variables that change during HUT (i.e., stroke volume [SV], cardiac output, DBP, mean arterial pressure [MAP], total peripheral resistance, and heart rate variability) [1,2]. Therefore, the purpose of the Chapter 3 study was to determine whether there were differences between AMS+ and AMS- individual’s
orthostatic stress response to HUT at their baseline elevation using several hemodynamic variables. A secondary purpose was to determine if and how those hemodynamic variables altered during HUT would correlate with AMS scores.

The changes in blood pressure variability (BPV) for SBP, DBP, and MAP during HUT tended to be higher in AMS+ individuals and moderately correlated with AMS scores. This could be because HUT and hypoxia result in increased sympathetic activity and an increase in BPV is an indicator of sympathetic predominance over the vascular system [95]. The change in BPV could be a promising measurement to consider because of the potential link between BPV during HUT and the differentiation of individuals who develop AMS+ and AMS- at high altitude through changes in sympathetic activity. The results of the present study support the findings by Lanfranchi et al. [68] and Niebauer et al. [67] who found an increased variability in SBP and lower SBP within the first three hours of hypoxic exposure in AMS+ individuals, respectively. These authors suggest there may be a disruption in BP control possibly from an exaggerated sympathetic chemoreflex response [67,68]. However, multiple factors can influence changes in BPV: baroreflex, neural vasoconstrictive mechanisms, adrenergic vasodilatory mechanisms, and nitric oxide production [96–99]. More research is needed to determine the causal mechanisms for BPV changes in response to HUT and hypoxia. Perhaps this could help determine why BPV from HUT can predict AMS-susceptibility.

Oxygen saturation was significantly different between AMS+ and AMS- individuals during supine rest and HUT at baseline elevation. However, the mean difference between these groups was 2%, which could be due to the margin of error
(±2%) of the pulse oximeter. This suggests that SpO₂ may not differentiate AMS+ and AMS- individuals prior to hypoxic exposure.

**RECOMMENDATIONS**

Caution is recommended when deciding to use HUT to identify AMS-susceptible individuals prior to hypoxic exposure. Though measuring BPV during HUT seems to be promising, the Chapter 3 study was under-powered, and results should be interpreted with caution. By recruiting more participants, we may be able to provide clarification of any results that are nearing significance. Future researchers should also recruit sea-level living individuals and use range of simulated elevations to determine its generalizability to different populations exposed to various elevations is possible.

**FUTURE DIRECTIONS**

Based on the results of Chapter 3, future researchers should determine neuro-endocrine mechanisms (i.e., baroreflex and chemoreflex [67,68]) related to changes in BPV during HUT and hypoxic exposure that will better link changes in BPV from HUT those during hypoxic exposure. Research should be conducted to determine if these changes in BPV regularly occur in AMS+ individuals during HUT (using this study’s HUT protocol) at baseline elevation in sea-level living participants. This will better determine if HUT responses, specific to BPV, could predict AMS-susceptibility prior to hypoxic exposure. If that is the case, HUT, including the continuous measurement of BP throughout the procedure, potentially could provide a tool for medical professionals to help counsel mountaineers aspiring to summit various peaks and military and firefighting personnel prior to their operations. By identifying AMS-susceptible individuals prior to
high altitude exposure, this could mitigate AMS through targeted prophylaxis treatment and/or altered itinerary plans for those at risk.
APPENDICES

APPENDIX A: DISCUSSION OF ADDITIONAL FINDINGS FROM CHAPTER 2

Not all studies have found a large differences in SpO$_2$ between AMS+ and AMS- or that AMS+ individuals had lower SpO$_2$ values [16,55,56,103]. A potential confounding variable may be the participants’ BW. This is because the meta-regression demonstrated a reduction in effect size by 0.13 for every increase of 1kg in BW. Heavier individuals, such as those with a body mass index [BMI] $\geq$ 30 kg/m$^2$, are more likely to become hypoxic at altitude due to increased work of breathing and reduced respiratory muscle efficiency and compliance [105–107]. However, the evidence is equivocal on a link between BMI and AMS [34,62,104,108]. This could be because BMI, just like BW, does not determine body composition or body fat distribution. Dobrosielski et al. [104] found that individuals with greater body fat distributed around the trunk and higher total body fat mass correlated with higher AMS scores at 4100 m ($r = 0.73$ and 0.71, respectively). A second reason could be that the association between BMI and AMS scores may vary based on the elevation reached. A stronger correlation between BMI and AMS scores was found at 4100 m ($r = 0.77$) with the strength of the correlation decreasing with decreasing elevation ($r = 0.50$ at 3800 m and $r = 0.47$ at 3400 m) [104]. Future research should be done to determine if elevation and body composition influence predictability of AMS-susceptibility.

Based on the findings from Chapter 2, future researchers should statistically control for body composition by using percent body fat rather than relying on BW or BMI as fat mass and fat distribution could impact AMS-susceptibility. This is because BW and BMI do not account for muscle mass. According to Arone et al. [109] and
Molfino et al. [110], an increase in BW resulting in obesity increases sympathetic activity which could confound AMS scores related to SpO$_2$. Age and measurement time after arriving at the desired elevation should also be controlled due to age-related arterial wall changes and differences in autonomic nervous system responses affecting HR and BP, respectively.

**APPENDIX B: DISCUSSION OF ADDITIONAL FINDINGS FROM CHAPTER 3**

AMS+ individuals had lower SV compared to AMS- individuals; however, a person’s body surface area (BSA) and sex can impact SV [111,112]. A *post-hoc* calculation of BSA and correlation between BSA and SV at end of tilt significantly correlated ($r = 0.63$, $p = 0.01$). Since there was a significant correlation, BSA was controlled for when comparing AMS+ and AMS- individuals and when correlating end of HUT SV to AMS scores. SV was no longer significantly different between AMS+ and AMS- when controlling for BSA ($p = 0.14$). The participant’s sex significantly correlated with end of tilt SV ($r = -0.66$, $p = 0.007$). When controlling for sex, the significant difference between AMS+ and AMS- individuals for SV remained ($p = 0.04$). Therefore, individual differences in BSA (smaller vs. larger participants) influenced SV results regardless of sex. This suggests end of tilt SV would not be a useful predictor of AMS-susceptibility since there are individual differences in BSA.
APPENDIX C: AMS SCREENING QUESTIONNAIRE

Inclusion/Exclusion Criteria

Preferred First Visit Dates & Times: ____________________________________________

Current Place of Residence: City - ____________________________________________

How Long? ___________

Yes      No

☐ ☐ Are you claustrophobic (afraid of being in small, tight spaces)?

☐ ☐ Are you anemic (have low levels of red blood cells)?

☐ ☐ Do you currently smoke cigarettes or have you smoked in the last 6 months?

☐ ☐ Do you have any known cardiovascular, renal, metabolic, or pulmonary disease or have a lower body injury?

If yes, please describe your illness or injury._________________________________________

☐ ☐ Have you traveled to an elevation higher than 6000ft in the last 2 months?

IF FEMALE

☐ ☐ Are you currently pregnant or are trying to become pregnant?

*If between 18-30 years, from Albuquerque, and answered “no” to every question, continue to the next page.*

*If not between 18-30 years, not from Albuquerque area or answered “yes” to one of the questions, thank them for their time, and say they do not qualify for participation.*
Predicting AMS Study Phone Screening

PARQ

Yes No

☐ ☐ Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?

☐ ☐ Do you feel pain in your chest when you do physical activity?

☐ ☐ In the past month, have you had chest pain when you are not doing physical activity?

☐ ☐ Do you lose your balance because of dizziness or do you ever lose consciousness?

☐ ☐ Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?

☐ ☐ Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?

☐ ☐ Do you know of any other reason why you should not do physical activity?

*If answered “no” to every question, continue to the next page.*

*If answered “yes” to at least one question, thank them for their time, and say they do not qualify for participation.*
Exercise History Questionnaire

On average, how many days per week do you exercise? __________________________

Of those days, how many times do you exercise at a moderate intensity? (i.e. sweating, heart rate is up, can still hold a conversation)___________________________

Of those days, how many times do you exercise at a vigorous intensity? (i.e. sweating a lot, heart rate is fast, difficult to hold a conversation) _____________________________

What is your main form of exercise? (i.e. aerobic dance, running, biking, weight lifting)________________________________________________________________________

Medical History Questionnaire

If you are allergic to latex, neoprene or any medications, foods, or other substances, please name them.

________________________________________________________________________

If you have been told that you have any chronic or serious illnesses, please list them.________________________________________________________________________

If answered previous two questions. Have you ever been hospitalized because of the previous allergies or illnesses described? Reason? Month & Year? City & State?

________________________________________________________________________

________________________________________________________________________

Subject #: __________________
### During the past 12 months

<table>
<thead>
<tr>
<th>Subject #: ________________</th>
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<tr>
<td><strong>Yes</strong></td>
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- [ ]  [ ] Has a physician prescribed any form of medication for you?
- [ ]  [ ] Has your weight fluctuated more than a few pounds?
- [ ]  [ ] Did you attempt to bring about this weight change through diet or exercise?
- [ ]  [ ] Have you experienced any faintness, light-headedness, or blackouts?
- [ ]  [ ] Have you experienced any blurred vision?
- [ ]  [ ] Have you had any severe headaches?
- [ ]  [ ] Have you experienced chronic morning cough?
- [ ]  [ ] Have you experienced any temporary change in your speech pattern, such as slurring or loss of speech?
- [ ]  [ ] Have you felt unusually nervous or anxious for no apparent reason?
- [ ]  [ ] Have you experienced unusual heartbeats such as skipped beats or palpitations?
- [ ]  [ ] Have you experienced periods in which your heart felt as though it were racing for no apparent reason?

### At present

- [ ]  [ ] Do you experience shortness or loss of breath while walking with others your own age?
- [ ]  [ ] Do you experience sudden tingling, numbness, or loss of feeling in your arms, hands, legs, feet, or face?
Have you ever noticed that your hands or feet sometimes feel cooler than other parts of your body?

Do you experience swelling of your feet and ankles?

Do you get pains or cramps in your legs?

Do you experience any pain or discomfort in your chest?

Do you experience any pressure or heaviness in your chest?

Have you ever been told that your blood pressure was abnormal?

Have you ever been told that your serum cholesterol or triglyceride level was high?

Do you have diabetes?

If yes, how is it controlled? Dietary means? Oral medications? Insulin injection?

Uncontrolled?

How often would you characterize your stress level as being high? Occasionally?

Frequently? Constantly?
Have you ever been told that you have any of the following illnesses?

☐ Myocardial infarction  ☐ Arteriosclerosis  ☐ Heart disease
☐ Thyroid disease  ☐ Coronary thrombosis  ☐ Rheumatic heart  ☐ Heart attack
☐ Heart valve disease  ☐ Coronary occlusion  ☐ Heart failure  ☐ Heart murmer
☐ Heart block  ☐ Aneurysm  ☐ Angina

Have you ever had any of the following medical procedures?

☐ Heart surgery  ☐ Pacemaker implant  ☐ Cardiac catheterization
☐ Defibrilator  ☐ Coronary angioplasty  ☐ Heart transplantation

Has any member of your immediate family (mother, father, sister, brother) been treated for or suspected to have had any of these conditions? Please identify their relationship to you.

Diabetes: __________________________________________
Heart Disease: _______________________________________________
Stroke: _________________________________________________________
High Blood Pressure: ___________________________________________

*If they do not answer questions indicating having signs or symptoms of cardiovascular, metabolic, renal, or pulmonary disease, thank them for their time, and say they qualify for participation. Email the informed consent.*

*If they do answer questions indicating having signs or symptoms of cardiovascular, metabolic, renal, or pulmonary disease, thank them for their time, and say they do not qualify for participation.*
REFERENCES


predicts acute mountain sickness on further ascent at 3000–4300 m altitudes.


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