Physiologic Variables Associated with the Development of Acute Mountain Sickness at the South Pole

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Physiologic Variables Associated with the Development of Acute Mountain Sickness at the South Pole

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Abstract

Introduction: Exposure to altitude >2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition. Research has attempted to identify factors associated with developing AMS without controlling important factors related to the ascent or collecting a comprehensive set of variables. **Methods:** The Antarctic Study of Altitude Physiology (ASAP) studied participants not using acetazolamide (N=98) in the United States Antarctic Program during austral summer months of 2010 and 2011. All subjects traveled to altitude rapidly via airplane. Collected data included personal history, anthropometrics, vital signs, blood samples, and pulmonary function at sea level and at altitude. Statistical analysis utilized independent sample t-tests to investigate between-group differences, $p<0.05$, and a forward, stepwise binary logistic regression analysis was performed. **Results:** Analysis of participants not using acetazolamide with complete data sets (n=90) found 30 participants developed AMS, defined by Lake Louise Symptom Score questionnaire, and 60 participants did not. Estimated plasma volume decreased significantly at altitude ($p=0.025$) in the AMS group as compared to the No AMS group while body weight did not change ($p=0.125$). Serum sodium ($p=0.045$) and LDL ($p=0.049$) levels were higher in the No AMS group. Two logistic regression equations placed nearly identical emphasis on the roles of LDL and eosinophil levels in the development of AMS. **Conclusion:** These results suggest body water regulation and inflammation are key factors in AMS development when all other factors such as the level of physical exertion during ascent, the rate and magnitude of ascent, and the use of acetazolamide are controlled.

Keywords: altitude illness; altitude; hypoxia; Antarctica;

Article Summary

1. Article Focus
    a. Incidence of acute mountain sickness among a population travelling rapidly to altitude.
    b. Broad data collection included numerous physiological variables at sea level and at altitude
2. Key Messages
    a. Incidence of acute mountain sickness was associated with variables associated with fluid dynamics and total body water.
    b. Incidence of acute mountain sickness was associated with variables associated with inflammation.
3. Strength and Limitations
    a. All subjects travelled to altitude in an identical and rapid fashion and did not descend to sleep.
    b. Our sample size permitted the exclusion of participants who opted to utilize acetazolamide prophylactically.

c. Our research oversight and ethics committee did not let us blind or regulate who opted to use acetazolamide. An individual's past experience with acute mountain sickness may have influenced their choice and introduced a bias.

Introduction

Exposure to altitude higher than 2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition that has been described as a "nuisance" in that it halts progression to higher altitudes and has a negative impact on quality of life rather than posing a serious health risk.[1,2] The development of AMS is not clearly associated with any one particular factor in the currently available literature nor has a definitive etiology of AMS been identified.[3-6] Rather many different factors such as age, gender, body habitus, physical fitness, tolerance of hypocapnia, rate of ascent, magnitude of ascent, recent prior ascents or simply individual susceptibility have been linked to increased risk of development of AMS but conflicting results are available related to the importance of each of these variables. [3,6-8] However, the research methods employed in these studies may have influenced the variability in the reported results: many of these variables were collected by self-assessment (i.e. physical fitness) or self-reporting (i.e. past medical history); the various destination altitudes and rates of ascent were not consistent; and the use of pharmaceutical prophylaxis (i.e. acetazolamide) was not regulated.[9-11]

Using the Lake Louise Criteria, the diagnosis of AMS is based on recent travel to altitude and the presence of subjective symptoms including headache, fatigue/weakness, dizziness/lightheadedness, gastrointestinal disruption, and sleep disturbances.[12] The subjective nature of the diagnosis likely compounds the difficulties in identifying factors to predict which

individuals are at an increased risk. Furthermore, the benefit of predicting future cases of AMS based on an individual's history of previous AMS diagnoses is likely lost on the afflicted person – they would like to know ahead of their first ascent that they are at risk for AMS. This is especially true in cases, such as military endeavors or Antarctic assignments, where the rate of ascent cannot be slowed. It is with this in mind that a well-controlled data collection methodology would be beneficial to maximize the likelihood of firmly identifying predictive factors.

The Antarctic Study of Altitude Physiology (ASAP) studied participants in the United States Antarctic Program during austral summer months of 2005-2006 and 2006-2007. This project provided unique opportunities to observe a large and well-controlled population to assess which variables and factors, particularly at sea-level, were associated with AMS development in susceptible individuals. All participants underwent medical screening prior to deployment to Antarctica, were available to the research team during the first seven days of their deployment, and travelled from McMurdo Station (sea-level) to Amundsen-Scott South Pole Station (2835m; physiologic altitude of ~3200m) via airplane in less than four hours. The breadth of the data collected plus the controlled and uniform manner in which all individuals travelled to altitude provided an opportunity to evaluate which, if any, factors are related to the development of AMS.

Methods

Participants. Acetazolamide was made available to all participants (N=248). However, for this presentation of results, only those who did not take acetazolamide (n=98) were included in the initial analysis. Subjects who did not complete all questionnaires, provide two blood samples, or complete two pulmonary function tests (PFT) were omitted from the final analysis (n=8). The final analysis was performed using 90 subjects.

Procedure. Data was collected during two austral summer expeditions to Amundsen-Scott South Pole Station. Ethical approval was obtained from Mayo Clinic, Rochester MN and all participants provided written informed consent. Participants were included in the study if their duties at Amundsen-Scott South Pole Station exceeded one week in duration. During 2006-2007, data was only collected from those who had not been a participant during the 2005-2006 expedition. The data collection, the subsequent data analyses, and dissemination of findings were performed in accordance with the STROBE principles.[13]

Following arrival at McMurdo Station, participants typically acclimatized to the ambient temperature and adjusted to the new timezone for ~2 weeks prior to departing for the Amundsen-Scott South Pole Station. During this time, participants underwent baseline testing and education

related to high altitude illness. Acetazolamide was made available to any participant who wished to employ AMS prophylaxis even though this resulted in the exclusion of that individual's data from this manuscript's analysis. Baseline questionnaire collection included Lake Louise Symptom Score questionnaires as well as an additional symptom questionnaire pertaining to 1) dyspnea (at rest and on exertion) 2) general health limitations 3) mental status changes 4) cough 5) peripheral edema. Further questionnaire data included information related to past medical history and chronic medical conditions, current medication use, lifestyle assessment (i.e. tobacco and alcohol use; exercise habits), and previous experience with altitude and/or Antarctic expeditions. Baseline anthropometric and physiological measurements included height, weight, heart rate, blood pressure, arterial oxygen saturation (SaO_2) and blood draw. Blood samples were analyzed for hemoglobin concentration and hematocrit; serum electrolyte and progesterone levels; circulating catecholamine levels; and thyroid, liver and kidney function. Changes in plasma volume were calculated using Dill and Costill's method.[14]

Participants completed the same questionnaire reporting AMS symptoms related to symptoms including the Lake Louise Symptom Score form on 9 separate occasions. Questionnaires were completed at baseline, on the plane to Amundsen-Scott South Pole Station, and daily for the first seven days following arrival. The completion of the first questionnaire at the Amundsen-Scott South Pole Station occurred prior to sleep on the first night and each of the subsequent questionnaires were completed upon waking. An individual was determined to be suffering from AMS if their Lake Louise Symptom Score was $\geq$ 3 concurrent with a headache.

Statistical Analysis. Visual inspection of all variables was performed to identify and remove any outliers (i.e. data point > ±3 SD) from the data set on a case-by-case basis. Statistical analyses were performed with SPSS 20.0 (IBM Corporation, Armonk NY). Comparison of means was performed using independent samples t-test for subjects without AMS (LLSS $\leq$2) (n=60) as compared to subjects with AMS (LLSS $\leq$3) (n=30). Significance was set as $p<0.05$. A forward, stepwise binary logistic regression analysis was also performed. All variables associated with the occurrence of AMS at $p<0.25$ in the initial analysis were then included in the generation of the final equation.[9] Using subjects who had been previously removed due to numerous missing data points (n=8) or for whom data points related to the regression equation generation were missing (n=21), the regression equation was applied to assess its reliability and validity in predicting the occurrence of AMS (n=29).

Results

Demographic and anthropometric data are presented in Table 1. No significant differences were observed between groups. Data is presented as mean ± standard deviation. Hematologic and

laboratory results are included in Table 2; Table 3 summarizes the endocrine results; Table 4 presents the PFT results.

The forward, stepwise binary logistic regression initially included 8 variables (chloride, aspartate aminotransferase (AST), low density lipoprotein (LDL), eosinophils, red blood cell distribution width (RDW), leptin, and epinephrine, $p<0.25$) for the generation of the model. Only subjects for whom all 8 variables were recorded and available were entered into the regression equation. For the AMS group, this resulted in n=19; for the No AMS group, this resulted in n=50. The logistic regression analysis generated a model that included LDL and eosinophils (eos) with a positive predictive value (PPV) of 55.6%, and negative predictive value (NPV) of 76.7%, sensitivity of 26.3%, and specificity of 92%. The equation is provided below:

$$Prob\ (AMS) = (e^{1.593 + (-0.037)(LDL) + (0.433)(eos)}) \times (1 + e^{1.593 + (-0.037)(LDL) + (0.433)(eos)})^{-1}$$

At the outset, 8 individuals were excluded from the analysis due to multiple missing data points (i.e. did not present for repeat blood draw at altitude; did not complete intake questionnaire, etc). From the AMS group, 10 individuals were not included in the generation of the regression equation while 11 individuals were not included from the No AMS group. Of these 29 subjects, 22 had data available with respect to their LDL and eosinophil levels and thus were used to verify the regression equation's accuracy. The model correctly categorized 57% of the participants.

Discussion

Currently AMS is a clinical diagnosis based on subjective and self-reported measures. However, identifying an objective series of variables from the subjective reports that may differentiate those at risk for suffering AMS as compared to those at a decreased risk has eluded many investigators. The present study controlled a number of variables that are recognized as contributory to the development AMS but which are not often well controlled across a study population. One of the most commonly identified factors is the altitude at which individuals sleep.[3,8,15,16] In some previous studies, this may have been a lower altitude than the one at which they were at during the day and often varied by individual. However, in the present study, all subjects worked and slept at the same constant altitude. An additional difference was the means by which our participants arrived at altitude. All participants boarded a short duration flight (<4h). Previous studies have reported a number of different rates of ascent and many of these ascents involved

varying degrees of physical exertion.[17] These factors, if not controlled, can influence the development of AMS and confound results in attempting to identify baseline characteristics placing an individual at risk of AMS.

Our results lend themselves to interpretation that supports a number of the hypothesized causes of AMS and these will be discussed. However, an important caveat is the magnitude of the differences between the AMS and the No AMS populations. While statistically significant and interesting in generating further hypotheses, these differences are too slight to permit a clinical prediction of who may or may not develop AMS on an expedition to altitude. For example, reliably differentiating between a blood pressure of 111/70 mmHg (AMS group) and 109/67 (No AMS group) in any single individual may be beyond the capability of many clinicians. The same can be said for many of the other statistically significant differences between the two groups. But rather than a considering this to be a weakness of the present study, this more likely speaks to the subtle nature of AMS, an often mild and self-limiting condition described as a nuisance.[1,2]

Two of the subtle differences of interest are the serum sodium (Na^+) levels and LDL cholesterol levels. These values differed within the normal ranges for those that developed AMS (Na^+ 138.5 and LDL 97.7) as compared to those that did not develop AMS (Na^+ 139.4 and LDL 105.9). Serum osmolarity is calculated using the following equation:

$$\text{Osmolarity} = 2 \times [Na^+] + [\text{Glucose}] \times 18^{-1} + [\text{Urea}] \times 2.8^{-1}$$

While glucose levels were recorded in this data set, unfortunately blood urea nitrogen (BUN) was not. However, BUN's influence is minimal as its levels are normally less than 20 mg/dL and only1/4 to 1/3 of its value is subsequently used to calculate osmolarity. Similarly for glucose, only a small proportion (approximately 6%) of its serum level plays a role in determining osmolarity. To further minimize the influence of glucose on this variable, no diabetics were included in the participant pool in the current study. Of the three variables within the equation, Na^+ has the largest influence in determining osmolarity. Increased serum Na+ would decrease the flow of fluid from the extracellular space to the intracellular space, thereby decreasing cellular edema. One of the hypothetical explanations for the occurrence of AMS suggests that tissue edema, particularly in the cerebral tissue, is a contributing factor.[2,3,16] A second variable that differed between those who suffered AMS from those who did not shares a similar characteristic. Serum LDL levels were significantly higher but still within the normal range in those who did not develop AMS as compared to those who did. In nephrotic syndrome, serum LDL concentration is inversely related to serum albumin concentration.[18-20] One of the explanations for the rapid and dramatic increase in LDL in hypoalbunemic states focuses on the body's attempt to maintain an adequate oncotic pressure. While our participants were not hypoalbunemic by clinical assessment, the elevated LDL levels may

have positively contributed to the prevention of AMS through increasing the oncotic pressures. Oncotic pressure, like serum osmolarity, is one of the means by which intravascular fluid (a component of the extracellular space) is kept within the vasculature in order to prevent edema. Furthermore, LDL was represented in both of our logistic regression models.

In continuing to examine a possible link between fluid distribution between the body's compartments and AMS, a significant decrease in plasma volume at altitude as compared to sea level baseline values was observed in our subjects who developed AMS. As significant differences were not observed for participant weights between the Sea Level and Altitude measurements for either group, it stands to reason that total body water remained relatively constant between the measurements. However, the AMS group saw a nearly 10% decrease in estimated plasma volume and this would suggest that the fluid left the intravascular space and likely caused either intracellular or extracellular edema whereas the participants in the No AMS group saw a minimal decrease in estimated plasma volume as compared to Sea Level. Previously, Loeppky et al.[21] have reported fluid retention occurs during the initial exposure to simulated altitude and our results suggest this retained fluid leaves the intravascular space. Related to fluid regulation, Hackett al.[22] have suggested abnormalities in handling body water as the common link between the two edematous conditions, HAPE and HACE, representing the more serious forms of altitude-related illness.

Three of the variables identified in our analysis are seemingly linked to each other and to hypothesized causes of AMS – vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and eosinophils. VEGF levels at altitude were significantly elevated in those that developed AMS as compared to those that did not. VEGF's primary role is to promote the formation of new blood vessels and it is seen in increased levels in conditions that are associated with decreased oxygen supply to tissues.[23] However, VEGF has also been linked to increased vascular permeability that contributes to the development of edema.[24,25] Serum eosinophil level was the other variable that was represented in the logistic regression model. While increased eosinophil levels are often associated with the immune response to a parasitic presence or a hypersensitive response such as asthma, it does increase the levels of VEGF in the blood.[25,26] These two variables are linked at altitude with hypoxia prolonging the viability of eosinophils while increasing the eosinophllic production of VEGF and other pro-inflammatory cytokines, prostoglandins, and leukotrienes.[25,27] A third inflammatory variable, TNF-α, was also found to differ between the groups - at sea level, the AMS group had significantly higher levels of TNF-α ($p=0.012$), further indicating the role of inflammation in the development of AMS.

The variables in our logistic regression equation themselves are worth dissecting. The constant for LDL indicates that an increase in serum LDL was associated with a decreased risk of AMS. Alternatively, the constant for eosinophil levels suggests that an increase in eosinophil levels

was associated with an increased risk of AMS. This suggestion is supported by Nissim Ben Efraim et al.'s work with hypoxic eosinophils.[25] One review paper suggests that a strong link exists between hypoxia and inflammation in the development of AMS that represents a cyclical process where hypoxic tissue becomes inflamed, inflamed tissue becomes increasingly hypoxic, and the magnitude of vascular leakage in response to the inflammatory response increases.[28] Other sources echo the role of inflammation and hypoxia in the development of altitude illness.[8] Anti-inflammatory medications such as dexamethasone and ibuprofen have demonstrated benefit in preventing and treating both AMS and the more serious high-altitude edemas.[2,16,29] An avenue of further research suggested by the analysis of our data and a review of the relevant literature is one focused on maintaining intravascular volume while minimizing inflammation. The significant elevations of LDL, while still within the limits of a normal, healthy adult range, suggests that even modest alterations and adjustments in fluid dynamics may be sufficient to prevent the occurrence of AMS. The positive association between AMS development and increased levels of eosinophils, when considered in light of the available literature that suggests either steroidal or non-steroidal anti-inflammatory medications are beneficial in the prevention of AMS, also is suggestive of means by which to prevent or treat AMS. Perhaps an effective solution may be as simple as a small bolus of colloid fluids (e.g. albumin) in conjunction with a long-acting steroid (e.g. methylprednisolone acetate).

Dopamine levels were significantly higher (0.036) in the No AMS group as compared to the AMS group. Dopamine can have a number of physiologic effects depending on the amount of dopamine administered. These effects are of interest to a population at risk for the development of AMS and addressing these multiple roles will require further work. Dopamine can effect the body's vascular response (i.e. dilation vs constriction, depending on amount administered) and urinary function that, coupled with research specific to fluid dynamics and body water management or chemoreflexive vasoconstrictive responses to hypoxia, may guide future work.[21,22,30,31] Dopamine can also have stimulatory or inhibitory affects on many of the humoral immune cells depending on cell type and state (mature and activated vs immature and inactivated).[32,33] Some of these immunosuppressive characteristics are specific to the central nervous system itself and may support a hypothesis focused on the role of vasogenic edema as it pertains to AMS.[33]

The PFT results also serve to drive future work – the ratio of the forced expiratory volume over one second as compared to the forced vital capacity (FEV1/FVC) differed significantly (p=0.016) between the two groups, with the AMS group demonstrating a smaller ratio. The means were above the pathological values used to diagnose obstructive lung disease, the association between eosinophilia and asthma in both allergic and non-allergic settings and the lack of association between asthma or chronic obstructive pulmonary disease with increased risk of AMS development deserve further investigation in light of our findings.[3,15,34] Perhaps PFT results in the low-normal range

warrant further investigation in light of Jafarian et al.'s) findings that an increased respiratory rate in the first hour at altitude predicts the development of severe AMS.[10]

Finally, a strength and a caveat of our methodology requires an address. The size of the present data set permitted the removal of individuals who opted to utilize acetazolamide as a prophylaxis against AMS. The National Science Foundation (NSF) provided oversight for this project and would not permit the regulation of acetazolamide such that two equal groups of users could be created nor would the NSF permit the use of a placebo among those individuals who wished to employ acetazolamide. This may have influenced our results as AMS is a subjective diagnosis based on self-reported symptoms; however, many of our collected variables were objective measures (i.e. electrolyte concentrations and hemotalogic variables) that are not controllable by the individual's thoughts or beliefs in treatment efficacy.

Conclusion

Our results lend further strength to a number of the findings reported in previous investigations into the pathophysiology of AMS. Our results and comprehensive methodology also support a link between many of the previously reported findings. The regulation of body fluid to maintain intravascular volume and minimize edema coupled with anti-inflammatory medication appears to be a promising avenue to consider for future work. Our findings of statistically significant results that would be difficult to detect clinically further suggests that the development of AMS is the result of minor derangements of normal.

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Conflicts of Interest

The authors have no disclosures.

Contributorship

Dr MF Harrison [resident physician (Henry Ford Hospital) and research associate (Mayo Clinic); Corresponding Author] – primary teammember responsible for data analysis, manuscript preparation and submission
Dr P Anderson [researcher (Mayo Clinic)] – member of data collection team, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document
Mr A Miller [researcher (Mayo Clinic)] - member of data collection team, assisted with data analysis, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document
Mrs K O'Malley [researcher (Mayo Clinic)] - member of data collection team, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document
Dr M Richert [researcher (Mayo Clinic)] - member of data collection team, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document
Mr J Johnson [researcher (Mayo Clinic)] - member of data collection team, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document
Dr BD Johnson [researcher and principal investigator (Mayo Clinic)] – research design conceptualization, member of data collection team, supervised data analysis, provided editorial comments and guidance during manuscript preparation, and has reviewed the final document

Data sharing

All authors have access to all the data that was collected as a part of this research endeavor but which is not included in this manuscript.

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Table 1 – Subject Demographics and Anthropometric Data

	No AMS (n=60)	AMS (n=30)
Sex (M, F)	37M, 23F	18M, 12F
Age (y)	36.2 ± 9.4	33.8 ± 9.2
Residence Altitude (m)	695.6 ± 785.8	818.3 ± 802.8
Height (m)	1.8 ± 0.1	1.7 ± 0.1
Weight (kg)		
• Sea Level	78.3 ± 14.8	70.2 ± 15.4
• Altitude	78.3 ± 14.3	71.2 ± 14.1
Body Mass Index (Wt/Ht^2)	26.1 ± 4.1	24.1 ± 2.5
Heart Rate (beats • min^{-1})		
• Sea Level	73.3 ± 12.2*	67.4 ± 10.0*
• Altitude	83.6 ± 12.4	80.5 ± 13.7
Blood Pressure (seated)		
Systolic (mmHg)		
• Sea Level	111.2 ± 13.3*	109.2 ± 9.9*
• Altitude	106.1 ± 12.7	101.1 ± 12.6
Diastolic (mmHg)		

• Sea Level • Altitude	70.3 ± 10.4* 69.1 ±9.0	67.0 ± 9.2* 63.3 ± 7.1
Oxygen Saturation (%) Resting • Sea Level • Altitude Post-Breath Hold • Sea Level • Altitude	 97.7 ± 1.2 88.8 ± 3.9 93.5 ± 4.7 82.7 ± 5.4	 97.5 ± 0.9 89.3 ± 3.0 94.9 ± 3.3 84.9 ± 4.6
Neck Circumference (cm)	35.9 ± 3.5	35.4 ± 3.2
Waist Circumference (cm)	88.0 ± 12.5	83.3 ± 10.5
Waist-to-Hip Ratio	0.9 ± 0.1	0.8 ± 0.1

* significant difference between the AMS and No AMS groups, p<0.05

Table 2 – Electrolyte, Blood Chemistry, and Hematology Results

	No AMS (n=60)	**AMS (n=30)**
Sodium (mEq • L^{-1})	139.4 ± 1.6*	138.5 ± 1.8*
Potassium (mEq • L^{-1})	4.2 ± 0.3	4.2 ± 0.4
Chloride (mEq • L^{-1})	102.1 ± 3.0	101.9 ± 1.7
Calcium (mg • dL^{-1})	9.6 ± 0.4	9.6 ± 0.3
Alkaline Phosphatase (U • L^{-1})	62.7 ± 16.4	66.5 ± 16.1
Transaminases • Alanine Aminotransferase (ALT) (U • L^{-1}) • Aspartate	 21.1 ± 11.1 20.9 ± 5.2	 18.4 ± 7.5 20.8 ± 5.6

Aminotrasnferase (AST) ($U \bullet L^{-1}$)		
Leukocytes ($10^3 \bullet \mu L^{-1}$)	5.8 ± 1.4	6.1 ± 1.9
Eosinophils ($10^3 \bullet \mu L^{-1}$)	1.9 ± 1.6*	2.7 ± 2.0*
Erythrocytes ($10^3 \bullet \mu L^{-1}$)	4.7 ± 0.5	4.8 ± 0.3
Hemoglobin ($g \bullet dL^{-1}$)	14.8 ± 1.4	15.1 ± 0.9
Hematocrit (%)	44.0 ± 4.0	44.9 ± 2.9
Mean Corpuscular Volume (μm^3)	92.9 ± 4.0	93.8 ± 3.8
Mean Corpuscular Hemoglobin ($pg \bullet cell^{-1}$)	31.3 ± 1.2	31.5 ± 0.9
Mean Corpuscular Hemoglobin Concentration (%)	33.7 ± 0.9	33.6 ± 0.9
Red Blood Cell Distribution Width (%)	13.7 ± 1.0	13.3 ± 0.8
Platelets ($10^3 \bullet \mu L^{-1}$)	237.6 ± 53.2	255.9 ± 52.3
Estimated ΔPlasma Volume (%)	-2.9 ± 9.4*	-9.4 ± 12.5*
Iron Studies		
• Iron ($\mu g \bullet dL^{-1}$)	113.9 ± 31.8	119.5 ± 42.0
• Iron Sat (%)	36.5 ± 12.6	37.4 ± 13.0
• Total Iron Binding Capacity ($\mu g \bullet dL^{-1}$)	325.0 ± 47.5	322.1 ± 37.4
• Unsaturated Iron Binding Capacity ($\mu g \bullet dL^{-1}$)	209.5 ± 56.9	202.6 ± 53.9
Low Density Lipoprotein ($mg \bullet dL^{-1}$)	105.9 ± 27.6*	97.7 ± 25.4*
High Density Lipoprotein ($mg \bullet dL^{-1}$)	60.2 ± 15.8	65.3 ± 17.4
Very Low Density Lipoprotein ($mg \bullet dL^{-1}$)	21.6 ± 12.8	20.3 ± 10.4
Triglycerides ($mg \bullet dL^{-1}$)	107.2 ± 62.9	101.4 ± 51.8

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 3 – Endocrine and Catecholamine Results

	No AMS (n=60)	AMS (n=30)
Progesterone ($ng \bullet mL^{-1}$)		
• Sea Level	1.8 ± 3.5	1.5 ± 2.7
• Altitude	1.4 ± 2.6	1.2 ± 1.8
Erythropoietin ($\mu IU \bullet mL^{-1}$)		
• Sea Level	11.0 ± 5.5	10.0 ± 4.7
• Altitude	31.7 ± 20.1	24.3 ± 9.0
Leptin ($ng \bullet mL^{-1}$)		
• Sea Level	8.4 ± 10.8	5.7 ± 5.5
• Altitude	6.9 ± 6.1	5.1 ± 4.4
Angiotensin II ($pg \bullet mL^{-1}$)		

• Sea Level • Altitude	7.6 ± 5.7 21.3 ± 33.4	11.5 ± 21.2 16.2 ± 17.2
Tumor Necrosis Factor-α (pg • mL^{-1}) • Sea Level • Altitude	1.3 ± 0.6* 1.3 ± 0.6	1.4 ± 0.7* 1.3 ± 0.6
Vascular Endothelial Growth Factor (pg • mL^{-1}) • Sea Level • Altitude	42.4 ± 22.7 57.0 ± 37.8*	43.5 ± 26.1 76.4 ± 42.5*
Atrial Natriuretic Peptide (pg • mL^{-1}) • Sea Level • Altitude	434.6 ± 263.8 583. 1 ± 300.6	562.5 ± 289.0 630.7 ± 339.0
Thyroid Stimulating Hormone (μIU • mL^{-1}) • Sea Level • Altitude	1.9 ± 1.0 2.2 ± 1.3	1.5 ± 0.6 1.9 ± 0.8
Norepiphrine (pg • mL^{-1}) • Sea Level • Altitude	402.4 ± 165.9 569.5 ± 227.1	357.9 ± 108.8 491.5 ± 159.7
Epinephrine (pg • mL^{-1}) • Sea Level • Altitude	42.0 ± 76.1 36.3 ± 25.2	29.2 ± 20.9 36.1 ± 30.1
Dopamine (pg • mL^{-1}) • Sea Level • Altitude	25.1 ± 62.7 24.4 ± 16.6*	13.4 ± 6.0 16.2 ± 14.8*

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 4 – Pulmonary Function Results

	No AMS (n=60)	**AMS (n=30)**
Forced Vital Capacity (FVC) (L) • Sea Level • Altitude	5.0 ± 1.0 4.9 ± 0.9	5.1 ± 1.0 5.2 ± 1.1
Forced Expiratory Volume in 1 second (FEV1) (L) • Sea Level • Altitude	4.0 ± 0.7 4.1 ± 0.7	4.1 ± 0.8 4.1 ± 0.9
FEV1 / FVC (%) • Sea Level • Altitude	81.2 ± 5.8 83.7 ± 5.6*	79.4 ± 5.8 80.4 ± 5.2*
Forced Expiratory Flow (FEF) (L • s^{-1})		

25% • Sea Level • Altitude 75% • Sea Level • Altitude Maximum • Sea Level • Altitude	 7.8 ± 2.0 9.0 ± 2.4 1.8 ± 0.6 2.1 ± 0.8 9.7 ± 2.1 10.8 ± 2.1	 7.2 ± 2.2 8.6 ± 2.6 1.8 ± 0.8 1.8 ± 0.6 9.6 ± 2.2 10.7 ± 2.6
Expiratory Reserve Volume (ERV) (L) • Sea Level • Altitude	 1.3 ± 0.5* 1.4 ± 0.5*	 1.7 ± 0.6* 1.6 ± 0.4*

*significant difference between the AMS and No AMS groups, p<0.05

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **PAGE 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **PAGE 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **PAGE 3**
Methods		
Study design	4	Present key elements of study design early in the paper **PAGE 4-5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **PAGE 3-5**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **PAGE 4-5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **PAGE 3-5, 6-9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **PAGE 4-5**
Bias	9	Describe any efforts to address potential sources of bias **PAGE3-5, 6-9**
Study size	10	Explain how the study size was arrived at **PAGE 4-5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **PAGE 4-5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **PAGE 4-5**
		(*b*) Describe any methods used to examine subgroups and interactions **PAGE 4-5**
		(*c*) Explain how missing data were addressed **PAGE 4-5**
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy **PAGE 4-5**
		(*e*) Describe any sensitivity analyses **PAGE 4-6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **PAGE 4-5**
		(b) Give reasons for non-participation at each stage **PAGE 4-5**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **TABLE 1**
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **PAGE 4-5, TABLE 1-4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **PAGE 6-9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **PAGE 6-9**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **PAGE 6-9**
Generalisability	21	Discuss the generalisability (external validity) of the study results **PAGE 6-9**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **PAGE 10**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Physiologic Variables Associated with the Development of Acute Mountain Sickness at the South Pole

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Physiologic Variables Associated with the Development of Acute Mountain Sickness at the South Pole

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Running Head or Short Title: Altitude illness in Polar Workers

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Abstract

Introduction: Exposure to altitude >2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition. Research has attempted to identify factors associated with developing AMS without controlling important factors related to the ascent or collecting a comprehensive set of variables. **Methods:** The Antarctic Study of Altitude Physiology (ASAP) studied participants not using acetazolamide (N=98) in the United States Antarctic Program during austral summer months of 2010 and 2011. All subjects traveled to altitude rapidly via airplane. Collected data included personal history, anthropometrics, vital signs, blood samples, and pulmonary function at sea level and at altitude. Statistical analysis utilized independent sample t-tests to investigate between-group differences, $p<0.05$, and a forward, stepwise binary logistic regression analysis was performed. **Results:** Analysis of participants not using acetazolamide with complete data sets (n=90) found 30 participants developed AMS, defined by Lake Louise Symptom Score questionnaire, and 60 participants did not. Estimated plasma volume decreased significantly at altitude ($p=0.025$) in the AMS group as compared to the No AMS group while body weight did not change ($p=0.125$). Serum sodium ($p=0.045$) and LDL ($p=0.049$) levels were higher in the No AMS group. Two logistic regression equations placed nearly identical emphasis on the roles of LDL and eosinophil levels in the development of AMS. **Conclusion:** These results suggest body water regulation and inflammation are key factors in AMS development when all other factors such as the level of physical exertion during ascent, the rate and magnitude of ascent, and the use of acetazolamide are controlled.

Keywords: altitude illness; altitude; hypoxia; Antarctica;

Introduction

Exposure to altitude higher than 2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition that has been described as a "nuisance" in that it halts progression to higher altitudes and has a negative impact on quality of life rather than posing a serious health risk.[1,2] The development of AMS is not clearly associated with any one particular factor in the currently available literature nor has a definitive etiology of AMS been identified.[3-6] Rather many different factors such as age, gender, body habitus, physical fitness, tolerance of hypocapnia, rate of ascent, magnitude of ascent, recent prior ascents or simply individual susceptibility have been linked to increased risk of development of AMS but conflicting results are available related to the importance of each of these variables. [3,6-8] However, the research methods employed in these studies may have influenced the variability in the reported results: many of these variables were collected by self-assessment (i.e. physical fitness) or self-reporting (i.e. past medical history); the various destination altitudes and rates of ascent were not consistent; and the use of pharmaceutical prophylaxis (i.e. acetazolamide) was not regulated.[9-11]

Using the Lake Louise Criteria, the diagnosis of AMS is based on recent travel to altitude and the presence of subjective symptoms including headache, fatigue/weakness, dizziness/lightheadedness, gastrointestinal disruption, and sleep disturbances.[12] The subjective nature of the diagnosis likely compounds the difficulties in identifying factors to predict which individuals are at an increased risk. Furthermore, the benefit of predicting future cases of AMS based on an individual's history of previous AMS diagnoses is likely lost on the afflicted person – they would like to know ahead of their first ascent that they are at risk for AMS. This is especially true in cases, such as military endeavors or Antarctic assignments, where the rate of ascent cannot be slowed. It is with this in mind that a well-controlled data collection methodology would be beneficial to maximize the likelihood of firmly identifying predictive factors.

The Antarctic Study of Altitude Physiology (ASAP) studied participants in the United States Antarctic Program during austral summer months of 2005-2006 and 2006-2007. This project provided unique opportunities to observe a large and well-controlled population to assess which variables and factors, particularly at sea-level, were associated with AMS development in susceptible individuals. All participants underwent medical screening prior to deployment to Antarctica, were available to the research team during the first seven days of their deployment, and travelled from McMurdo Station (sea-level) to Amundsen-Scott South Pole Station (2835m; physiologic altitude of ~3200m) via airplane in less than four hours. The breadth of the data collected plus the controlled and uniform manner in which all individuals travelled to altitude provided an opportunity to evaluate which, if any, factors are related to the development of AMS.

Methods

Participants. Acetazolamide was made available to all participants (N=248). However, for this presentation of results, only those who did not take acetazolamide (n=98) were included in the initial analysis. Subjects who did not complete all questionnaires, provide two blood samples, or complete two pulmonary function tests (PFT) were omitted from the final analysis (n=8). The final analysis was performed using 90 subjects.

Procedure. Data was collected during two austral summer expeditions to Amundsen-Scott South Pole Station. Ethical approval was obtained from Mayo Clinic, Rochester MN and all participants provided written informed consent. Participants were included in the study if their duties at Amundsen-Scott South Pole Station exceeded one week in duration. During 2006-2007, data was only collected from those who had not been a participant during the 2005-2006 expedition. The data collection, the subsequent data analyses, and dissemination of findings were performed in accordance with the STROBE principles.[13]

Following arrival at McMurdo Station, participants typically acclimatized to the ambient temperature and adjusted to the new timezone for ~2 weeks prior to departing for the Amundsen-Scott South Pole Station. Participants flew to the South Pole in an airplane that was pressurized after take-off but depressurized during the flight so that cabin pressure had equilibrated with ambient atmospheric pressure at the time of landing. During the acclimatization period at sea level, participants underwent baseline testing and education related to high altitude illness. Acetazolamide was made available to any participant who wished to employ AMS prophylaxis even though this resulted in the exclusion of that individual's data from this manuscript's analysis. Baseline questionnaire collection included Lake Louise Symptom Score questionnaires as well as an additional symptom questionnaire pertaining to 1) dyspnea (at rest and on exertion) 2) general health limitations 3) mental status changes 4) cough 5) peripheral edema. Further questionnaire data included information related to past medical history and chronic medical conditions, current medication use, lifestyle assessment (i.e. tobacco and alcohol use; exercise habits), and previous experience with altitude and/or Antarctic expeditions. Baseline anthropometric and physiological measurements included height, weight, heart rate, blood pressure, arterial oxygen saturation (SaO_2) and blood draw. Blood draws were performed after acclimatizing to sea-level 1-2 days prior to departure to altitude. A repeat blood draw was performed on the third day after arrival to altitude. Blood samples were analyzed for hemoglobin concentration and hematocrit; serum electrolyte and progesterone levels; circulating catecholamine levels; and thyroid, liver and kidney function. Changes in plasma volume were calculated using Dill and Costill's method.[14]

Participants completed the same questionnaire reporting AMS symptoms related to symptoms including the Lake Louise Symptom Score form on 9 separate occasions. Questionnaires were completed at baseline, on the plane to Amundsen-Scott South Pole Station, and daily for the first seven days following arrival. The completion of the first questionnaire at the Amundsen-Scott South Pole Station occurred prior to sleep on the first night and each of the subsequent questionnaires were completed upon waking. An individual was determined to be suffering from AMS if their Lake Louise Symptom Score was $\geq$ 3 concurrent with a headache. Any individual that reported a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the first 7 days at altitude was analyzed with the AMS group. Individuals in the No AMS group did not report a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the evaluation period.

Statistical Analysis. Visual inspection of all variables was performed to identify and remove any outliers (i.e. data point > ±3 SD) from the data set on a case-by-case basis. Statistical analyses were performed with SPSS 20.0 (IBM Corporation, Armonk NY). Comparison of means was performed using independent samples t-test for subjects without AMS (LLSS $\leq$2) (n=60) as compared to subjects with AMS (LLSS $\geq$3) (n=30). Significance was set as $p<0.05$. A forward, stepwise binary logistic regression analysis was also performed. All variables associated with the occurrence of AMS at $p<0.25$ in the initial analysis were then included in the generation of the final equation.[9] Using subjects who had been previously removed due to numerous missing data points (n=8) or for whom data points related to the regression equation generation were missing (n=21), the regression equation was applied to assess its reliability and validity in predicting the occurrence of AMS (n=29).

Results

Demographic and anthropometric data are presented in Table 1. No significant differences were observed between groups. Data is presented as mean ± standard deviation. Hematologic and laboratory results are included in Table 2; Table 3 summarizes the endocrine results; Table 4 presents the PFT results.

The forward, stepwise binary logistic regression initially included 8 variables (chloride, aspartate aminotransferase (AST), low density lipoprotein (LDL), eosinophils, red blood cell distribution width (RDW), leptin, and epinephrine, $p<0.25$) for the generation of the model. Only subjects for whom all 8 variables were recorded and available were entered into the regression equation. For the AMS group, this resulted in n=19; for the No AMS group, this resulted in n=50. The logistic regression analysis generated a model that included LDL and eosinophils (eos) with a

positive predictive value (PPV) of 55.6%, and negative predictive value (NPV) of 76.7%, sensitivity of 26.3%, and specificity of 92%. The equation is provided below:

$$Prob\ (AMS) = (e^{1.593 + (-0.037)(LDL) + (0.433)(eos)}) \times (1 + e^{1.593 + (-0.037)(LDL) + (0.433)(eos)})^{-1}$$

At the outset, 8 individuals were excluded from the analysis due to multiple missing data points (i.e. did not present for repeat blood draw at altitude; did not complete intake questionnaire, etc). From the AMS group, 10 individuals were not included in the generation of the regression equation while 11 individuals were not included from the No AMS group. Of these 29 subjects, 22 had data available with respect to their LDL and eosinophil levels and thus were used to verify the regression equation's accuracy. The model correctly categorized 57% of the participants.

Discussion

Currently AMS is a clinical diagnosis based on subjective and self-reported measures. Reliably identifying objective variables that may differentiate those at risk for suffering AMS as compared to those at a decreased risk has eluded many investigators. Our study controlled many variables that are recognized as contributory to AMS development but which are not often well controlled; for example, the altitude at which individuals sleep or the means or rate by which individuals arrived at altitude.[3,8,15,16] In other studies, sleeping may have occurred at a lower altitude than the day's peak altitude and varied day by day, the rate of ascent may have differed by days, and the level of exertion often differed from subject to subject. In our study, all subjects worked and slept at the same constant altitude and all participants travelled to altitude on a short duration flight (<4h) with minimal exertion. These factors, if not controlled, can influence the development of AMS and confound results in attempting to identify physiologic characteristics placing an individual at increased risk of developing AMS.

Our results support a number of hypotheses about causes of AMS that warrant discussion. An important caveat is the magnitude of the differences between the populations. While statistically significant and interesting in generating further hypotheses, these differences may be too slight to permit a clinical prediction of who will develop AMS at altitude. For example, the difference between a blood pressure of 111/70 mmHg (AMS group) and 109/67 (No AMS group) in any single individual on any given day is related to a number of factors (hydration, caffeine intake, etc) that would inevitably lead to intra-individual variability. But rather than a considering this to be a weakness of

our study, this more likely speaks to the subtle nature of AMS, an often mild and self-limiting condition described as a nuisance.[1,2]

Two of the subtle differences of interest are the serum sodium (Na^+) levels and LDL cholesterol levels. These values differed within the normal ranges in the both the AMS group (Na^+ 138.5 and LDL 97.7) the No AMS group (Na^+ 139.4 and LDL 105.9). Serum Na+ has the largest influence on serum osmolarity, using the standard equation:

$$\text{Osmolarity} = 2 \times [Na^+] + [\text{Glucose}] \times 18^{-1} + [\text{Urea}] \times 2.8^{-1}$$

Increased serum Na+ would decrease the flow of fluid from the extracellular space to the intracellular space, thereby decreasing cellular edema. One of the hypothetical explanations for the occurrence of AMS suggests that tissue edema, particularly in the cerebral tissue, is a contributing factor.[2,3,16] Similarly, LDL levels were significantly higher but still within the normal range in those who did not develop AMS as compared to those who did. In nephrotic syndrome, serum LDL concentration is inversely related to serum albumin concentration.[17-19] The rapid and dramatic increase in LDL in hypoalbunemic states focuses on the body's attempt to maintain an adequate oncotic pressure. While our participants were not hypoalbunemic by clinical assessment, the elevated LDL levels may have positively contributed to the prevention of AMS through increasing the oncotic pressures. Oncotic pressure, like serum osmolarity, is one of the means by which intravascular fluid (a component of the extracellular space) is kept within the vasculature in order to prevent edema.

Furthering the possible link between fluid distribution between the body's compartments and AMS, a significant decrease in plasma volume at altitude was observed in AMS group. As significant differences were not observed for participant weights between the Sea Level and Altitude measurements for either group, it stands to reason that total body water remained relatively constant between the measurements. However, the AMS group saw a nearly 10% decrease in estimated plasma volume and this would suggest a fluid shift from the intravascular space to either the intracellular or the extracellular space. Previously, Loeppky et al.[20] have reported fluid retention occurs during the initial exposure to simulated altitude and our results suggest this retained fluid does not remain in the vasculature. Hackett al.[21] have suggested abnormalities in handling body water as the common link between the two edematous conditions, HAPE and HACE, representing the more serious forms of altitude-related illness. Research has shown that subclinical pulmonary edema occurs amongst those with concomitant AMS.[22] This diagnosis in these individuals is made by the appearance of "comet tails" on ultrasonography and offers a specific example of an extravascular fluid shift.

Three of the variables identified in our analysis are seemingly linked to each other and to hypothesized causes of AMS – vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and eosinophils. VEGF levels at altitude were significantly elevated in the AMS group. VEGF's primary role is to promote the formation of new blood vessels and it increases in conditions that are associated with decreased oxygen supply to tissues.[25] However, VEGF has also been linked to increased vascular permeability that contributes to the development of edema.[24,25] Serum eosinophil level was the other variable that was represented in the logistic regression model. While increased eosinophil levels are often associated with the immune response to a parasitic presence or a hypersensitive response such as asthma, they will also increase the serum concentration of VEGF.[25,26] At altitude, hypoxia prolongs the viability of eosinophils while increasing the eosinophllic production of VEGF and other pro-inflammatory cytokines, prostaglandins, and leukotrienes.[25,27] The serum concentration of a third inflammatory variable, TNF-α, was also higher in the AMS group ($p=0.012$). A cyclical link has been suggested between hypoxia and inflammation in the development of AMS – hypoxic tissue becomes inflamed, inflamed tissue becomes increasingly hypoxic, and the magnitude of vascular leakage in response to the inflammatory response increases.[8,28] Anti-inflammatory medications such as dexamethasone and ibuprofen have demonstrated benefit in preventing and treating both AMS and the more serious high-altitude edemas.[2,16,29]

Our data and a review of the relevant literature would suggest a focus on maintaining intravascular volume while minimizing inflammation. The statistically significant elevations of LDL, while still within the limits of a normal healthy adult range, suggests that even modest alterations in fluid dynamics may be protective at altitude. The positive association between AMS development and several inflammatory markers, when considered in light of the available literature that suggests either steroidal or non-steroidal anti-inflammatory medications can prevent the symptoms of AMS, is suggestive of means of prevention or treatment. Perhaps an effective solution may be as simple as a small bolus of colloid fluids (e.g. albumin) in conjunction with a long-acting steroid (e.g. dexamethasone).

Dopamine,concentration was higher in the No AMS group and it can have a number of physiologic effects depending its levels. It can effect the body's vascular response (i.e. dilation vs constriction, depending on amount administered) and urinary function.[20,21,30,31] Dopamine can also have stimulatory or inhibitory affects on many of the humoral immune cells depending on cell type and state (mature and activated vs immature and inactivated).[32,33] Some of these immunosuppressive characteristics are specific to the central nervous system itself and may support a hypothesis focused on the role of vasogenic edema or inflammation as it pertains to AMS.[33]

The PFT results also serve to drive future work – the ratio of the forced expiratory volume over one second as compared to the forced vital capacity (FEV1/FVC) differed significantly with the

AMS group demonstrating a smaller ratio. The association between eosinophilia and asthma in both allergic and non-allergic settings and the lack of association between asthma or chronic obstructive pulmonary disease with increased risk of AMS development deserve further investigation in light of our findings.[3,15,34] Perhaps PFT results in the low-normal range warrant further investigation in light of Jafarian et al.'s) findings that an increased respiratory rate in the first hour at altitude predicts the development of severe AMS or in light of the report of subclinical pulmonary edema in AMS sufferers.[10,22]

Finally, a strength and a caveat of our methodology requires addressing. The size of the present data set permitted the removal of individuals who opted to utilize acetazolamide as a prophylaxis against AMS. The National Science Foundation (NSF) provided oversight for this project and would not permit the regulation of acetazolamide such that two equal groups of users could be created nor would the NSF permit the use of a placebo among those individuals who wished to employ acetazolamide. This may have influenced our results as AMS is a subjective diagnosis based on self-reported symptoms; however, many of our collected variables were objective measures (i.e. electrolyte concentrations and hemotalogic variables) that are not controllable by the individual's thoughts or beliefs in treatment efficacy.

Conclusion

Our results lend further strength to a number of the findings reported in previous investigations into the pathophysiology of AMS. Our results and comprehensive methodology also support a link between many of the previously reported findings. The regulation of body fluid to maintain intravascular volume and minimize edema coupled with anti-inflammatory medication appears to be a promising avenue to consider for future work. Our findings of statistically significant results that would be difficult to detect clinically further suggests that the development of AMS is the result of minor derangements of normal.

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Conflicts of Interest

The authors have no disclosures.

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Table 1 – Subject Demographics and Anthropometric Data

	No AMS (n=60)	AMS (n=30)
Sex (M, F)	37M, 23F	18M, 12F
Age (y)	36.2 ± 9.4	33.8 ± 9.2
Residence Altitude (m)	695.6 ± 785.8	818.3 ± 802.8
Height (m)	1.8 ± 0.1	1.7 ± 0.1
Weight (kg)		
• Sea Level	78.3 ± 14.8	70.2 ± 15.4
• Altitude	78.3 ± 14.3	71.2 ± 14.1
Body Mass Index (Wt/Ht^2)	26.1 ± 4.1	24.1 ± 2.5
Heart Rate ($beats \bullet min^{-1}$)		
• Sea Level	73.3 ± 12.2*	67.4 ± 10.0*
• Altitude	83.6 ± 12.4	80.5 ± 13.7
Blood Pressure (seated)		
Systolic (mmHg)		
• Sea Level	111.2 ± 13.3*	109.2 ± 9.9*
• Altitude	106.1 ± 12.7	101.1 ± 12.6
Diastolic (mmHg)		
• Sea Level	70.3 ± 10.4*	67.0 ± 9.2*
• Altitude	69.1 ±9.0	63.3 ± 7.1
Oxygen Saturation (%)		
Resting		
• Sea Level	97.7 ± 1.2	97.5 ± 0.9
• Altitude	88.8 ± 3.9	89.3 ± 3.0
Post-Breath Hold		
• Sea Level	93.5 ± 4.7	94.9 ± 3.3
• Altitude	82.7 ± 5.4	84.9 ± 4.6
Neck Circumference (cm)	35.9 ± 3.5	35.4 ± 3.2
Waist Circumference (cm)	88.0 ± 12.5	83.3 ± 10.5
Waist-to-Hip Ratio	0.9 ± 0.1	0.8 ± 0.1

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 2 – Electrolyte, Blood Chemistry, and Hematology Results

	No AMS (n=60)	AMS (n=30)
Sodium ($mEq \bullet L^{-1}$)	139.4 ± 1.6*	138.5 ± 1.8*
Potassium ($mEq \bullet L^{-1}$)	4.2 ± 0.3	4.2 ± 0.4
Chloride ($mEq \bullet L^{-1}$)	102.1 ± 3.0	101.9 ± 1.7
Calcium ($mg \bullet dL^{-1}$)	9.6 ± 0.4	9.6 ± 0.3
Alkaline Phosphatase ($U \bullet L^{-1}$)	62.7 ± 16.4	66.5 ± 16.1
Transaminases		
• Alanine Aminotransferase (ALT) ($U \bullet L^{-1}$)	21.1 ± 11.1	18.4 ± 7.5
• Aspartate Aminotrasnferase (AST) ($U \bullet L^{-1}$)	20.9 ± 5.2	20.8 ± 5.6
Leukocytes ($10^3 \bullet \mu L^{-1}$)	5.8 ± 1.4	6.1 ± 1.9
Eosinophils ($10^3 \bullet \mu L^{-1}$)	1.9 ± 1.6*	2.7 ± 2.0*
Erythrocytes ($10^3 \bullet \mu L^{-1}$)	4.7 ± 0.5	4.8 ± 0.3
Hemoglobin ($g \bullet dL^{-1}$)	14.8 ± 1.4	15.1 ± 0.9
Hematocrit (%)	44.0 ± 4.0	44.9 ± 2.9
Mean Corpuscular Volume (μm^3)	92.9 ± 4.0	93.8 ± 3.8
Mean Corpuscular Hemoglobin ($pg \bullet cell^{-1}$)	31.3 ± 1.2	31.5 ± 0.9
Mean Corpuscular Hemoglobin Concentration (%)	33.7 ± 0.9	33.6 ± 0.9
Red Blood Cell Distribution Width (%)	13.7 ± 1.0	13.3 ± 0.8
Platelets ($10^3 \bullet \mu L^{-1}$)	237.6 ± 53.2	255.9 ± 52.3
Estimated ΔPlasma Volume (%)	-2.9 ± 9.4*	-9.4 ± 12.5*
Iron Studies		
• Iron ($\mu g \bullet dL^{-1}$)	113.9 ± 31.8	119.5 ± 42.0
• Iron Sat (%)	36.5 ± 12.6	37.4 ± 13.0
• Total Iron Binding Capacity	325.0 ± 47.5	322.1 ± 37.4

($\mu g \bullet dL^{-1}$) • Unsaturated Iron Binding Capacity ($\mu g \bullet dL^{-1}$)	209.5 ± 56.9	202.6 ± 53.9
Low Density Lipoprotein ($mg \bullet dL^{-1}$)	105.9 ± 27.6*	97.7 ± 25.4*
High Density Lipoprotein ($mg \bullet dL^{-1}$)	60.2 ± 15.8	65.3 ± 17.4
Very Low Density Lipoprotein ($mg \bullet dL^{-1}$)	21.6 ± 12.8	20.3 ± 10.4
Triglycerides ($mg \bullet dL^{-1}$)	107.2 ± 62.9	101.4 ± 51.8

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 3 – Endocrine and Catecholamine Results

	No AMS (n=60)	AMS (n=30)
Progesterone ($ng \bullet mL^{-1}$)		
• Sea Level	1.8 ± 3.5	1.5 ± 2.7
• Altitude	1.4 ± 2.6	1.2 ± 1.8
Erythropoietin ($\mu IU \bullet mL^{-1}$)		
• Sea Level	11.0 ± 5.5	10.0 ± 4.7
• Altitude	31.7 ± 20.1	24.3 ± 9.0
Leptin ($ng \bullet mL^{-1}$)		
• Sea Level	8.4 ± 10.8	5.7 ± 5.5
• Altitude	6.9 ± 6.1	5.1 ± 4.4
Angiotensin II ($pg \bullet mL^{-1}$)		
• Sea Level	7.6 ± 5.7	11.5 ± 21.2
• Altitude	21.3 ± 33.4	16.2 ± 17.2
Tumor Necrosis Factor-α ($pg \bullet mL^{-1}$)		
• Sea Level	1.3 ± 0.6*	1.4 ± 0.7*
• Altitude	1.3 ± 0.6	1.3 ± 0.6
Vascular Endothelial Growth Factor ($pg \bullet mL^{-1}$)		
• Sea Level	42.4 ± 22.7	43.5 ± 26.1
• Altitude	57.0 ± 37.8*	76.4 ± 42.5*
Atrial Natriuretic Peptide ($pg \bullet mL^{-1}$)		
• Sea Level	434.6 ± 263.8	562.5 ± 289.0
• Altitude	583. 1 ± 300.6	630.7 ± 339.0
Thyroid Stimulating Hormone ($\mu IU \bullet mL^{-1}$)		
• Sea Level	1.9 ± 1.0	1.5 ± 0.6
• Altitude	2.2 ± 1.3	1.9 ± 0.8
Norepinephrine ($pg \bullet mL^{-1}$)		
• Sea Level	402.4 ± 165.9	357.9 ± 108.8
• Altitude	569.5 ± 227.1	491.5 ± 159.7
Epinephrine ($pg \bullet mL^{-1}$)		
• Sea Level	42.0 ± 76.1	29.2 ± 20.9
• Altitude	36.3 ± 25.2	36.1 ± 30.1
Dopamine ($pg \bullet mL^{-1}$)		
• Sea Level	25.1 ± 62.7	13.4 ± 6.0
• Altitude	24.4 ± 16.6*	16.2 ± 14.8*

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 4 – Pulmonary Function Results

	No AMS (n=60)	AMS (n=30)
Forced Vital Capacity (FVC) (L)		
• Sea Level	5.0 ± 1.0	5.1 ± 1.0
• Altitude	4.9 ± 0.9	5.2 ± 1.1
Forced Expiratory Volume in 1 second (FEV1) (L)		
• Sea Level	4.0 ± 0.7	4.1 ± 0.8
• Altitude	4.1 ± 0.7	4.1 ± 0.9
FEV1 / FVC (%)		
• Sea Level	81.2 ± 5.8	79.4 ± 5.8
• Altitude	83.7 ± 5.6*	80.4 ± 5.2*
Forced Expiratory Flow (FEF) ($L \bullet s^{-1}$)		
25%		
• Sea Level	7.8 ± 2.0	7.2 ± 2.2
• Altitude	9.0 ± 2.4	8.6 ± 2.6
75%		
• Sea Level	1.8 ± 0.6	1.8 ± 0.8
• Altitude	2.1 ± 0.8	1.8 ± 0.6
Maximum		
• Sea Level	9.7 ± 2.1	9.6 ± 2.2
• Altitude	10.8 ± 2.1	10.7 ± 2.6
Expiratory Reserve Volume (ERV) (L)		
• Sea Level	1.3 ± 0.5*	1.7 ± 0.6*
• Altitude	1.4 ± 0.5*	1.6 ± 0.4*

*significant difference between the AMS and No AMS groups, $p<0.05$

Physiologic Variables Associated with the Development of Acute Mountain Sickness at the South Pole

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Abstract

Introduction: Exposure to altitude >2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition. Research has attempted to identify factors associated with developing AMS without controlling important factors related to the ascent or collecting a comprehensive set of variables. **Methods:** The Antarctic Study of Altitude Physiology (ASAP) studied participants not using acetazolamide (N=98) in the United States Antarctic Program during austral summer months of 2010 and 2011. All subjects traveled to altitude rapidly via airplane. Collected data included personal history, anthropometrics, vital signs, blood samples, and pulmonary function at sea level and at altitude. Statistical analysis utilized independent sample t-tests to investigate between-group differences, $p<0.05$, and a forward, stepwise binary logistic regression analysis was performed. **Results:** Analysis of participants not using acetazolamide with complete data sets (n=90) found 30 participants developed AMS, defined by Lake Louise Symptom Score questionnaire, and 60 participants did not. Estimated plasma volume decreased significantly at altitude ($p=0.025$) in the AMS group as compared to the No AMS group while body weight did not change ($p=0.125$). Serum sodium ($p=0.045$) and LDL ($p=0.049$) levels were higher in the No AMS group. Two logistic regression equations placed nearly identical emphasis on the roles of LDL and eosinophil levels in the development of AMS. **Conclusion:** These results suggest body water regulation and inflammation are key factors in AMS development when all other factors such as the level of physical exertion during ascent, the rate and magnitude of ascent, and the use of acetazolamide are controlled.

Keywords: altitude illness; altitude; hypoxia; Antarctica;

Introduction

Exposure to altitude higher than 2500m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition that has been described as a "nuisance" in that it halts progression to higher altitudes and has a negative impact on quality of life rather than posing a serious health risk.[1,2] The development of AMS is not clearly associated with any one particular factor in the currently available literature nor has a definitive etiology of AMS been identified.[3-6] Rather many different factors such as age, gender, body habitus, physical fitness, tolerance of hypocapnia, rate of ascent, magnitude of ascent, recent prior ascents or simply individual susceptibility have been linked to increased risk of development of AMS but conflicting results are available related to the importance of each of these variables. [3,6-8] However, the research methods employed in these studies may have influenced the variability in the reported results: many of these variables were collected by self-assessment (i.e. physical fitness) or self-reporting (i.e. past medical history); the various destination altitudes and rates of ascent were not consistent; and the use of pharmaceutical prophylaxis (i.e. acetazolamide) was not regulated.[9-11]

Using the Lake Louise Criteria, the diagnosis of AMS is based on recent travel to altitude and the presence of subjective symptoms including headache, fatigue/weakness, dizziness/lightheadedness, gastrointestinal disruption, and sleep disturbances.[12] The subjective nature of the diagnosis likely compounds the difficulties in identifying factors to predict which individuals are at an increased risk. Furthermore, the benefit of predicting future cases of AMS based on an individual's history of previous AMS diagnoses is likely lost on the afflicted person – they would like to know ahead of their first ascent that they are at risk for AMS. This is especially true in cases, such as military endeavors or Antarctic assignments, where the rate of ascent cannot be slowed. It is with this in mind that a well-controlled data collection methodology would be beneficial to maximize the likelihood of firmly identifying predictive factors.

The Antarctic Study of Altitude Physiology (ASAP) studied participants in the United States Antarctic Program during austral summer months of 2005-2006 and 2006-2007. This project provided unique opportunities to observe a large and well-controlled population to assess which variables and factors, particularly at sea-level, were associated with AMS development in susceptible individuals. All participants underwent medical screening prior to deployment to Antarctica, were available to the research team during the first seven days of their deployment, and travelled from McMurdo Station (sea-level) to Amundsen-Scott South Pole Station (2835m; physiologic altitude of ~3200m) via airplane in less than four hours. The breadth of the data collected plus the controlled and uniform manner in which all individuals travelled to altitude provided an opportunity to evaluate which, if any, factors are related to the development of AMS.

Methods

Participants. Acetazolamide was made available to all participants (N=248). However, for this presentation of results, only those who did not take acetazolamide (n=98) were included in the initial analysis. Subjects who did not complete all questionnaires, provide two blood samples, or complete two pulmonary function tests (PFT) were omitted from the final analysis (n=8). The final analysis was performed using 90 subjects.

Procedure. Data was collected during two austral summer expeditions to Amundsen-Scott South Pole Station. Ethical approval was obtained from Mayo Clinic, Rochester MN and all participants provided written informed consent. Participants were included in the study if their duties at Amundsen-Scott South Pole Station exceeded one week in duration. During 2006-2007, data was only collected from those who had not been a participant during the 2005-2006 expedition. The data collection, the subsequent data analyses, and dissemination of findings were performed in accordance with the STROBE principles.[13]

Following arrival at McMurdo Station, participants typically acclimatized to the ambient temperature and adjusted to the new timezone for ~2 weeks prior to departing for the Amundsen-Scott South Pole Station. Participants flew to the South Pole in an airplane that was pressurized after take-off but depressurized during the flight so that cabin pressure had equilibrated with ambient atmospheric pressure at the time of landing. During the acclimatization period at sea level~~is time~~, participants underwent baseline testing and education related to high altitude illness. Acetazolamide was made available to any participant who wished to employ AMS prophylaxis even though this resulted in the exclusion of that individual's data from this manuscript's analysis. Baseline questionnaire collection included Lake Louise Symptom Score questionnaires as well as an additional symptom questionnaire pertaining to 1) dyspnea (at rest and on exertion) 2) general health limitations 3) mental status changes 4) cough 5) peripheral edema. Further questionnaire data included information related to past medical history and chronic medical conditions, current medication use, lifestyle assessment (i.e. tobacco and alcohol use; exercise habits), and previous experience with altitude and/or Antarctic expeditions. Baseline anthropometric and physiological measurements included height, weight, heart rate, blood pressure, arterial oxygen saturation (SaO_2) and blood draw. Blood draws were performed after acclimatizing to sea-level 1-2 days prior to departure to altitude. A repeat blood draw was performed on the third day after arrival to altitude. Blood samples were analyzed for hemoglobin concentration and hematocrit; serum electrolyte and progesterone levels; circulating catecholamine levels; and thyroid, liver and kidney function. Changes in plasma volume were calculated using Dill and Costill's method.[14]

Participants completed the same questionnaire reporting AMS symptoms related to symptoms including the Lake Louise Symptom Score form on 9 separate occasions. Questionnaires were completed at baseline, on the plane to Amundsen-Scott South Pole Station, and daily for the first seven days following arrival. The completion of the first questionnaire at the Amundsen-Scott South Pole Station occurred prior to sleep on the first night and each of the subsequent questionnaires were completed upon waking. An individual was determined to be suffering from AMS if their Lake Louise Symptom Score was ≥ 3 concurrent with a headache. Any individual that reported a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the first 7 days at altitude was analyzed with the AMS group. Individuals in the No AMS group did not report a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the evaluation period.

Statistical Analysis. Visual inspection of all variables was performed to identify and remove any outliers (i.e. data point > ±3 SD) from the data set on a case-by-case basis. Statistical analyses were performed with SPSS 20.0 (IBM Corporation, Armonk NY). Comparison of means was performed using independent samples t-test for subjects without AMS (LLSS ≤2) (n=60) as compared to subjects with AMS (LLSS <>3) (n=30). Significance was set as $p<0.05$. A forward, stepwise binary logistic regression analysis was also performed. All variables associated with the occurrence of AMS at $p<0.25$ in the initial analysis were then included in the generation of the final equation.[9] Using subjects who had been previously removed due to numerous missing data points (n=8) or for whom data points related to the regression equation generation were missing (n=21), the regression equation was applied to assess its reliability and validity in predicting the occurrence of AMS (n=29).

Results

Demographic and anthropometric data are presented in Table 1. No significant differences were observed between groups. Data is presented as mean ± standard deviation. Hematologic and laboratory results are included in Table 2; Table 3 summarizes the endocrine results; Table 4 presents the PFT results.

The forward, stepwise binary logistic regression initially included 8 variables (chloride, aspartate aminotransferase (AST), low density lipoprotein (LDL), eosinophils, red blood cell distribution width (RDW), leptin, and epinephrine, $p<0.25$) for the generation of the model. Only subjects for whom all 8 variables were recorded and available were entered into the regression equation. For the AMS group, this resulted in n=19; for the No AMS group, this resulted in n=50. The logistic regression analysis generated a model that included LDL and eosinophils (eos) with a

positive predictive value (PPV) of 55.6%, and negative predictive value (NPV) of 76.7%, sensitivity of 26.3%, and specificity of 92%. The equation is provided below:

$$Prob\ (AMS) = (e^{1.593 + (-0.037)(LDL) + (0.433)(eos)}) \times (1 + e^{1.593 + (-0.037)(LDL) + (0.433)(eos)})^{-1}$$

At the outset, 8 individuals were excluded from the analysis due to multiple missing data points (i.e. did not present for repeat blood draw at altitude; did not complete intake questionnaire, etc). From the AMS group, 10 individuals were not included in the generation of the regression equation while 11 individuals were not included from the No AMS group. Of these 29 subjects, 22 had data available with respect to their LDL and eosinophil levels and thus were used to verify the regression equation's accuracy. The model correctly categorized 57% of the participants.

Discussion

Currently AMS is a clinical diagnosis based on subjective and self-reported measures. ~~However,~~ Reliably i~~i~~dentifying ~~an~~ objective ~~series of~~ variables ~~from the subjective reports~~ that may differentiate those at risk for suffering AMS as compared to those at a decreased risk has eluded many investigators. ~~The present~~Our study controlled ~~a number of~~ many variables that are recognized as contributory to ~~the development A~~AMS development but which are not often well controlled ~~across a study population;~~ for example~~.~~, ~~One of the most commonly identified factors is~~ the altitude at which individuals sleep or the means or rate by which individuals arrived at altitude.[3,8,15,16,~~17~~] In other~~some previous~~ studies, ~~this may have been a~~sleeping may have occurred at a lower altitude than the day's ~~the one at which they were at during the day~~peak altitude and varied day by day, the rate of ascent may have differed by days, and the level of exertion often differed from subject to subject ~~and often varied by individual.~~ In our~~However, in the present~~ study, all subjects worked and slept at the same constant altitude and all~~.~~ ~~An additional difference was the means by which our participants arrived at altitude. All~~ participants ~~boarded~~ travelled to altitude on a short duration flight (<4h) with minimal exertion. ~~Previous studies have reported a number of different rates of ascent and many of these ascents involved varying degrees of physical exertion.[17]~~ These factors, if not controlled, can influence the development of AMS and confound results in attempting to identify ~~baseline~~ physiologic characteristics placing an individual at increased risk of developing AMS.

Our results ~~lend themselves to interpretation that~~ support~~s~~ a number of ~~the~~ hypothes~~es~~ized about causes of AMS ~~and these will be~~that warrant ~~discussed~~discussion. A~~However, a~~n important

caveat is the magnitude of the differences between the ~~AMS and the No AMS~~ populations. While statistically significant and interesting in generating further hypotheses, these differences ~~are~~ may be too slight to permit a clinical prediction of who will~~may or may not~~ develop AMS ~~on an expedition to~~at altitude. For example, ~~reliably differentiating~~the difference between a blood pressure of 111/70 mmHg (AMS group) and 109/67 (No AMS group) in any single individual on any given day ~~may be beyond the capability of many clinicians~~is related to a number of factors (hydration, caffeine intake, etc) that would inevitably lead to intra-individual variability. ~~The same can be said for many of the other statistically significant differences between the two groups.~~ But rather than a considering this to be a weakness ~~of the present~~of our study, this more likely speaks to the subtle nature of AMS, an often mild and self-limiting condition described as a nuisance.[1,2]

Two of the subtle differences of interest are the serum sodium (Na^+) levels and LDL cholesterol levels. These values differed within the normal ranges ~~for those that developed~~in the both the AMS group (Na^+ 138.5 and LDL 97.7) ~~as compared to those that did not develop~~the No AMS group (Na^+ 139.4 and LDL 105.9). Serum Na+ has the largest influence on serum osmolarity, using ~~is calculated using the following~~the standard equation:

$$\text{Osmolarity} = 2 \times [Na^+] + [\text{Glucose}] \times 18^{-1} + [\text{Urea}] \times 2.8^{-1}$$

~~While glucose levels were recorded in this data set, unfortunately blood urea nitrogen (BUN) was not. However, BUN's influence is minimal as its levels are normally less than 20 mg/dL and only 1/4 to 1/3 of its value is subsequently used to calculate osmolarity. Similarly for glucose, only a small proportion (approximately 6%) of its serum level plays a role in determining osmolarity. To further minimize the influence of glucose on this variable, no diabetics were included in the participant pool in the current study. Of the three variables within the equation, Na^+ has the largest influence in determining osmolarity.~~ Increased serum Na+ would decrease the flow of fluid from the extracellular space to the intracellular space, thereby decreasing cellular edema. One of the hypothetical explanations for the occurrence of AMS suggests that tissue edema, particularly in the cerebral tissue, is a contributing factor.[2,3,16] ~~A second variable that differed between those who suffered AMS from those who did not shares a similar characteristic. Serum~~Similarly, LDL levels were significantly higher but still within the normal range in those who did not develop AMS as compared to those who did. In nephrotic syndrome, serum LDL concentration is inversely related to serum albumin concentration.[17~~,~~18~~,~~19~~,~~20~~] ~~One of the explanations for t~~The rapid and dramatic increase in LDL in hypoalbunemic states focuses on the body's attempt to maintain an adequate oncotic pressure. While our participants were not hypoalbunemic by clinical assessment, the elevated LDL levels may have positively contributed to the prevention of AMS through increasing the oncotic pressures. Oncotic pressure, like serum osmolarity, is one of the means by which intravascular fluid (a

component of the extracellular space) is kept within the vasculature in order to prevent edema. ~~Furthermore, LDL was represented in both of our logistic regression models.~~

~~In continuing to examine a~~Furthering the possible link between fluid distribution between the body's compartments and AMS, a significant decrease in plasma volume at altitude ~~as compared to sea level baseline values~~ was observed in ~~our subjects who developed~~ AMS group. As significant differences were not observed for participant weights between the Sea Level and Altitude measurements for either group, it stands to reason that total body water remained relatively constant between the measurements. However, the AMS group saw a nearly 10% decrease in estimated plasma volume and this would suggest ~~that the~~ a fluid ~~left~~ shift from the intravascular space ~~and likely caused to~~ either the intracellular or the extracellular ~~edema whereas the participants in the No AMS group saw a minimal decrease in estimated plasma volume as compared to Sea Level.~~space. Previously, Loeppky et al.[20~~1~~] have reported fluid retention occurs during the initial exposure to simulated altitude and our results suggest this retained fluid ~~leaves the intravascular space~~does not remain in the vasculature. ~~Related to fluid regulation,~~ Hackett al.[2~~1~~2] have suggested abnormalities in handling body water as the common link between the two edematous conditions, HAPE and HACE, representing the more serious forms of altitude-related illness. ~~While there were no cases of HAPE in our study despite this fluid shift, research~~Research has shown that subclinical pulmonary edema occurs amongst those with concomitant AMS.[2~~2~~3] Thise diagnosis in these individuals is made by the appearance of "comet tails" on ultrasonography and offers a specific example of an extravascular fluid shift.

Three of the variables identified in our analysis are seemingly linked to each other and to hypothesized causes of AMS – vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and eosinophils. VEGF levels at altitude were significantly elevated in the ~~those that developed~~ AMS group ~~as compared to those that did not~~. VEGF's primary role is to promote the formation of new blood vessels and it ~~is seen in~~ increase~~d level~~s in conditions that are associated with decreased oxygen supply to tissues.[2~~5~~4~~3~~] However, VEGF has also been linked to increased vascular permeability that contributes to the development of edema.[2~~4~~4~~5~~4,2~~5~~6~~5~~] Serum eosinophil level was the other variable that was represented in the logistic regression model. While increased ~~d~~ eosinophil levels ~~are~~ are often associated with the immune response to a parasitic presence or a hypersensitive response such as asthma, they will also ~~it does~~ increase the ~~levels~~ serum concentration of VEGF ~~in the blood~~.[2~~5~~6~~5~~,2~~6~~7~~6~~] ~~These two variables are linked~~ Aat altitude, ~~with~~ hypoxia prolong~~s~~ing the viability of eosinophils while increasing the eosinophllic production of VEGF and other pro-inflammatory cytokines, prost~~a~~oglandins, and leukotrienes.[2~~5~~6~~5~~,2~~7~~8~~7~~] The serum concentration of a ~~A~~ third inflammatory variable, TNF-α, was also ~~found~~ higher in the AMS group~~to~~

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differ between the groups - at sea level, the AMS group had significantly higher levels of TNF-α (p=0.012), further indicating the role of inflammation in the development of AMS. A

The variables in our logistic regression equation themselves are worth dissecting. The constant for LDL indicates that an increase in serum LDL was associated with a decreased risk of AMS. Alternatively, the constant for eosinophil levels suggests that an increase in eosinophil levels was associated with an increased risk of AMS. This suggestion is supported by Nissim Ben Efraim et al.'s work with hypoxic eosinophils.[25] One review paper suggests that a cyclicalstrong link has been suggested exists between hypoxia and inflammation in the development of AMS – that represents a cyclical process where hypoxic tissue becomes inflamed, inflamed tissue becomes increasingly hypoxic, and the magnitude of vascular leakage in response to the inflammatory response increases.[8,28,8] Other sources echo the role of inflammation and hypoxia in the development of altitude illness.[8] Anti-inflammatory medications such as dexamethasone and ibuprofen have demonstrated benefit in preventing and treating both AMS and the more serious high-altitude edemas.[2,16,29,30,29] An avenue of further research suggested by the analysis of

Oour data and a review of the relevant literature would suggest ais one focused on maintaining intravascular volume while minimizing inflammation. The statistically significant elevations of LDL, while still within the limits of a normal, healthy adult range, suggests that even modest alterations and adjustments in fluid dynamics may be sufficient to prevent the occurrence of AMSprotective at altitude. The positive association between AMS development and increased levels of eosinophilsseveral inflammatory markers, when considered in light of the available literature that suggests either steroidal or non-steroidal anti-inflammatory medications are beneficial in the can preventiion the symptoms of AMS, also is suggestive of means by which to of prevention or treatment AMS. Perhaps an effective solution may be as simple as a small bolus of colloid fluids (e.g. albumin) in conjunction with a long-acting steroid (e.g. dexamethasonemethylprednisolone acetate).

Dopamine, levels were significantly higher (0.036) in the No AMS group as compared to the AMS group. Dopamineconcentration was higher in the No AMS group and it can have a number of physiologic effects depending on the amount of dopamine administeredits levels. These effects are of interest to a population at risk for the development of AMS and addressing these multiple roles will require further work. DopamineIt can effect the body's vascular response (i.e. dilation vs constriction, depending on amount administered) and urinary function that, coupled with research specific to fluid dynamics and body water management or chemoreflexive vasoconstrictive responses to hypoxia, may guide future work.[20,21,22,30,30,31,21] Dopamine can also have stimulatory or inhibitory affects on many of the humoral immune cells depending on cell type and state (mature and activated vs immature and inactivated).[32,32,33,43] Some of these immunosuppressive characteristics are specific

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to the central nervous system itself and may support a hypothesis focused on the role of vasogenic edema or inflammation as it pertains to AMS.[3,34,3]

The PFT results also serve to drive future work – the ratio of the forced expiratory volume over one second as compared to the forced vital capacity (FEV1/FVC) differed significantly ~~(p=0.016) between the two groups,~~ with the AMS group demonstrating a smaller ratio. ~~The means were above the pathological values used to diagnose obstructive lung disease, t~~The association between eosinophilia and asthma in both allergic and non-allergic settings and the lack of association between asthma or chronic obstructive pulmonary disease with increased risk of AMS development deserve further investigation in light of our findings.[3,15,34,54] Perhaps PFT results in the low-normal range warrant further investigation in light of Jafarian et al.'s) findings that an increased respiratory rate in the first hour at altitude predicts the development of severe AMS or in light of the report of subclinical pulmonary edema in AMS sufferers.[10,22,3]

Finally, a strength and a caveat of our methodology requires ~~an~~ addressing. The size of the present data set permitted the removal of individuals who opted to utilize acetazolamide as a prophylaxis against AMS. The National Science Foundation (NSF) provided oversight for this project and would not permit the regulation of acetazolamide such that two equal groups of users could be created nor would the NSF permit the use of a placebo among those individuals who wished to employ acetazolamide. This may have influenced our results as AMS is a subjective diagnosis based on self-reported symptoms; however, many of our collected variables were objective measures (i.e. electrolyte concentrations and hemotalogic variables) that are not controllable by the individual's thoughts or beliefs in treatment efficacy.

Conclusion

Our results lend further strength to a number of the findings reported in previous investigations into the pathophysiology of AMS. Our results and comprehensive methodology also support a link between many of the previously reported findings. The regulation of body fluid to maintain intravascular volume and minimize edema coupled with anti-inflammatory medication appears to be a promising avenue to consider for future work. Our findings of statistically significant results that would be difficult to detect clinically further suggests that the development of AMS is the result of minor derangements of normal.

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Conflicts of Interest

The authors have no disclosures.

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Table 1 – Subject Demographics and Anthropometric Data

	No AMS (n=60)	AMS (n=30)
Sex (M, F)	37M, 23F	18M, 12F
Age (y)	36.2 ± 9.4	33.8 ± 9.2
Residence Altitude (m)	695.6 ± 785.8	818.3 ± 802.8
Height (m)	1.8 ± 0.1	1.7 ± 0.1
Weight (kg)		
• Sea Level	78.3 ± 14.8	70.2 ± 15.4
• Altitude	78.3 ± 14.3	71.2 ± 14.1
Body Mass Index (Wt/Ht^2)	26.1 ± 4.1	24.1 ± 2.5
Heart Rate (beats • min^{-1})		
• Sea Level	73.3 ± 12.2*	67.4 ± 10.0*
• Altitude	83.6 ± 12.4	80.5 ± 13.7
Blood Pressure (seated)		
Systolic (mmHg)		
• Sea Level	111.2 ± 13.3*	109.2 ± 9.9*
• Altitude	106.1 ± 12.7	101.1 ± 12.6
Diastolic (mmHg)		
• Sea Level	70.3 ± 10.4*	67.0 ± 9.2*
• Altitude	69.1 ±9.0	63.3 ± 7.1
Oxygen Saturation (%)		
Resting		
• Sea Level	97.7 ± 1.2	97.5 ± 0.9
• Altitude	88.8 ± 3.9	89.3 ± 3.0
Post-Breath Hold		
• Sea Level	93.5 ± 4.7	94.9 ± 3.3
• Altitude	82.7 ± 5.4	84.9 ± 4.6
Neck Circumference (cm)	35.9 ± 3.5	35.4 ± 3.2
Waist Circumference (cm)	88.0 ± 12.5	83.3 ± 10.5
Waist-to-Hip Ratio	0.9 ± 0.1	0.8 ± 0.1

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 2 – Electrolyte, Blood Chemistry, and Hematology Results

	No AMS (n=60)	AMS (n=30)
Sodium ($mEq \bullet L^{-1}$)	139.4 ± 1.6*	138.5 ± 1.8*
Potassium ($mEq \bullet L^{-1}$)	4.2 ± 0.3	4.2 ± 0.4
Chloride ($mEq \bullet L^{-1}$)	102.1 ± 3.0	101.9 ± 1.7
Calcium ($mg \bullet dL^{-1}$)	9.6 ± 0.4	9.6 ± 0.3
Alkaline Phosphatase ($U \bullet L^{-1}$)	62.7 ± 16.4	66.5 ± 16.1
Transaminases		
• Alanine Aminotransferase (ALT) ($U \bullet L^{-1}$)	21.1 ± 11.1	18.4 ± 7.5
• Aspartate Aminotrasnferase (AST) ($U \bullet L^{-1}$)	20.9 ± 5.2	20.8 ± 5.6
Leukocytes ($10^3 \bullet \mu L^{-1}$)	5.8 ± 1.4	6.1 ± 1.9
Eosinophils ($10^3 \bullet \mu L^{-1}$)	1.9 ± 1.6*	2.7 ± 2.0*
Erythrocytes ($10^3 \bullet \mu L^{-1}$)	4.7 ± 0.5	4.8 ± 0.3
Hemoglobin ($g \bullet dL^{-1}$)	14.8 ± 1.4	15.1 ± 0.9
Hematocrit (%)	44.0 ± 4.0	44.9 ± 2.9
Mean Corpuscular Volume (μm^3)	92.9 ± 4.0	93.8 ± 3.8
Mean Corpuscular Hemoglobin ($pg \bullet cell^{-1}$)	31.3 ± 1.2	31.5 ± 0.9
Mean Corpuscular Hemoglobin Concentration (%)	33.7 ± 0.9	33.6 ± 0.9
Red Blood Cell Distribution Width (%)	13.7 ± 1.0	13.3 ± 0.8
Platelets ($10^3 \bullet \mu L^{-1}$)	237.6 ± 53.2	255.9 ± 52.3
Estimated ΔPlasma Volume (%)	-2.9 ± 9.4*	-9.4 ± 12.5*
Iron Studies		
• Iron ($\mu g \bullet dL^{-1}$)	113.9 ± 31.8	119.5 ± 42.0
• Iron Sat (%)	36.5 ± 12.6	37.4 ± 13.0
• Total Iron Binding Capacity	325.0 ± 47.5	322.1 ± 37.4

($\mu g \bullet dL^{-1}$) • Unsaturated Iron Binding Capacity ($\mu g \bullet dL^{-1}$)	209.5 ± 56.9	202.6 ± 53.9
Low Density Lipoprotein ($mg \bullet dL^{-1}$)	105.9 ± 27.6*	97.7 ± 25.4*
High Density Lipoprotein ($mg \bullet dL^{-1}$)	60.2 ± 15.8	65.3 ± 17.4
Very Low Density Lipoprotein ($mg \bullet dL^{-1}$)	21.6 ± 12.8	20.3 ± 10.4
Triglycerides ($mg \bullet dL^{-1}$)	107.2 ± 62.9	101.4 ± 51.8

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 3 – Endocrine and Catecholamine Results

	No AMS (n=60)	AMS (n=30)
Progesterone ($ng \bullet mL^{-1}$)		
• Sea Level	1.8 ± 3.5	1.5 ± 2.7
• Altitude	1.4 ± 2.6	1.2 ± 1.8
Erythropoietin ($\mu IU \bullet mL^{-1}$)		
• Sea Level	11.0 ± 5.5	10.0 ± 4.7
• Altitude	31.7 ± 20.1	24.3 ± 9.0
Leptin ($ng \bullet mL^{-1}$)		
• Sea Level	8.4 ± 10.8	5.7 ± 5.5
• Altitude	6.9 ± 6.1	5.1 ± 4.4
Angiotensin II ($pg \bullet mL^{-1}$)		
• Sea Level	7.6 ± 5.7	11.5 ± 21.2
• Altitude	21.3 ± 33.4	16.2 ± 17.2
Tumor Necrosis Factor-α ($pg \bullet mL^{-1}$)		
• Sea Level	1.3 ± 0.6*	1.4 ± 0.7*
• Altitude	1.3 ± 0.6	1.3 ± 0.6
Vascular Endothelial Growth Factor ($pg \bullet mL^{-1}$)		
• Sea Level	42.4 ± 22.7	43.5 ± 26.1
• Altitude	57.0 ± 37.8*	76.4 ± 42.5*
Atrial Natriuretic Peptide ($pg \bullet mL^{-1}$)		
• Sea Level	434.6 ± 263.8	562.5 ± 289.0
• Altitude	583. 1 ± 300.6	630.7 ± 339.0
Thyroid Stimulating Hormone ($\mu IU \bullet mL^{-1}$)		
• Sea Level	1.9 ± 1.0	1.5 ± 0.6
• Altitude	2.2 ± 1.3	1.9 ± 0.8
~~Norepiphrine~~Norepinephrine ($pg \bullet mL^{-1}$)		
• Sea Level	402.4 ± 165.9	357.9 ± 108.8
• Altitude	569.5 ± 227.1	491.5 ± 159.7
Epinephrine ($pg \bullet mL^{-1}$)		
• Sea Level	42.0 ± 76.1	29.2 ± 20.9
• Altitude	36.3 ± 25.2	36.1 ± 30.1
Dopamine ($pg \bullet mL^{-1}$)		
• Sea Level	25.1 ± 62.7	13.4 ± 6.0
• Altitude	24.4 ± 16.6*	16.2 ± 14.8*

* significant difference between the AMS and No AMS groups, $p<0.05$

Table 4 – Pulmonary Function Results

	No AMS (n=60)	AMS (n=30)
Forced Vital Capacity (FVC) (L)		
• Sea Level	5.0 ± 1.0	5.1 ± 1.0
• Altitude	4.9 ± 0.9	5.2 ± 1.1
Forced Expiratory Volume in 1 second (FEV1) (L)		
• Sea Level	4.0 ± 0.7	4.1 ± 0.8
• Altitude	4.1 ± 0.7	4.1 ± 0.9
FEV1 / FVC (%)		
• Sea Level	81.2 ± 5.8	79.4 ± 5.8
• Altitude	83.7 ± 5.6*	80.4 ± 5.2*
Forced Expiratory Flow (FEF) ($L \bullet s^{-1}$)		
25%		
• Sea Level	7.8 ± 2.0	7.2 ± 2.2
• Altitude	9.0 ± 2.4	8.6 ± 2.6
75%		
• Sea Level	1.8 ± 0.6	1.8 ± 0.8
• Altitude	2.1 ± 0.8	1.8 ± 0.6
Maximum		
• Sea Level	9.7 ± 2.1	9.6 ± 2.2
• Altitude	10.8 ± 2.1	10.7 ± 2.6
Expiratory Reserve Volume (ERV) (L)		
• Sea Level	1.3 ± 0.5*	1.7 ± 0.6*
• Altitude	1.4 ± 0.5*	1.6 ± 0.4*

*significant difference between the AMS and No AMS groups, p<0.05

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **PAGE 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **PAGE 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **PAGE 3**
Methods		
Study design	4	Present key elements of study design early in the paper **PAGE 4-5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **PAGE 3-5**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **PAGE 4-5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **PAGE 3-5, 6-9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **PAGE 4-5**
Bias	9	Describe any efforts to address potential sources of bias **PAGE3-5, 6-9**
Study size	10	Explain how the study size was arrived at **PAGE 4-5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **PAGE 4-5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **PAGE 4-5**
		(*b*) Describe any methods used to examine subgroups and interactions **PAGE 4-5**
		(*c*) Explain how missing data were addressed **PAGE 4-5**
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy **PAGE 4-5**
		(*e*) Describe any sensitivity analyses **PAGE 4-6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **PAGE 4-5**
		(b) Give reasons for non-participation at each stage **PAGE 4-5**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **TABLE 1**
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **PAGE 4-5, TABLE 1-4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **PAGE 6-9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **PAGE 6-9**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **PAGE 6-9**
Generalisability	21	Discuss the generalisability (external validity) of the study results **PAGE 6-9**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **PAGE 10**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.