Original Article

Physiological Variables Associated with the Development of Acute Mountain Sickness

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Key words: altitude sickness; hypoxia; physiology

Objective To identify the physiological variables associated with the development of acute mountain sickness (AMS).

Methods 84 young Chinese men residing at low altitude were taken to an elevation of 4000 m within 40 hours. At sea level and at altitude, the heart rate, blood pressure, and peripheral oxygen saturation (SpO₂) were measured respectively. We also collect blood samples from each participants before and after their elevation. The blood routine and biochemical examinations were performed for all blood samples. The revised Lake Louise Criteria was adopted to diagnose AMS after arrived at the target high altitude. We assessed the association between the presence of AMS and subjects' physiological variables.

Results Of 84 participants, 34 (40.5%) developed AMS. Compared with non AMS group, in the AMS group, the percentage of neutrophils was significantly higher ($64.5\% \pm 11.2\%$ vs $58.1\% \pm 8.8\%$, $P=0.014$), while the level of SpO₂ was significantly lower ($79.4\% \pm 5.4\%$ vs $82.7\% \pm 5.6\%$, $P=0.008$). Binary logistic regression analyses emphasized the association of neutrophils ($OR: 1.06$, 95% $CI: 1.01-1.12$, $P=0.034$) and SpO₂ level ($OR: 0.87$, 95% $CI: 0.79-0.95$, $P=0.004$) with the development of AMS.

Conclusion The ability to sustain SpO₂ after altitude elevation and the increase of neutrophils were associated with the development of AMS in young males.

Due to improved accessibility, there has been an increasing number of visitors in high-altitude areas. People who have not acclimatized to high altitude yet ascend to altitude higher than 2500m in a short period are prone to acute high-altitude illness, a collective term for acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). Among these high-altitude illnesses, AMS is the most common form, which generally occurs within 6 to 12 hours after high altitude exposure. The prevalence of AMS can reach 10% at 2500 m and increase with altitude.¹ Common symptoms of AMS consist of headache, dizziness, gastrointestinal symptoms, fatigue, and controversial sleep disturbance.² Although undoubtedly it is the acute exposure to hypoxia that triggers AMS, the exact process is unclear.³ Objective variables correlated with AMS has been studied in the past decade, for they could provide hints of possible mechanisms and allow objective assessment. However, none of these objective variables were well acknowledged, and AMS is still a clinical diagnosis relying on questionnaires.

The Lake Louise Questionnaire has been revised to a new version in 2018.² In this study, we

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used the updated version of Lake Louise Questionnaire to assess the occurrence of AMS in 84 participants who experienced acute exposure to high altitude. Respective physiological variables of those suffered AMS and those did not were compared and examined. We hope this study can provide an opportunity to evaluate which factors, if any, are related to the development of AMS.

Materials and Methods

Participants

This study was approved by the Institutional Review Board of the Chinese PLA General Hospital. Individual informed consent was obtained. Recruitment took place from January to April in 2016. Inclusion criteria specified Chinese male adults aged 18 to 35 years without previous experience of exposure to high altitude. Exclusion criteria included history of primary headache, cerebral neoplasm, heart failure, or chronic obstructive pulmonary disease. Totally 84 young Chinese males were enrolled in the study. All participants completed the questionnaires and the physiological measurements.

Study design

We collected participants' demographic data, including age, height, weight, and body mass index (BMI), measured heart rate, blood pressures, peripheral oxygen saturation (SpO₂), and performed blood draws for each participants at sea level altitude (Beijing) prior to departure as baseline data. Participants were then taken to Geermu, Qinghai Province in China (2800m), traveling by train for 30 hours. After staying at Geermu for several hours, the participants travelled by bus to the destination (4000m) in 3 hours. The dynamic electrocardiogram and ambulatory blood pressure monitoring were initiated at the altitude of 2800m and terminated at the destination. In about 6-8 hours after arrival at the destination, all participants completed the Lake Louise Questionnaire, afterwards, took SpO₂ measurement again in the next 2 hours, and received the secondary blood draw. For all blood samples we examined hemoglobin, white blood cell and its subsets, platelet, liver and kidney function, serum electrolyte, and myocardial damage markers.

The classic version of Lake Louise Questionnaire invests 5 symptoms: headache, gastrointestinal symptoms (anorexia, nausea, or vomiting), fatigue/weakness, dizziness/lightheadedness, and difficulty of sleeping. The revised version we used eliminated the symptom of disturbed sleep. The threshold is still set as 3 points and the headache is kept as a necessary symptom.²

Statistical methods

The qualitative parameters are described as counts and percentage, the quantitative parameters are described as mean±SD. The comparison of quantitative parameter between two groups was performed with Student's *t* test or Wilcoxon rank sum test, according to the result of normality test. Binary logistic regression analysis was used to determine whether variables were independently associated with AMS. All data analyses were conducted with SPSS (version 17.0) in two-tail, and *P*<0.05 was considered to be statistically significant.

RESULTS

Of the 84 participants, 34(40.5%) developed AMS. Comparisons of the demographic data between participants with and without AMS are presented in **Table 1**, which demonstrates that participants who developed AMS were slightly younger than those did not.

Hematological results, at sea level and at altitude, are revealed in **Table 2** and **Table 3**. After acute exposure to high altitude, participants who developed AMS had significantly higher percentage of neutrophils than those did not (64.5% ± 11.2% vs. 58.1% ± 8.8%, *P*=0.014),

accompanied with significantly lower percentages of lymphocytes ($29.3\% \pm 10.5\%$ vs. $34.9\% \pm 8.1\%$, $P=0.014$) and monocytes ($3.9\% \pm 1.0\%$ vs. $4.9\% \pm 1.3\%$, $P<0.001$).

Table 4 presents the monitoring results of SpO₂, dynamic electrocardiogram, and ambulatory blood pressure. Participants who developed AMS showed significantly lower SpO₂ level at high altitude than those did not ($79.4\% \pm 5.4\%$ vs. $82.7\% \pm 5.6$, $P=0.008$).

Variables in logistic regression analysis were selected in the initial analysis on the basis of $P<0.10$. Because the low level of lymphocytes or monocytes might be a relative result of high level neutrophils in AMS group, both were excluded from the regression analysis. Since BMI was proposed as a factor associated with AMS by some researchers,⁴ it was included in the regression analysis. As a result, variables of age, BMI, percentage of neutrophils, SpO₂, hemoglobin, as well as serum creatinine were included in the binary logistic regression analysis. The percentage of neutrophils ($OR: 1.06$, 95% CI 1.01-1.12, $P=0.034$) and SpO₂ (OR 0.87, 95% CI 0.79-0.95, $P=0.004$) were found to be significantly associated with the development of AMS (**Table 5**).

Table 1 Demographics of subjects and comparison between AMS and non AMS group

Variables	AMS(+) $n=34$	AMS(-) $n=50$	t/Z	$P^{\dagger}$
Age(y)	25.0 $\pm$ 1.9	25.6 $\pm$ 2.4	-2.096	0.036*
Weight(kg)	71.6 $\pm$ 9.0	71.4 $\pm$ 8.4	0.093	0.501 [†]
Height(cm)	175.3 $\pm$ 4.7	174.6 $\pm$ 4.7	0.676	0.926 [†]
BMI(kg m ⁻²)	23.3 $\pm$ 2.6	23.4 $\pm$ 2.6	-0.561	0.575*

[†] Student's t test; * Wilcoxon rank sum test

AMS, acute mountain sickness; BMI, body mass index

Table 2 Comparisons of blood routine matrixes of AMS and non-AMS participants

Variables	AMS(+) $n=34$		AMS(-) $n=50$		$t/Z^{(a)}$	$P^{(a)}$	$t/Z^{(b)}$	$P^{(b)}$
	Sea level	Altitude	Sea level	Altitude				
RBC($10^{12}/L$)	5.3 $\pm$ 0.4	5.3 $\pm$ 0.3	5.2 $\pm$ 0.4	5.2 $\pm$ 0.4	1.349	0.181	1.987	0.050
Hb(g/L)	158.0 $\pm$ 8.4	164.2 $\pm$ 7.5	155.3 $\pm$ 8.9	161.0 $\pm$ 8.6	1.351	0.180	1.804	0.075
MCH(pg)	30.0 $\pm$ 1.1	30.7 $\pm$ 1.3	30.2 $\pm$ 0.9	31.0 $\pm$ 1.0	-0.616	0.539	-1.111	0.270
MCHC(g/L)	335.8 $\pm$ 7.4	339.4 $\pm$ 10.2	335.0 $\pm$ 9.0	338.1 $\pm$ 7.0	0.410	0.683	-1.537	0.124*
MCV(fl)	89.5 $\pm$ 3.2	90.4 $\pm$ 2.9	90.1 $\pm$ 2.6	91.6 $\pm$ 3.0	-0.974	0.333	-1.275	0.202*
WBC($10^9/L$)	7.2 $\pm$ 1.8	8.7 $\pm$ 2.5	6.5 $\pm$ 1.7	8.1 $\pm$ 1.7	1.653	0.102	1.169	0.248
Neutrophil (%)	54.5 $\pm$ 8.4	64.5 $\pm$ 11.2	52.8 $\pm$ 6.9	58.1 $\pm$ 8.8	0.969	0.335	-2.461	0.014*
Monocyte (%)	5.5 $\pm$ 1.2	3.9 $\pm$ 1.0	6.0 $\pm$ 1.3	4.9 $\pm$ 1.3	-1.223	0.221*	-3.521	<0.001*
Basophil (%)	0.6 $\pm$ 0.3	0.6 $\pm$ 0.3	0.6 $\pm$ 0.3	0.6 $\pm$ 0.3	-0.010	0.992*	-0.089	0.929*
Lymphocyte (%)	36.5 $\pm$ 7.5	29.3 $\pm$ 10.5	38.3 $\pm$ 6.6	34.9 $\pm$ 8.1	-1.177	0.243	-2.699	0.008
Eosinophil (%)	2.9 $\pm$ 3.6	1.6 $\pm$ 1.4	2.8 $\pm$ 4.3	1.5 $\pm$ 1.2	-0.343	0.731*	-0.247	0.805*
Platelet($10^9/L$)	233.6 $\pm$ 38.6	220.6 $\pm$ 52.8	225.6 $\pm$ 47.7	232.4 $\pm$ 45.4	0.790	0.432	-1.081	0.283

(a). Comparing variables at sea level between subjects with and without AMS; (b). Comparing variables at high altitude between subjects with and without AMS. [†] Student's t test; * Wilcoxon rank sum test exceptionally. RBC, red blood cell; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; WBC, white blood cell.

Table 3. Comparisons of blood biochemical matrixes of AMS and non-AMS participants

Variables	AMS(+) n=34		AMS(-) n=50		t/Z ^(a)	P ^{†(a)}	t/Z ^(b)	P ^{†(b)}
	Sea level	Altitude	Sea level	Altitude				
ALT(U/L)	22.5±12.7	22.6±17.6	22.6±17.6	21.4±13.6	-1.678	0.093*	-0.274	0.784*
ALP(U/L)	69.4±12.8	73.6±19.0	68.0±20.4	77.3±20.6	-0.702	0.483*	-0.980	0.327*
TP(g/L)	75.6±3.3	78.3±3.9	75.4±3.2	77.5±4.2	0.345	0.731	0.839	0.404
ALB(g/L)	48.4±2.1	51.6±2.2	48.7±2.2	52.1±2.5	-0.635	0.527	-0.961	0.339
BUN(mmol/L)	4.6±1.2	5.0±0.8	4.7±1.0	5.0±1.0	-1.058	0.290*	-0.584	0.559*
Scr(μmol/L)	77.3±8.8	84.3±12.8	77.8±9.7	79.4±11.5	-0.244	0.808	1.833	0.071
Tc(mmol/L)	4.2±0.6	4.3±0.7	4.2±0.7	4.5±0.6	-0.002	0.999	0.598	0.119
HDL(mmol/L)	1.4±0.3	1.3±0.3	1.5±0.3	1.4±0.3	-1.421	0.159	-0.628	0.531
LDL(mmol/L)	2.6±0.6	2.5±0.7	2.6±0.7	2.7±0.6	-0.020	0.984	-0.912	0.364
TBil(μmol/L)	14.1±5.5	7.9±4.3	14.5±5.9	8.4±3.7	-0.105	0.917*	-0.916	0.360*
DBil(μmol/L)	4.8±2.0	3.1±1.8	4.9±1.6	3.2±1.0	-0.146	0.884	-1.615	0.106*
cTnT(μg/L)	0.005±0.002	0.005±0.001	0.005±0.001	0.005±0.001	-1.445	0.148*	-0.221	0.825*
Na+(mmol/L)	141.6±1.5	143.3±2.0	142.0±2.0	143.6±1.9	-0.959	0.338*	-1.482	0.138*
Cl-(mmol/L)	99.1±2.5	102.3±2.0	99.4±3.0	102.7±1.7	-0.531	0.597	-1.345	0.179*

(a). Comparing variables of sea level between subjects with and without AMS ; (b). Comparing variables of high altitude between subjects with and without AMS. † Student's t test; * Wilcoxon rank sum test exceptionally. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; Tc, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TBil, total bilirubin; DBil, direct bilirubin.

Table 4 Comparisons of peripheral oxygen saturation, heart rate and blood pressure of AMS and non-AMS participants

Variables	AMS(+) n=34		AMS(-) n=50		t/Z ^(a)	P ^{†(a)}	t/Z ^(b)	P ^{†(b)}
	Sea level	Altitude	Sea level	Altitude				
SpO2(mmHg)	98.3±1.2	79.4±5.4	98.3±1.3	82.7±5.6	-0.074	0.941*	-2.698	0.008
HR max(/min)	130±10	134±12	132±14	133±16	-0.921	0.360	0.154	0.878
HR min(/min)	48±5	53±7	48±5	52±7	0.166	0.869	0.894	0.374
HR mean(/min)	72±6	82±8	73±8	81±10	-0.480	0.632	0.542	0.590
HRVTI	53.5±13.2	35.3±10.7	51.8±15.5	39.4±10.6	-0.869	0.385*	-1.554	0.125
SBPmean(mmHg)	113.5±6.4	119.6±8.3	114.7±6.7	119.5±8.1	-0.792	0.431	0.021	0.983
DBPmean(mmHg)	69.1±5.9	75.4±7.1	69.9±5.6	74.4±6.8	-0.592	0.555	0.637	0.526
SCV(%)	15.7±5.9	15.6±5.3	15.4±6.7	16.6±6.0	-0.637	0.524*	-0.803	0.424
DCV(%)	25.0±10.3	25.7±10.6	24.4±9.2	25.1±8.8	-0.195	0.845*	-0.080	0.936*

(a). Comparing variables of sea level between subjects with and without AMS ; (b). Comparing variables of high altitude between subjects with and without AMS. † Student's t test; * Wilcoxon rank sum test exceptionally. SpO2, Peripheral oxygen saturation ; HR, heart rate; HRVTI, heart rate variability triangular index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SCV, systolic blood pressure coefficient of variation; DCV, diastolic blood pressure coefficient of variation

Table 5 Logistic regression analyses of variables independently associated with AMS

Variables	OR	95% CI	P
Age(y)	0.82	0.63-1.08	0.157
BMI(kg /m ²)	0.91	0.74-1.12	0.376
Neutrophil (%)	1.06	1.01±1.12	0.034
SpO2(mmHg)	0.87	0.79-0.95	0.004
Hb(g/L)	1.05	0.98-1.12	0.200
Scr(μmol/L)	1.02	0.97-1.06	0.459

DISCUSSION

Currently, AMS is still a clinical diagnosis based on the presence of a series of subjective symptoms. Questionnaire-based diagnostic tools for AMS consist of the Lake Louise Questionnaire Score (LLQS), the Acute Mountain Sickness–Cerebral (AMS-C) score, the Hackett score, and the Clinical Functional Score (CFS).⁵ In this study, we applied the updated Lake Louise Criteria which was revised by the consensus group in 2018. The group declared that by eliminating the disturbed sleep, more people with true AMS will be identified.² Certain factors which may interfere the incidence of AMS were controlled in the study, such as gender, altitude illness history, the means and the rate of ascent and the altitude attained.^{1, 6} Otherwise, these factors can confound the results when attempting to identify relevant physiological variables.

Young age was considered as a possible risk factor for AMS in previous studies.^{1, 3, 7} This may attribute to more activeness and larger brain size (“tight-fit” theory) of young people. In our initial analysis, participants in the AMS group were observed slightly younger. However, after adjusting other variables, the difference of age in two groups was no longer statistically significant, which may result from the fact that the average age of both two groups was under 30 years old, whereas the age which differentiated a susceptibility was usually around 50 years old.^{1, 3, 7} Additionally, the mean BMI of two groups did not show significantly differences as well, in contrast with other studies which found an association between obesity and AMS.⁴

This study found that at altitude neutrophils of the two groups differed significantly but within the normal range. Neutrophils, as the most abundant white blood cells in the blood, are part of the innate immune system and on the front-line of defense against infection and tissue damage.⁸ Neutrophils can be activated by bacterial products, toxins, free radicals and various cytokines. After activation, neutrophils can release abundant antibacterial proteins, inflammatory mediators and reactive oxygen species (ROS). Therefore, inappropriate or excessive activation of neutrophils would result in host tissue damage and loss of organ function. Immune system is sensitive to environmental stress.⁹ The argument that hypoxia can lead to inflammation has gained well acceptance.¹⁰ Serum levels of interleukin-6, the interleukin-6 receptor, interleukin-17a, endothelin-1(ET-1) and C reactive protein were found increased at high altitude compared to baseline.^{11, 12} Furthermore, the association between inflammatory and AMS has also been demonstrated. Endothelin-1, released in response to endothelial injury or activation, has been found to be an independent predictor of AMS and its severity. Endothelin-1 was also a proinflammatory mediator, which can trigger the release of interleukin-6 and the expression of adhesion molecule.¹² Some researchers indicated that hypoxia-induced inflammatory mediators, such as vascular endothelial growth factor, histamine, inducible nitric oxide synthase, bradykinin,

are involved in the development of AMS.^{7, 13} Also, some researchers proposed that the ability to form anti-inflammatory response after exposure to altitude may help to prevent AMS.¹⁴ This inflammatory hypothesis has been indirectly proved by the efficacy of dexamethasone in preventing and treating AMS. Another possibility is that AMS is caused partially by hypoxia-induced ROS. Several studies have shown that oxidative stress is aggravated after acute exposure to high altitudes. The relationship between oxidative stress and AMS severity has also been suggested.¹⁵⁻¹⁷ Releases of both inflammatory mediators and ROS would lead to the disruption of blood brain barrier (BBB), inducing the capillary leakage and finally causing the cerebral edema (BBB theory).³ As the leading cells in host response, neutrophils undoubtedly play an important role in the complex networks.

The damage of intestinal mucosa may also serve to prime and activate neutrophils.¹⁸ Hypoxia can affect gastrointestinal function and cause damage to the gastrointestinal mucosa.^{19, 20} Acute exposure to altitude can induce various gastrointestinal symptoms, such as anorexia, nausea, vomiting, gasing, and abdominal pain, which can attribute in part to the hypobaric hypoxia of high altitude.²¹ The relationship between altitude and damage of gastrointestinal mucosa has been reported.^{22, 23} In addition, gut injury and loss of normal immune barrier function are key elements in gut-origin system inflammatory reaction syndrome (SIRS).¹⁹ Zhang *et al.* proposed that high altitude illness might share a common pathophysiology basis with SIRS.²⁴ Once again, neutrophils are regarded as a key component in this process.

Among other important changes in altitude ascending, such as low temperature, high winds, and intense solar radiation, the defining environmental feature at altitude is the drop of barometric pressure, which results in decreases of partial pressure of oxygen along the decreases of oxygen transport cascade from air to cellular mitochondria.⁶ Previous evidence had shown a correlation between the incidence of AMS and a low arterial oxygen saturation.²⁵ Consistently, some researchers indicated that a low ventilatory response to hypoxia, especially at exercise, was involved in the variety of individual susceptibility, while other researchers suggested SpO₂ as a poor measurement for assessing predisposition, presence, or severity of AMS.²⁶ Moreover, the efficacy of drugs aiming at preventing AMS was not always related to the improvement of oxygen saturation in previous trials.²⁷⁻²⁹ In the present study, SpO₂ was significantly lower in the AMS group compared with non AMS group, and it remained to be significantly associated with AMS after adjusting other variables. Thus we speculated that the ability to preserve oxygen saturation after acute exposure to altitude was associated with the development of AMS.

There are two limitations in this study. Firstly, the relatively small numbers of subjects may have limited the power of the results. Prospective study with large sample size is needed to further confirm the findings. Secondly, the participants in the present study are all young male adults. The results of this article need to be verified in general population.

In conclusion, the present study shows that the ability to preserve oxygen saturation may be associated with the development of AMS. The activation of neutrophils caused by various possible reasons may participate in the process of AMS. However, the role of neutrophils in the complex networks need to be further investigated.

Conflict of Interests statement

All authors declared no conflicting interest.

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