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Original Article

Physiological responses to acute hypoxia and indictors of acute mountain sickness in males

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Abstract: Currently, acute hypoxia and the underlying mechanisms of acute mountain sickness (AMS) have not been characterized. Here, we investigated the responses of the cardiopulmonary system and cerebral blood flow (CBF) to acute hypoxia and the related compensatory factors for AMS. A total of 123 healthy young male subjects were recruited in Chengdu (500 m) and arrived in Lhasa (3700 m) by plane. Demographic information was recorded within 24 h after their arrival. Physiological parameters and AMS symptoms were measured at resting conditions. The incidence of AMS was 58.5% (72/123) after acute exposure to 3700 m. The AMS group had significant increases in cardiac output (CO), heart rate (HR), epinephrine, norepinephrine and lower oxygen saturation (SaO_2) and significant differences in electrocardiographic parameters and tricuspid regurgitation pressure compared with the non-AMS group (all *P*-values < 0.05). Combining indicators including HR ≥ 85/min, MCAv (Middle cerebral artery flow velocity) ≥ 66 cm/s, SaO_2 ≤ 88% and tricuspid regurgitation (TR) pressure ≥ 25 mmHg can contribute to AMS diagnosis, with a positive predictive value and specificity of 97.87% and 98.04%, respectively. HR (≥ 85/min), MCAv (≥ 66 cm/s), SaO_2 (≤ 88%) and TR pressure (≥ 25 mmHg) are the key compensatory factors for DO_2 (oxygen delivery) and may play a key role in the physiological responses involved in the acclimatization to acute hypoxia. These factors may be related to the mechanism of AMS development and can be used as objective indicators for AMS diagnosis.

Keywords: Acute hypoxia, oxygen delivery, compensatory factors, acute mountain sickness

Introduction

An increasing number of people living at sea level travel to high altitudes for occupational or scientific requirements or to enjoy tourism, as is the case for soldiers, workers, scientists, and hikers. However, AMS may occur after acute exposure to high altitudes, resulting in a negative impact on quality of life and work efficiency, severe cases may develop fatal pulmonary edema or high altitude cerebral edema [1, 2]. Accordingly, it is necessary to determine the effects of acute hypoxia on the physiological responses of the human body.

After acute exposure to high altitudes, the initial physiological response to hypobaric hypoxia is characterized by a reduction in arterial oxygen partial pressure (PO_2). Thus, cardiovascular and cerebral oxygen delivery (DO_2) plays an important role in the physiological adaptation to hypoxia [3]. This process is regulated by a decrease in arterial oxyhemoglobin saturation (SaO_2) according to the needs of the tissues [4]. Acute hypoxia stimulates the carotid sinus and aortic bodies and induces sympathetic activity, with an increase in cardiac output (CO), heart rate (HR) [5-7], and cerebral blood flow (CBF) to maintain oxygen delivery matched to oxygen consumption [8].

Individuals often develop acute mountain sickness (AMS) within a few hours after acute exposure to high altitudes above 2500 m [9, 10]. AMS, a syndrome of nonspecific symptoms, is usually diagnosed using the Lake Louise self-assessment scoring system (LLS) based on the occurrence of headache in addition to one or more of the following symptoms: gastrointestinal symptoms (anorexia, nausea or vomiting), insomnia, weakness or dizziness, and lassitude or fatigue [11-13]. Although the symptoms of

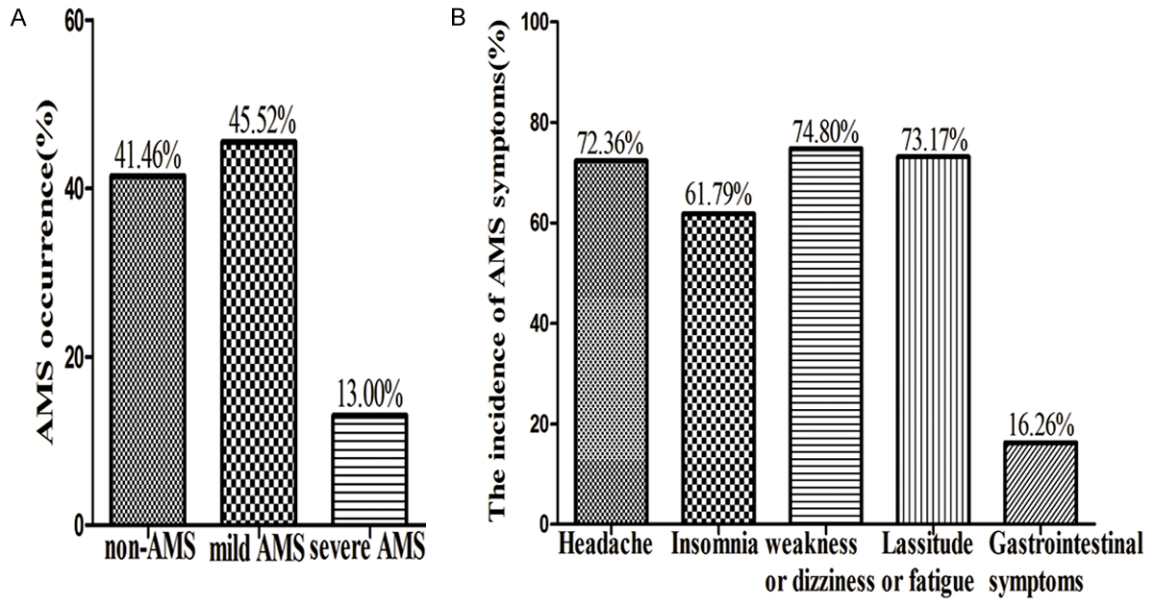

Figure 1. AMS occurrence and the diagnosis of AMS symptoms based on LLS after acute exposure to 3700 m. A: Incidences of the severity of AMS; B: Different incidences of the AMS symptoms.

AMS have been studied for decades, the underlying pathogenesis and pathophysiological mechanisms of AMS are still not comprehensively understood. This issue includes the effects of the cardiovascular and cerebral DO_2 compensatory reactions, factors involved in the development of AMS, and changes in the cardiopulmonary system and CBF. Research into the relationships between cardiovascular and cerebral DO_2 and AMS is lacking, as is research into the physiological responses associated with AMS. Additionally, most of the previous studies were conducted with a small sample size and were often focused on hypoxic simulations [3, 5, 9, 14, 15].

Based on the results of previous investigations [3, 14, 16, 17], The objectives of the present study were as follows: (1) to determine the DO_2 compensatory responses and factors that contribute to acute hypoxia; (2) to identify auxiliary objective indicators for AMS diagnosis; and (3) to evaluate the effects of acute hypoxia on the compensatory factors of DO_2 (HR, MCAv, SaO_2 and TR) and to determine whether the levels contribute to AMS prediction.

Materials and methods

Participants and study design

A total of 123 young Chinese males, aged between 18 and 30 years (mean age = 23.77±4.5 years), were recruited for the study according to the inclusion and exclusion criteria. Before entering the high altitude area, the participants had no organic diseases and had lived at the altitude of 500 m without exposure to high altitudes in the previous 12 months. The exclusion criteria were as follows: migraine disease, autoimmune diseases, respiratory diseases, cardiovascular diseases, malignancy, liver and kidney dysfunction, active infection or a bad cold and psychiatric disorders or neuroses that interfered with the completion of the questionnaires. The subjects did not take medication or receive any intervention before the ascent to high altitude.

All of the recruited participants were familiar with the purpose and process, and signed informed consent forms before the study. All of the study protocols were approved by the Ethics Committee of Xinqiao Hospital, the Second Clinic Medical College of the Third Military Medical University.

The 123 subjects ascended from 500 m (Chengdu) to 3700 m (Lhasa) in 2 hours by airplane. Data collection was performed between 19 and 24 h after the arrival at 3700 m. The baselines were examined at 500 m 1 week before their departure. All of the participants completed the structured case report form (CRF) questionnaires to self-reported demo-

Table 1. Comparison of DO_2, DO_2C and compensatory factors between 500 m and 3700 m

Parameters	500 m	3700 m	*P*-value
SaO_2 (%)	98.41±0.94	89.20±2.67	< 0.01
HR (beats/min)	63.67±8.93	81.58±9.84	< 0.01
SBP (mmHg)	115.37±14.08	121.14±10.78	< 0.01
DBP (mmHg)	74.54±9.41	80.36±9.10	< 0.01
MBP (mmHg)	87.60±1.27	90.27±1.58	< 0.01
Hb (g/L)	141.47±10.52	141.78±12.73	> 0.05
EP (ng/ml)	7.57±1.56	10.40±2.45	< 0.01
NE (ng/ml)	117.54±15.35	146.43±11.79	< 0.01
Cardiovascular system			
DO_2 (ml/min)	816.75±12.97	966.69±55.85	< 0.01
RA (cm)	35.37±2.31	34.75±2.05	< 0.05
RV (cm)	34.75±2.17	33.94±2.44	< 0.05
RV-Tei	0.25±0.05	0.31±0.07	< 0.01
mPAP (mmHg)	14.46±3.79	23.84±4.41	< 0.01
EF (%)	61.37±5.30	66.67±4.35	< 0.05
SV (ml)	64.79±11.29	64.91±8.37	> 0.05
CO (L/min)	4.00±0.81	5.30±1.12	< 0.01
ET (ms)	295.58±28.53	271.76±24.10	< 0.01
Electrocardiographic parameters			
PR (ms)	157.86±17.40	156.24±15.63	> 0.05
QRS (ms)	92.53±9.51	90.46±8.81	> 0.05
QT (ms)	388.72±27.47	380.46±26.97	< 0.01
QTc (ms)	394.11±16.89	411.41±25.80	< 0.05
QTcd (ms)	45.30±11.05	48.41±13.00	> 0.05
V3TpTe (ms)	86.25±9.61	76.58±8.35	< 0.01
V3TpTec (ms)	85.05±10.35	88.86±10.42	< 0.01
CFB			
DO_2C (units)	57.66±1.16	57.13±1.94	> 0.05
MCAv (cm/s)	58.58±1.02	65.09±2.31	< 0.01
R_{MCA} (units)	1.65±0.03	1.37±0.06	< 0.01

graphic data (age, height and weight, and smoking and alcohol consumption that was classified as follows: 1 = no smoking/drinking history, 2 = present smoking/drinking, and 3 = past smoking/drinking history) and AMS symptoms. AMS was diagnosed on the basis of the LLS, with headache and an LLS score ≥ 3 representing AMS [3, 14]. Vital signs were also measured. Morning fasting venous blood was collected to test routine blood parameters. Color Doppler ultrasonography examinations were performed to measure CO, stroke volume (SV), PAP, tricuspid regurgitation conditions, and ventricular repolarization. Transcranial Doppler (TCD) sonography was implemented to measure the cerebral hemodynamic parameters.

All of the questionnaires and measurements were non-invasive. All of the trial procedures were performed in Chengdu within one week before ascending and within 24 h after arrival in Lhasa. Examinations were performed approximately 8:00 A.M.-12:00 P.M. the morning after arrival. The minimal and the maximal time from arrival to examination were 19 hours and 24 hours, respectively.

AMS diagnosis

The severity of AMS was diagnosed based on the LLS, including five self-reported symptoms: headache, dizziness or light headedness, gastrointestinal symptoms (anorexia, nausea, or vomiting), insomnia, and weakness or fatigue [16, 17]. All of the items were assessed on a 0 to 3 Likert scale, with 0 indicating none, 1 for light, 2 for moderate, and 3 for severe. Clinical diagnosis of AMS was defined as a total score of the additive 5 items ≥ 3, including headache and one other symptom. AMS with a score of 3-4 was defined as mild AMS, while severe AMS had a score of 5 or more [18, 19].

Vital signs

The levels of HR and SaO_2 were determined with a fingertip pulse oximeter (Nonin Onyx® 9500, Nonin Medical, Inc., USA). BP (blood pressure) was measured using a wrist sphygmomanometer (HEM-6200, OMRON, Japan). The systolic pressure (SBP) and diastolic pressure (DBP) and mean arterial pressure (MAP) were recorded. All the test items were measured in triplicate after the subjects had been seated for 30 min.

Cardiopulmonary functions

After the subjects rested for 30 min and were in the left lateral position, color Doppler ultraso-

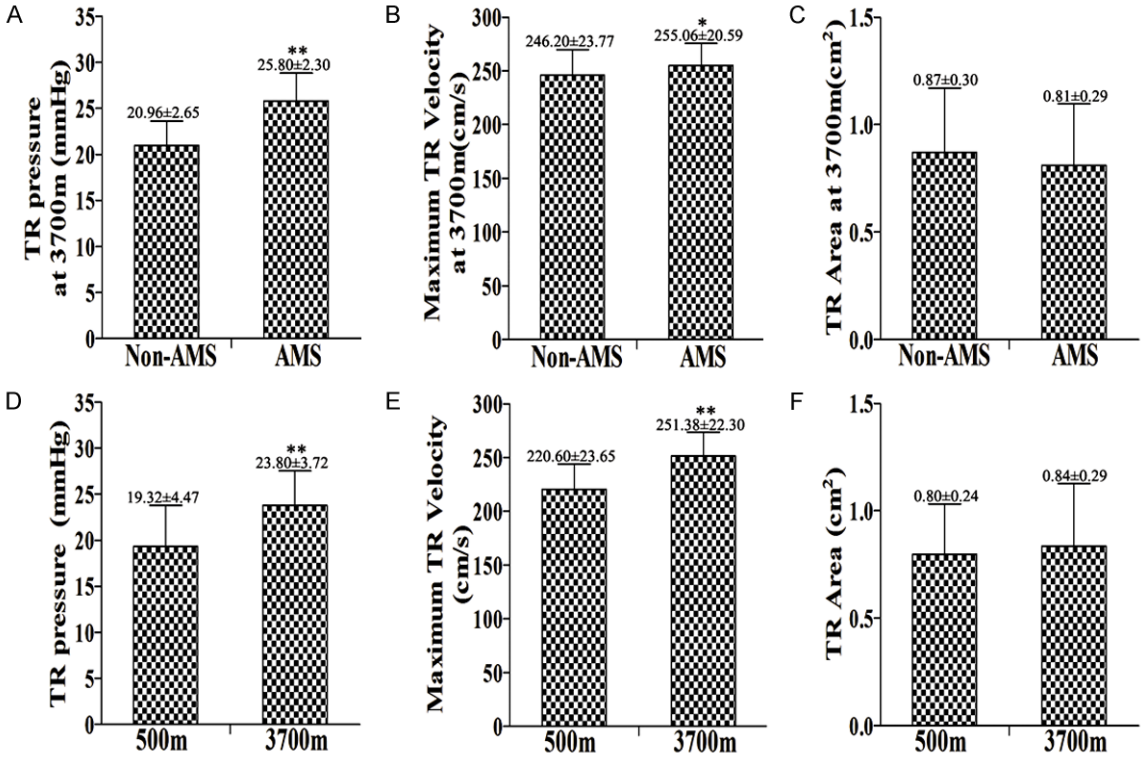

Figure 2. Changes in the parameters related to tricuspid regurgitation (TR) from 500 m to 3700 m and AMS and Non-AMS group. A: The TR pressure in AMS and Non-AMS group; B: Maximum TR velocity in AMS and Non-AMS group; C: TR area in AMS and Non-AMS groups; D: The TR pressure from 500 m to 3700 m; E: Maximum TR velocity from 500 m to 3700 m; F: TR area from 500 m to 3700 m. *P < 0.05, **P < 0.01.

nography examinations with a 2.5 Hz probe (Philip CX50, USA) were performed via parasternal to measure cardiopulmonary functions. The parameters included CO, SV, ejection fraction (EF), acceleration time of pulmonary blood flow (AT), pulmonary ejection time (ET), tricuspid diastolic interval time (DT), and the tricuspid regurgitation conditions. The mean pulmonary arterial pressure (mPAP) was calculated as followed: if AT ≥ 120 ms, mPAP = 90-(0.45×AT); if AT < 120 ms, mPAP = 90-(0.62×AT) [20, 21]. The right ventricle Tei index (RV-Tei) was calculated as: RV-Tei = (DT-ET)/ET [21]. An electrocardiogram (NIHON KOHD, 1350P, Japan) was used to detect the relative parameters of ventricular repolarization, including heart rate-corrected QT (QTc) interval, heart rate-corrected T-peak to T-end (TpTec) on the V3 lead, QT interval, and TpTe interval on the V3 lead. All of the subjects were placed in the supine position for 5 min prior to the electrocardiogram examinations of ventricular repolarization. The electrocardiograms used 12-lead ECG recording, with a speed of 25 mm/s; the horizontal pitch of the electrocardiogram was set to 10 mm/mV.

Analysis of CBF

After resting for 30 min, all subjects received TCD examination of the bilateral MCA (Middle cerebral artery) with a 2 Hz probe (EME TC3021, NICOLET, USA). MCAv (Middle cerebral artery flow velocity) was measured through the temporal window (depth: 52 mm) and averaged over 3 cardiac cycles after 15 seconds stability. The resistance index of the bilateral MCAs (RMCA) was calculated as: RMCA = MBP (Mean arterial pressure)/MCAv. Cardiovascular DO_2 DO_2 = CO×Hb×SaO_2×1.39. The calculation formula of brain oxygen delivery unit (DO_2C): DO_2C = MCAv×SaO_2 [22, 23].

Collection of blood samples and analysis of routine blood parameters and blood biochemical indices

Morning fasting venous blood (4 ml) was collected (with EDTA-K2), and 2 ml of the samples were assayed for routine blood parameters within 2 hours using a hematology analyzer (Sysmex XE-2100, Japan). All equipment was used in accordance with the manufacturers'

Table 2. Comparison of the demographic characteristics between the AMS and non-AMS groups

Demographic factors	AMS group (n = 72)	Non-AMS group (n = 51)	*P*-value
Age	23.11±3.20	23.90±4.37	0.253
Height (cm)	172.17±5.03	172.85±4.18	0.636
Weight (kg)	63.94±7.77	65.69±5.13	0.167
BMI (kg/m^2)	21.66±3.09	22.07±2.12	0.416
Smoking			0.238
1	11 (15.3)	14 (27.45)	
2	44 (61.1)	28 (54.9)	
3	17 (23.6)	9 (17.65)	
Alcohol consumption			0.894
1	12 (16.7)	9 (17.65)	
2	3 (4.2)	3 (5.9)	
3	57 (79.17)	39 (76.5)	

Age and BMI are presented as the means ± standard deviations. High altitude exposure, smoking and alcohol consumption are expressed as numbers (percentages). BMI, body mass index; 1 = no smoking/drinking history, 2 = currently smoking/drinking and 3 = past smoking/drinking history.

Table 3. Comparison of DO_2, DO_2C and compensatory factors between the AMS group and the non-AMS group at 3700 m

Items	AMS group (n = 72)	Non-AMS group (n = 51)
Physiological parameters		
LLS score	4.45±1.54**	1.73±0.49
SaO_2 (%)	88.05±2.48**	90.72±2.18
HR (beats/min)	85.62±8.72**	75.88±8.46
SBP (mmHg)	119.61±9.74	123.31±11.70
DBP (mmHg)	80.13±7.02	80.71±11.32
MBP (mmHg)	91.21±1.04	88. 96±1.22
EP (ng/ml)	10.96±2.12*	9.62±2.69
NE (ng/ml)	148.26±12.01*	143.49±10.94
Cardiovascular system		
DO_2 (ml/min)	1009.53±21.24**	906.22±24.05
mPAP (mmHg)	24.31±2.83	24.03±2.13
CO (L/min)	5.54±1.10**	4.96±1.05
QT (ms)	373.14±20.64*	389.96±31.87
QTc (ms)	418.63±24.91*	401.57±23.97
V3TpTe (ms)	75.19±8.03*	78.80±8.38
V3TpTec (ms)	90.63±10.05*	86.35±10.52
CFB		
DO_2C (units)	58.31±1.31	55.47±1.36
MCAv (cm/s)	66.31±1.32**	63.37±2.33
R_{MCA} (units)	1.32±0.03*	1.44±0.03

Normally distributed data are presented as the means ± SDs. *P < 0.05, **P < 0.01, AMS group vs. non-AMS group at 3700 m.

protocols. Additional blood samples (2 ml) were centrifuged at 4000 r/min for 10 min to separate serum and were stored at -80°C until analyzed. The concentrations of blood biochemical indices, including epinephrine and norepinephrine, were measured with a fully automated biochemistry analyzer (Olympus Au2700, Japan) at Xinqiao Hospital.

Statistical analysis

Results are presented as the means ± standard deviations (SD). Statistical analyses were performed using SPSS software (version 18.0, IBM Corporation, Armonk, New York, USA). Differences in physiological parameters between 500 m and 3700 m were analyzed using paired-sample t-tests. Independent t-tests were used to compare the normally distributed variables between the AMS group and the non-AMS group at 3700 m. The Mann-Whitney U test was applied to evaluate differences between ordinal or non-normally distributed data. Stepwise binary logistic regression analysis and correlation analysis was performed to identify the relationship between the DO_2 compensatory factors and the LLS. $P < 0.05$ was considered to be statistically significant.

Results

Analysis of the demographic data

The demographic data for 123 analyzed subjects were collected in the study. The mean age of the subjects was 23.77±4.59 years of age, the mean height was 172.16±4.82 cm, and the mean BMI was 21.54±2.04 kg/m^2. The percentage of participants who smoked or drank was 79.67% (98/123) or 82.9% (102/123), respectively. In the present study, the incidence of AMS after acute exposure to 3700 m was 58.5% (72/123), in which mild AMS accounted for 45.52% (56/123) and severe AMS accounted for 13.0% (16/123) (**Figure 1A**). Based on the LLS, the incidences of AMS symptoms including headache, weakness or dizziness, gastrointestinal symptoms, insomnia,

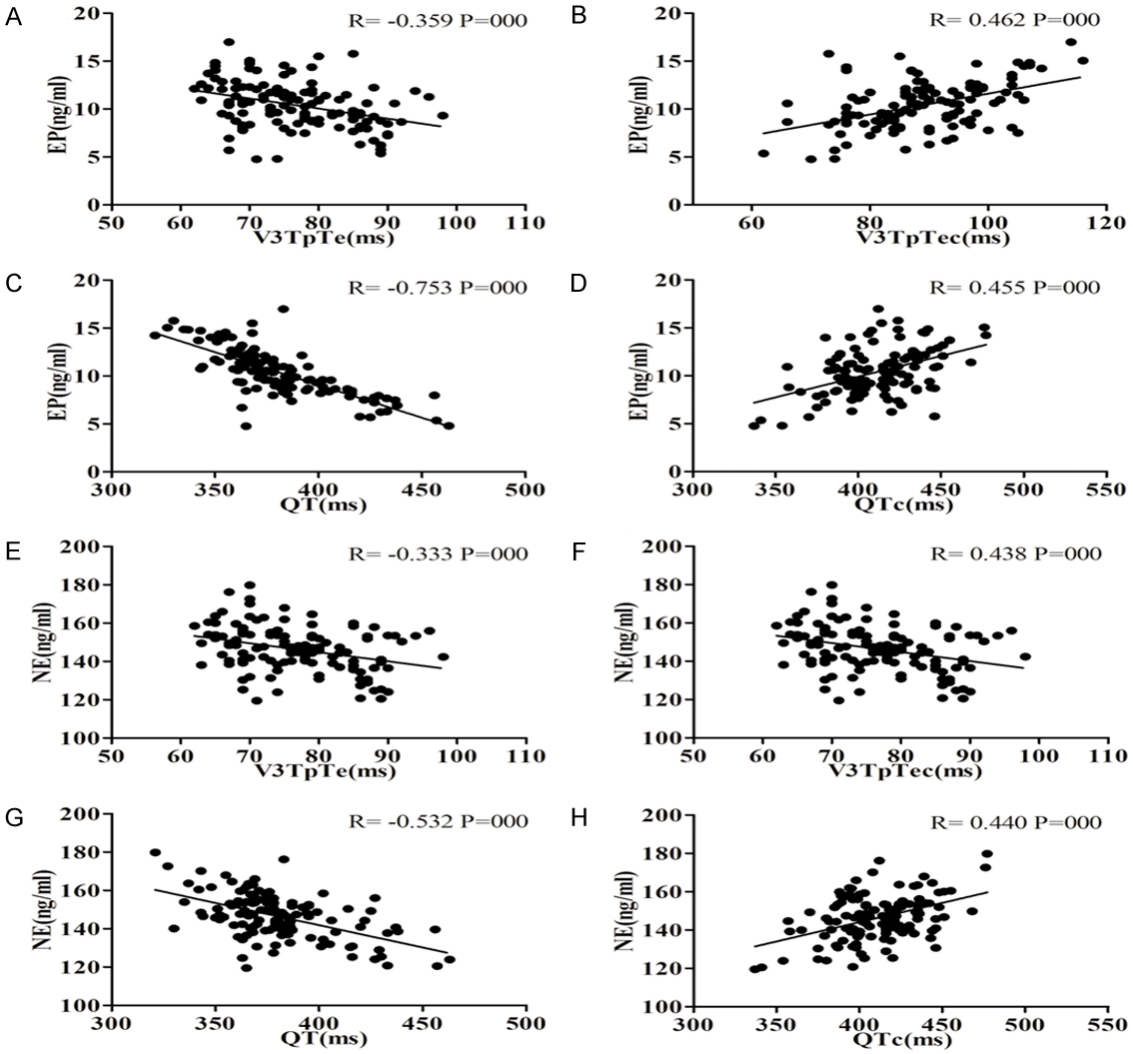

Figure 3. The correlation between neurotransmitters and ventricular repolarization changes after acute exposure to 3700 m. A: V3TpTe (P = 0.000); B: V3TpTec (P = 0.000); C: QT (P = 0.000); D: QTc (P = 0.000). E: V3TpTe (P = 0.0000); F: V3TpTec (P = 0.000); G: QT (P = 0.000); H: QTc (P = 0.000).

and lassitude or fatigue were 72.36%, 74.80%, 16.26%, 61.79%, and 73.17%, respectively (**Figure 1B**).

Comparison of DO_2, DO_2C and the compensatory factors between 500 m and 3700 m

The changes in DO_2, DO_2C and the compensatory factors after exposure to 3700 m are shown in **Table 1**. The SaO_2 level was significantly lower at 3700 m than at 500 m ($P < 0.01$), while the HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MBP), epinephrine (EP) level, and norepinephrine (NE) level were increased significantly (all *P*-values < 0.01) at 3700 m compared with 500 m. However, no significant difference in the Hb values was found between 500 m and 3700 m.

As shown in **Table 1**, the levels of DO_2 and CO increased 18.4% and 32.5% from 500 m to 3700 m (all *P*-values < 0.01), respectively. However, no significant difference in SV was found between 500 m and 3700 m. Additionally, the values of RV-Tei ($P < 0.01$), mPAP ($P < 0.01$), and EF ($P < 0.05$) increased sharply, while RA ($P < 0.05$), RV ($P < 0.05$) and ET ($P < 0.01$) decreased significantly from 500 m to 3700 m. The values of the electrocardiographic parameters QT and V3TpTe were significantly lower ($P < 0.01$, respectively), while QTc ($P < 0.01$) and V3TpTec ($P < 0.01$) were significantly

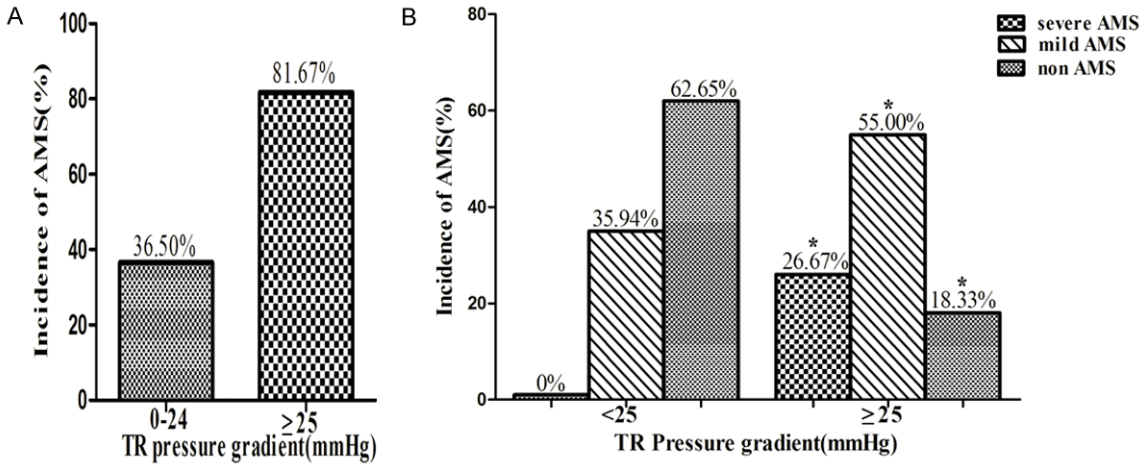

Figure 4. Tricuspid regurgitation (TR) pressure gradient and incidence of AMS after acute exposure to 3700 m. A: Incidences of AMS in subject with different TR pressure gradients; B: Different incidences of the severity AMS in subjects with different TR pressure gradients. *P < 0.05.

Table 4. Relationship between LLS score and DO_2 and compensatory factors at 3700 m

Parameters	Spearman r	*P*-value
DO_2	0.812	0.000
CO	0.273	0.002
HR	0.569	0.000
SaO_2	-0.393	0.000
EP	0.263	0.003
NE	0.219	0.015
MCAv	0.535	0.000
RMCA	-0.763	0.000
TR pressure	0.669	0.000
QT	-0.238	0.008
QTc	0.225	0.012
V3TpTe	-0.237	0.008
V3TpTec	0.196	0.030

higher at 3700 m compared with 500 m. However, other parameters had no significant differences between 500 m and 3700 m (**Table 1**). Although the change of DO_2C was not statistically significant, the MCAv (P < 0.01) increased 12% and the R_{MCA} (P < 0.01) decreased significantly from 500 m to 3700 m (**Table 1**).

We also investigated parameters related to tricuspid regurgitation (TR), and found that the subjects with acute exposure to 3700 m had significantly higher values of TR pressure (P < 0.01) (**Figure 2D**) and maximum TR velocity (P < 0.01) (**Figure 2E**). However, no significant change in TR area was found between 500 m and 3700 m (**Figure 2C**).

Comparison of demographic characteristics between the AMS and non-AMS groups after acute exposure to 3700 m

Among the 123 participants, 72 were diagnosed as suffering with AMS after acute exposure to 3700 m. No significant differences in demographic data, including age, height, BMI, smoking and alcohol consumption, were found between the groups (**Table 2**).

Differences in DO_2 and DO_2C characteristics between the AMS group and the non-AMS group

After acute exposure to 3700 m, the AMS group experienced significantly lower SaO_2 (P < 0.01) and higher HR (P < 0.01), EP (P < 0.05), and NE (P < 0.05) compared to the non-AMS group; no significant differences were detected in SBP, DBP, and MBP (all *P*-values > 0.05) (**Table 3**). In the cardiovascular system, no significant difference was detected in mPAP (P > 0.05). However, the variations in DO_2 and CO (all *P*-values < 0.01), and electrocardiographic parameters including QT, QTc, V3TpTe, V3TpTec, TR pressure and maximum TR velocity (all *P*-values < 0.05) in the AMS subjects were significantly different from the non-AMS subjects (**Table 3**; **Figure 2A** and **2B**). Additionally, EP was negatively correlated with V3TpTe (P = 0.000) (**Figure 3A**) and QT (P = 0.000) (**Figure 3C**) and positively correlated with V3TpTec (P = 0.000) (**Figure 3B**) and QTc (P = 0.000) (**Figure 3D**). NE was negatively correlated with V3TpTe (P = 0.000) (**Figure 3E**)

Table 5. Logistic regression analysis of the DO_2 compensatory factors associated with AMS

Factors	Odds ratio (OR)	95% CI	*P*-value
a: HR ≥ 85/min	3.231	1.069-9.771	0.038
b: MCAv ≥ 66 cm/s	3.248	1.128-9.347	0.029
c: TR pressure ≥ 25 mmHg	3.566	1.158-10.978	0.027
d: SaO_2 (%) ≤ 88	8.271	2.87-23.818	0.000

and QT (P = 0.042) (**Figure 3G**) and positively correlated with V3TpTec (P = 0.000) (**Figure 3F**) and QTc (P = 0.000) (**Figure 3H**). When we compared the tricuspid regurgitation conditions between the two groups, we found that the incidence of AMS reached 81.67% in the subjects with TR pressure great than or equal to 25 mmHg, which was much higher than the 36.50% observed in the subjects with TR pressure between 0 and 24 mmHg (all *P*-values < 0.05) (**Figure 4A**). Furthermore, the subjects who suffered from severe AMS or mild AMS accounted for 26.67% and 55.00% of those with TR pressure great than or equal to 25 mmHg, respectively, while the subjects with severe AMS or mild AMS accounted for 0% and 35.94% of those with TR pressure between 0 and 25 mmHg, respectively (all *P*-values < 0.05) (**Figure 4B**). The AMS subjects had significant differences in MCAv and R_{MCA} compared with the non-AMS subjects (all *P*-values < 0.05) at 3700 m. However, there was no significant difference in DO_2C between the groups (P > 0.05) (**Table 3**).

The relationships among the DO_2 alterations, the compensatory factors, and the LLS at 3700 m

The relationships among the alterations in DO_2, the compensatory factors, and the LLS were assessed by correlation analysis. The changes in DO_2, CO, HR, EP, NE, MCAv, TR pressure, QTc and V3TpTec significantly positively correlated with the LLS (P = 0.000, 0.002, 0.000, 0.003, 0.015, 0.000, 0.000, 0.012 and 0.030, respectively), while the level of SaO_2, RMCA, QT, and V3TpTe were significantly negatively (P = 0.000, 0.000, 0.008 and 0.008, respectively) associated with the LLS (**Table 4**).

The indicators for diagnostic analysis of AMS

Analysis by logistic regression (The mean value of HR, TR, SaO_2 and MCAv in AMS group was using used as the standard) revealed that the following factors were risk factors for AMS: HR (≥ 85/min), MCAv (≥ 66 cm/s), SaO_2 (≤ 88%) and TR pressure (≥ 25 mmHg). As shown in **Table 5**, the possibility of AMS occurrence in subjects with HR ≥ 85/min, MCAv ≥ 66 cm/s, SaO_2 (≤ 88%) or TR pressure ≥ 25 mmHg was 3.23 times, 3.25 times, 3.47 times or 8.27 times greater than in subjects with HR < 85/min, MCAv < 66 cm/s, SaO_2 > 88% or TR pressure < 25 mmHg, respectively. Finally, we analyzed whether these factors could be used as indicators for AMS diagnosis. To some degree, HR ≥ 85/min, MCAv ≥ 66 cm/s, SaO_2 ≤ 88% or TR pressure ≥ 25 could be used to assess AMS, with positive predictive values of 82.25%, 79.36%, 85.24% and 83.63%, respectively. Combining the three factors improved AMS diagnostic accuracy, with a positive predictive value of 97.87% and specificity of 98.04% (**Table 6**).

Discussion

Currently, millions of people rapidly traveling to or working at high altitudes may suffer from AMS, resulting in a negative impact on quality of life and work efficiency, severe cases may progress to fatal high altitude pulmonary edema and brain edema [24-26]. AMS has been recognized over the past two centuries. However, little is known about the pathogenesis of AMS symptoms [26, 27] and no objective diagnostic methods exist.

After acute exposure to high altitudes, there is a decrease in SaO_2 due to hypoxia, followed by a variety of pathophysiological changes. Severe cases may lead to the risk of pulmonary edema and even life threating [3, 7, 11, 12]. Therefore, it is important to study DO_2 and the compensatory factors. Previous studies have indicated that cardiovascular DO_2 level remains unchanged after hypoxia exposure [3, 28]. But, in the present study, the cardiovascular DO_2 was elevated by 18.4% after acute exposure from 500 to 3700 meters of altitude. The main reason for the inconsistent results may be come from the difference between simulated hypoxia environment and the real existence of hypobaric and hypoxia environment, and also the measuring time differences [3, 28]. In this study we

Table 6. Diagnostic analysis of AMS by HR, MCA_v, and TR pressure

Factors	AMS (case)	non-AMS (case)	Total (case)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
a: HR ≥ 85/min				69.44	76.47	82.25	76.47
Yes	50	12	62				
No	22	39	61				
b: MCAv ≥ 66 cm/s				69.44	74.50	79.36	63.33
Yes	50	13	63				
No	22	38	60				
c: TR pressure ≥ 25 mmHg				72.22	82.35	85.24	67.74
Yes	52	9	61				
No	20	42	62				
d: SaO_2 (%) ≤ 88				63.88	82.35	83.63	58.33
Yes	46	9	55				
No	26	42	72				
a+b+c+d				63.88	98.04	97.87	65.79
Yes	46	1	47				
No	26	50	76				

found DO_2 appeared to be a continuous adjustment related to an increase in the sympathetic levels induced by hypoxia [29]. Therefore, the CO, HR, SV and BP rates rose to compensate for the reduction in SaO_2 levels to ensure oxygen supply to the body [3, 11, 30]. Previous studies have found that acute hypoxia induced pulmonary vascular reactivity, and then caused a transient pulmonary hypertension and right ventricular diastolic function [11, 12, 13, 31]. In this study, the cardiopulmonary system also had a series of compensatory responses to the SaO_2 decrease. The results showed that mPAP was increased and the right heart diastolic diameter became smaller, indicating that the right ventricular (RV) diastolic function was decreased. Consequently, tricuspid transvalvular pressure was elevated, followed by a rise in TR pressure and velocity. However, the increase in the transvalvular pressure had no effect on the TR area. Tricuspid transvalvular reflux area is mainly determined by the expansion of the right heart [32]. In current situation, the structure of right heart has no significant change even exposure to acute hypoxia, while the right ventricular function decreased. Therefore, even if the TR pressure and velocity were significantly increased, the TR area was still normal after hypoxia. Ventricular repolarization changed significantly after acute exposure to 3700 meters of altitudes, consistent with the results of a previous study [33]. EP and NE were significantly correlated with the QT interval, QTc, TpTe, and TpTec, which indicated that sympathetic activation caused EP and NE participation in the ventricular repolarization process with the increasing altitude [34, 35]. For brain DO_2C and RMCA, the results showed a 12% elevation in MCAv, while a 12% reduction in SaO_2. Such compensation mechanism keeps the levels of DO_2C unchanged, which indicates precise cerebral adjustment to hypoxia [8, 15]. Moreover, the decrease of RMCA may be related to the expansion of cerebral blood vessel [8, 15].

In the current study, AMS incidence reached 58.5% among all subjects. In response to acute hypoxia, the participants with AMS had lower SaO_2 and higher HR, DO_2, CO, EP, and NE compared to the non-AMS subjects [3, 11-13]. Additionally, compared with the Non-AMS group, QTc and TpTec interval were significantly prolonged, but QT and TpTe interval were significantly shortened in AMS group [34, 35]. This change could be induced by sympathetic activation responses to the SaO_2 decrease [3, 11-13]. The increase in HR served as an independent risk factor for AMS occurrence, which may be related to the physiological adaptation to SaO_2 decrease [36, 37]. Higher HR induced by sympathetic activation in the subjects with AMS can also prolong the time course of HR-corrected ventricular repolarization. Although no significant difference in mPAP was found between the AMS group and the non-AMS group, the incidence and the severity of

AMS were significantly higher in the subjects with TR pressure above 25 mmHg compared to subjects with TR pressure below 25 mmHg, which indicated that increased mPAP may not be the only initial factor to trigger and aggravate TR. Decreased SaO_2 can also initiate TR by affecting the tricuspid valve annulus and papillary muscles function [3, 11-13]. No changes of DO_2C were found between AMS and non-AMS groups except for the higher MCAv and lower RMCA in AMS group which suggested that the AMS group should increases the cerebral blood flow and the expansion of cerebral blood vessels to maintain the level of DO_2C [8, 15]. Therefore, increases in HR, CO, TR pressure, ventricular repolarization and MCAv in combination with sympathetic nerve participation compensated for SaO_2 reduction. Thus, AMS may occur if the response exceeds the threshold for compensation.

Finally, we confirmed DO_2, CO, HR, MCAv, EP, NE QTc, V3TpTec and TR pressure were significantly positively correlated with the LLS, while SaO_2, RMCA, QT, and V3TpTe were significantly negatively correlated with the LLS. As previously reported, HR and SaO_2 served as an independent risk factor for AMS [36-38]. But, in this study, we found HR (≥ 85/min), MCAv (≥ 66 cm/s), SaO_2 (≤ 88%) and TR pressure (≥ 25 mmHg) served as an independent risk factor for AMS occurrence, Separately. When combined, the use of the compensatory factors of DO_2 (HR ≥ 85/min, MCAv ≥ 66 cm/s, SaO_2 ≤ 88% and TR pressure ≥ 25 mmHg) to diagnose AMS resulted in a positive predictive value and specificity of 97.87% and 98.04%, respectively. The assessment method combined with HR, MCAv, SaO_2 and TR can be used as auxiliary objective indicators to diagnose AMS. In the future, we will further explore more sensitive objective indicators for AMS diagnosis.

Conclusions

HR (≥ 85/min), MCAv (≥ 66 cm/s), SaO_2 (≤ 88%) and TR pressure (≥ 25 mmHg) are the key compensatory factors for DO_2 (oxygen delivery) and may play a key role in the physiological responses involved in the acclimatization to acute hypoxia. These factors may be related to the mechanism of AMS development and can be used as objective indicators for AMS diagnosis.

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Disclosure of conflict of interest

None.

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