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ORIGINAL ARTICLE

Early Warning of Acute Altitude Sickness by Physiological Variables and Noninvasive Cardiovascular Indicators

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Key words: acute altitude sickness; physiological variables; noninvasive cardiovascular indicators; acute high altitude exposure; early warning

Objective To examine if the variations at sea level would be able to predict subsequent susceptibility to acute altitude sickness in subjects upon a rapid ascent to high altitude.

Methods One hundred and six Han nationality male individuals were recruited to this research. Dynamic electrocardiogram, treadmill exercise test, echocardiography, routine blood examination and biochemical analysis were performed when subjects at sea level and entering the plateau respectively. Then multiple regression analysis was performed to construct a multiple linear regression equation using the Lake Louise Score as dependent variable to predict the risk factors at sea level related to acute mountain sickness (AMS).

Results Approximately 49.05% of the individuals developed AMS. The tricuspid annular plane systolic excursion (22.0±2.66 *vs*. 23.2±3.19 mm, t=1.998, P=0.048) was significantly lower in the AMS group at sea level, while count of eosinophil [(0.264±0.393)×10^9/L *vs*. (0.126±0.084)×10^9/L, t=-2.040, P=0.045], percentage of differences exceeding 50 ms between adjacent normal number of intervals (PNN50, 9.66%±5.40% *vs*. 6.98%±5.66%, t=-2.229, P=0.028) and heart rate variability triangle index (57.1±16.1 *vs*. 50.6±12.7, t=-2.271, P=0.025) were significantly higher. After acute exposure to high altitude, C-reactive protein (0.098±0.103 *vs*. 0.062±0.045 g/L, t=-2.132, P=0.037), aspartate aminotransferase (19.7±6.72 *vs*. 17.3±3.95 U/L, t=-2.231, P=0.028) and creatinine (85.1±12.9 *vs*. 77.7±11.2 mmol/L, t=-3.162, P=0.002) were significantly higher in the AMS group, while alkaline phosphatase (71.7±18.2 *vs*. 80.6±20.2 U/L, t=2.389, P=0.019), standard deviation of normal-to-normal RR intervals (126.5±35.9 *vs*. 143.3±36.4 ms, t=2.320, P=0.022), ejection time (276.9±50.8 *vs*. 313.8±48.9 ms, t=3.641, P=0.001) and heart rate variability triangle index (37.1±12.9 *vs*. 41.9±11.1, t=2.020, P=0.047) were significantly lower. Using the

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Lake Louise Score as the dependent variable, prediction equation were established to estimate AMS: Lake Louise Score=3.783+0.281×eosinophil−0.219×alkaline phosphatase+0.032×PNN50.

Conclusions We elucidated the differences of physiological variables as well as noninvasive cardiovascular indicators for subjects after high altitude exposure compared with those at sea level. We also created an acute high altitude reaction early warning equation based on the physiological variables and noninvasive cardiovascular indicators at sea level.

WHEN individuals rapidly ascend from the plains to the plateau, or to the higher altitude area from the plateau, they almost always suffer from varying degrees of headache, dizziness, fatigue, nausea, vomiting, palpitation, shortness of breath and other symptoms which are generally known as acute mountain sickness (AMS). Following the expansion of railway and air travel in Qinghai and Tibet, increasing numbers of people travel to high altitudes for work or recreation, such as mining, tourism, trekking and deployment. AMS has become a major public health problem.[1, 2] The etiology of AMS is not well understood because it is a multifactorial condition.[3, 4]

In order to prevent the occurrence and development of AMS, researchers tried to prevent the high altitude reaction with various drugs, but the verify of the effectiveness of these drugs is mainly based on animal experiments as well as the individual's self-perception of the relief of symptoms.[5-8] What we are lacking is the effective, objective and repeatable index, especially the objective and quantitative indexes which can be used to warn the occurrence and progression of AMS at sea level.

Early recognition of susceptible individuals through measurement of biological indicators at sea level may provide a useful screening tool for the expedition doctor who may want to consider targeted pharmacological prophylaxis and thus prevent AMS at high altitude. In the present study, we aimed to find out the biological variations at sea level that can predict subsequent susceptibility to AMS of individuals who ascent to high altitude rapidly.

SUBJECTS AND METHODS

Ethics statement

This study has been approved by the Institutional Review Board (IRB) of the Chinese PLA General Hospital, Beijing, China. The IRB approved number is "S2014-070-01". The individuals in this manuscript gave written informed consents and a verbal explanation concerning the study prior to obtaining the written informed consent for their participation.

Participants

We included 106 Chinese male adults who aged 18 to 35 years and resided principally at an elevation of 250 m or lower. Enrollment of volunteers took place from Jan 2016 through Apr 2016. Recruitment was restricted to the individuals who had not altitude exposure above 2500 m previously. We excluded those who had history of primary headache, any causes of vomiting, chronic obstructive pulmonary disease, heart failure, cerebral neoplasm, and who were taking medicine to promote blood circulation and increase immunity and anti-oxidant capacity.

Study design

Baseline assessment including treadmill exercise test, blood gas analysis, dynamic electrocardiogram, ambulatory blood pressure monitoring, routine blood test and blood biochemical analysis was made at sea level (50 m).

The subjects began a 28-hour journey by train from Beijing to Geermu, Qinghai Province (2800 m). Holter monitoring and ambulatory blood pressure monitoring were recorded when the volunteers arrived at 2800 m. They rested 10 hours for sleep and overnight then they were transported by bus from the altitude of 2800 m to 4000 m within 2 hours. Holter monitoring and ambulatory blood pressure monitoring were removed just before the treadmill exercise test. Blood gas analysis was checked immediately after the treadmill exercise test. Venous blood was collected for routine blood test and blood biochemical analysis before the subjects descended from the high altitude.

Primary outcome measure was incidence of AMS at altitude. AMS was diagnosed according to Lake Louise Score (LLS), which includes 5 self-reporting symptoms: headache, gastrointestinal symptoms, fatigue/weakness, dizziness/lightheadedness, and difficulty in sleeping. Each symptom is scored 0-3, with 0 indicating none and 1-3 indicating mild, moderate, and severe, respectively. AMS is defined by a total score of 3 or more in the presence of headache.

Statistical analysis

Statistical analysis was performed with SPSS Statistics (IBM, USA). Quantitative variables were tested for standard normal distribution by the Lilliefors test and for homogeneity of variances by the Bartlett test, and expressed as mean values±SD unless otherwise stated. Differences of normal distributing data between the AMS and non-AMS groups were analyzed with Student's *t*-test. When data were not normally distributed or variances were not sufficiently homogeneous, corresponding nonparametric tests were used as indicated when data of such analysis are presented. Qualitative variables were reported as number (percent).

Multiple regression analysis was performed by starting with a model that included all potential predictors as independent variables, followed by stepwise elimination of variables that did not contribute significantly to the overall variance of the model, using the Lake Louise Score as dependent variable. All tests were 2-tailed. Differences were considered statistically significant if $P<0.05$.

RESULTS

Physiological variables at sea level and at high altitude in subjects with AMS and without AMS

Approximately 49.05% of the individuals developed AMS. As shown in **Table 1**, count of eosinophil was significantly higher in the AMS group compared with the non-AMS group ($t=-2.040$, $P=0.045$) at sea level.

After acute exposure to high altitude, C-reactive protein ($t=-2.132$, $P=0.037$), aspartate aminotransferase ($t=-2.231$, $P=0.028$) and creatinine ($t=-3.162$, $P=0.002$) were significantly higher in the AMS group compared with the non-AMS group, while alkaline phosphatase ($t=2.389$, $P=0.019$) was significantly lower in the AMS group compared with the non-AMS group.

Noninvasive cardiovascular indicators in subjects with AMS and without AMS at sea level and at high altitude

As shown in **Table 2**, the percentage of differences exceeding 50 ms between adjacent normal number of intervals (PNN50) ($t=-2.229$, $P=0.028$) and heart rate variability (HRV) triangle index ($t=-2.271$, $P=0.025$) were significantly higher in the AMS group at sea level compared with the non-AMS group, while the tricuspid annular plane systolic excursion (TAPSE) ($t=1.998$, $P=0.048$) were significantly lower in the AMS group compared with the non-AMS group.

After acute exposure to high altitude, the standard deviation of normal-to-normal RR intervals (SDNN) ($t=2.320$, $P=0.022$), ejection time (ET) ($t=3.641$, $P=0.001$) and HRV triangle index ($t=2.020$, $P=0.047$) significantly lower in the AMS group compared with non-AMS group.

Multiple regression model for predicting the risk factors at sea level related to AMS

We also investigated the affecting factors at sea level which associated with the LLS after high altitude exposure using multiple regression analysis (**Table 3**). Multiple regression analysis initially included the variables which were significantly differences between the AMS and non-AMS groups. Using the change of LLS as the dependent variable, count of eosinophil was entered in step 1 ($\beta=5.038$, $R^2=0.066$, $P=0.010$), alkaline phosphatase was entered in step 2 ($\beta=-0.033$, $R^2=0.042$, $P=0.043$), and PNN50 was entered in step 3 ($\beta=0.088$, $R^2=0.032$, $P=0.089$). These variables accounted for 14 percent of the change of LLS when individuals quickly reached the plateau ($F=4.280$, $P=0.007$). The prediction equation was as following: Lake Louise Score=3.783+0.281×eosinophil–0.219×alkaline phosphatase+0.032×PNN50.

DISCUSSION

Acute high altitude sickness is a hitherto unsolved problem, affecting the individuals who long inhabited in the plains quickly reached the plateau.[9-11] In the present study, approximately 49.05% of the individuals developed AMS. We analyzed the differences of physiological variables and noninvasive cardiovascular indicators at sea level and after high altitude exposure between volunteers with or without acute high altitude reaction. The count of eosinophil and TAPSE were significantly lower in the AMS group at sea level, while PNN50 and HRV triangle index were significantly higher. Serum eosinophil, alkaline phosphatase and PNN50 at sea level were the variables that were represented in the logistic regression model which may predict subsequent susceptibility to AMS of individuals upon a rapid ascent to high altitude.

Eosinophils, sometimes called eosinophiles, are a variety of white blood cells and one of the immune system components. At altitude, hypoxia prolongs the viability of eosinophils while increasing the eosinophllic production of vascular endothelial growth factor and other

Table 1. Physiological variables in healthy subjects at sea level and at high altitude[§]

Variables	AMS (−) (*n*=54)	AMS (+) (*n*=52)	*t* value	*P* value
Blood routine tests				
Red blood cell (10^9/L)				
Sea level	5.16±0.36	5.25±0.38	-1.216	0.227
Altitude	5.21±0.36	5.21±0.78	-0.041	0.967
Hemoglobin (g/L)				
Sea level	155.4±8.89	157.9±9.05	-1.396	0.166
Altitude	161.4±8.63	163.6±8.19	-1.341	0.183
Platelet (10^9/L)				
Sea level	227.6±48.8	222.6±37.6	0.578	0.565
Altitude	231.3±45.6	220.8±47.1	1.152	0.252
White blood cell (10^9/L)				
Sea level	6.58±1.72	6.73±1.69	-0.422	0.674
Altitude	8.07±1.72	8.21±2.37	-0.352	0.726
Hematocrit (%)				
Sea level	46.3±2.61	47.1±2.65	-1.579	0.118
Altitude	47.8±2.53	47.3±6.82	-0.928	0.356
Eosinophil (10^9/L)				
Sea level	0.126±0.084	0.264±0.393	-2.040	0.045[#]
Altitude	0.126±0.090	0.115±0.098	0.610	0.543
Blood biochemistry				
Potassium (mmol/L)				
Sea level	4.13±0.30	4.11±0.30	0.317	0.752
Altitude	4.08±0.33	4.16±0.33	-1.315	0.191
Magnesium (mmol/L)				
Sea level	0.88±0.05	0.88±0.05	0.000	1.000
Altitude	0.85±0.04	0.85±0.06	0.677	0.500
Chlorine (mmol/L)				
Sea level	99.8±2.81	98.8±2.40	1.855	0.067
Altitude	102.7±1.66	102.4±1.89	0.661	0.510
C-reactive protein (g/L)				
Sea level	0.109±0.082	0.109±0.053	-0.030	0.976
Altitude	0.062±0.045	0.098±0.103	-2.132	0.037[*]
Creatinine (mmol/L)				
Sea level	77.2±9.53	77.4±9.53	-0.093	0.926
Altitude	77.7±11.2	85.1±12.9	-3.162	0.002[*]
Uric acid (mmol/L)				
Sea level	345.4±64.4	361.4±65.9	-1.254	0.213
Altitude	346.3±65.3	369.0±92.7	-1.453	0.149
Alkaline phosphatase (U/L)				
Sea level	70.7±19.7	66.5±13.7	1.288	0.201
Altitude	80.6±20.2	71.7±18.2	2.389	0.019[*]
Lactate dehydrogenase (U/L)				
Sea level	189.1±54.4	179.8±27.2	1.104	0.272
Altitude	188.1±43.9	176.5±24.9	1.685	0.095
Aspartate aminotransferase (U/L)				
Sea level	17.6±5.37	19.8±6.74	-1.858	0.066
Altitude	17.3±3.95	19.7±6.72	-2.231	0.028[*]
Glucose (mmol/L)				
Sea level	4.93±0.44	4.87±0.41	0.526	0.600
Altitude	5.43±0.57	5.59±0.83	-1.098	0.275

§: Plus-minus values are means±SD.

AMS: acute mountain sickness.

[#]The AMS (+) group *vs*. AMS (−) group at sea level; [*]The AMS (+) group *vs*. AMS (−) group at high altitude.

Table 2. Noninvasive cardiovascular indicators at sea level and at high altitude between the two groups[§]

Variables	AMS (−) (*n*=54)	AMS (+) (*n*=52)	*t* value	*P* value
Holter monitoring				
Mean heart rate (beats/min)				
Sea level	70.8±9.20	72.0±8.11	-0.719	0.474
Altitude	79.2±8.83	81.1±9.37	-1.068	0.288
PNN50 (%)				
Sea level	6.98±5.66	9.66±5.40	-2.229	0.028[#]
Altitude	5.33±4.36	5.10±5.01	0.269	0.788
SDSD (ms)				
Sea level	50.6±20.7	55.5±20.5	-1.179	0.241
Altitude	47.6±33.9	43.6±24.6	0.680	0.498
SDNN (ms)				
Sea level	167.3±35.4	169.8±35.3	-0.361	0.719
Altitude	143.3±36.4	126.5±35.9	2.320	0.022[*]
HRV Triangle Index				
Sea level	50.6±12.7	57.1±16.1	-2.271	0.025[#]
Altitude	41.9±11.1	37.1±12.9	2.020	0.047[*]
Treadmill tests				
Exercise time (min)				
Sea level	514.2±94.7	488.8±56.1	1.389	0.170
Altitude	428.6±69.1	431.4±59.5	-0.218	0.828
Mets				
Sea level	10.1±0.23	10.0±0.42	0.630	0.531
Altitude	9.21±1.59	9.20±1.18	0.028	0.977
Pre-exercise heart rate (beats/min)				
Sea level	85.9±14.8	84.0±15.6	0.532	0.596
Altitude	90.2±13.5	95.0±13.1	-1.836	0.069
Post-exercise heart rate (beats/min)				
Sea level	129.6±23.5	130.2±22.7	-0.122	0.903
Altitude	139.6±17.2	142.7±15.3	-0.988	0.326
Echocardiogram				
Pulmonary systolic blood pressure (mm Hg)				
Sea level	21.7±7.01	20.1±7.12	1.146	0.255
Altitude	20.6±9.82	20.8±9.71	-0.083	0.934
Ejection time (ms)				
Sea level	289.8±45.1	279.8±42.9	1.134	0.259
Altitude	313.8±48.9	276.9±50.8	3.641	0.001[*]
TAPSE (mm)				
Sea level	23.2±3.19	22.0±2.66	1.998	0.048[#]
Altitude	22.8±3.24	22.6±3.73	0.316	0.753

§: Plus-minus values are means±SD.

PNN50 represents as percentage of differences exceeding 50 ms between adjacent normal number of intervals; SDSD represents as standard deviation of the length difference between adjacent NN intervals; SDNN represents as the standard deviation of NN intervals; HRV represents as heart rate variability; TAPSE represents as the tricuspid annular plane systolic excursion.

[#]The AMS (+) group *vs*. AMS (−) group at sea level; [*]The AMS (+) group *vs*. AMS (−) group at high altitude.

Table 3. Results of multiple regression analysis

Variables	Unstandardized coefficients		Standardized coefficients		
	β	Std. error	β	R^2	*P* value
Constant	3.783	1.165		0.140	0.002
Eosinophil	5.038	1.909	0.281	0.066	0.010
Alkaline phosphatase	−0.033	0.016	−0.219	0.042	0.043
PNN50	0.088	0.051	0.181	0.032	0.089

proinflammatory cytokines, such as prostaglandins and leukotrienes, which may promote the formation of new blood vessels and increase in conditions that are associated with decreased oxygen supply to tissues.[12-14]

HRV reflected the activity of cardiac autonomic nervous system. It can be used as a reliable index to study function of cardiac autonomic nervous system. It is also an important index to evaluate sympathetic nerve and parasympathetic nerve activities and their balance.[15-17] High altitude hypoxia environment is a kind of stress on human body. In HRV time domain analysis, PNN50 can be used as a sensitive index to evaluate parasympathetic nervous function. The individuals with higher autonomic activity and stronger response to stress have heavier symptom of AMS, which indicated that HRV can predict AMS in a certain extent.[18] This present study confirms that indexes of HRV such as HRV triangle index and PNN50 were indeed higher in the AMS group before rushing to high altitude.

Alkaline phosphatase is a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including nucleotides, proteins, and alkaloids. In humans, alkaline phosphatase is present in all tissues throughout the entire body, but is particularly concentrated in the liver, bile duct, kidney, bone, intestinal mucosa and placenta. Alkaline phosphatase affects inflammatory responses and may play a direct role in preventing organ damage. Previous study has shown that lower level of alkaline phosphatase was associated with the development of high altitude pulmonary edema.[19] In the present study, we found that after acute exposure to high altitude alkaline phosphatase was significantly lower in the AMS group. TAPSE responds to right ventricular longitudinal motion and is a quantitative indicator of right ventricular systolic function. TAPSE decreased significantly after rapid entry to high altitude, and the degree of decline was consistent with that of right ventricular function.[20]

After acute exposure to high altitude, C-reactive protein, aspartate aminotransferase and creatinine were significantly higher in the AMS group, while SDNN, ejection time and HRV triangle index were significantly lower.

In the plain, the sympathetic and parasympathetic nerves of autonomic nervous system are relatively balanced, which ensures relative stability and strain capacity of heart rate. However, the balance of autonomic nervous system will be changed from adaptive regulation to state of hypobaric hypoxia.[21] SDNN reflects the overall situation of heart rate variability, and can be used to evaluate autonomic nervous regulation function. The reduction of SDNN and HRV triangle index reflected the results that sympathetic nerve excitability increased and cardiac function decreased after rapid entry to high altitude, consistent with the decrease in ejection fraction.

Previous study has shown that renal function declined when ascending from low to high altitude.[22] Serum creatinine is an byproduct of muscle metabolism that is excreted unchanged by the kidneys, meanwhile it is important indicator of renal health because it easily measured. Creatinine is removed from blood chiefly by the kidneys and it is the most commonly used indicator of renal function. C-reactive protein is used mainly as a marker of inflammation and elevated basal levels of C-reactive protein indicate an increased risk of cardiovascular disease. The level of aspartate aminotransferasere is commonly measured clinically as biomarkers for liver health. The increase of C-reactive protein, aspartate aminotransferase and creatinine upon acute exposure to high altitude indicated that the volunteers in the AMS group suffered from heart, liver and kidney damages.

In summary, the present study confirmed that some of the physiological variables and noninvasive cardiovascular indicators were different at sea level and after high altitude exposure between volunteers with and without AMS. Using the Lake Louise Score as the dependent variable and the variables which were significantly differences between the AMS and non-AMS groups as the independent variable, prediction equation to estimate AMS were established. The equation may help us to

identify people prone to AMS in plains, therefore they can avoid travelling to high altitude district, climb a mountain slowly, or use pharmacological prophylaxis so as to prevent AMS. The disadvantage of the present study is that the equation is not validated in large population and we will validate this equation in future research.

Conflict of Interests Statement

The authors declare no conflict of interests.

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