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 variation at sea level would predict subsequent susceptibility to acute altitude sickness upon a rapid ascent to high altitude.

Methods One hundred and six Han nationality male individuals were recruited to the research. Dynamic electrocardiogram, treadmill exercise test, echocardiography, blood routine examination and biochemical analysis were performed at sea level and entering the plateau. 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.

Results Approximately 49.05% of the individuals developed acute mountain sickness (AMS). The tricuspid annular plane systolic excursion (22.0±2.66 vs. 23.2±3.19 mm, \( t=1.998, P=0.027 \)) was significantly lower in the AMS group at sea level, while the count of eosinophil (0.264±0.393 vs. 0.126±0.084, \( t=-2.040, P=0.045 \)), the percentage of differences exceeding 50 ms between adjacent normal number of intervals (9.35±5.49 vs. 7.04±4.98 %, \( t=-2.229, P=0.027 \)) and heart rate variability triangle

Received April 29, 2019. Published online January 20, 2010

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This study was supported by National Science and Technology Major Projects for Major New Drugs Innovation and Development (2014ZX09J14102-02A), Special Topic on Military Health care (17bjz41), and National Natural Science Foundation of China (81170249 and 30700305).
index (57.1±16.1 vs. 50.6±12.7, t=-2.271, P=0.027) 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 the alkaline phosphatase (71.7±18.2 vs. 80.6±20.2 U/L, t=2.389, P=0.019), the 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 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 (percentage of differences exceeding 50 ms between adjacent normal number of intervals).

**Conclusions** We elucidated the difference of physiological variables and noninvasive cardiovascular indicators after high altitude exposure. We also created 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, the 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.\textsuperscript{[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 acute mountain sickness at sea level.

Early recognition of susceptible individuals through the 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 examine if the biological variation at sea level would predict subsequent susceptibility to AMS upon a rapid ascent to high altitude.

**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 were given written informed consents and a verbal explanation concerning the study prior to obtaining the written informed consent for their participation.

**Participants**

We included Chinese male adults aged 18 to 35 years who 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 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 were made at sea level (50 m).

The subjects begin 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 the 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 distributed data between the AMS and non-AMS groups were analyzed with Student’s t-test. When data were not normally...
distributed or variance was 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, with 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, the 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 the alkaline phosphatase \((t=2.389, P=0.019)\) was significantly lower in the AMS group compared with the non-AMS group.

**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         | Altitude          | t-value | p-value |
|--------------------------------|-------------------|-------------------|---------|---------|
| **White blood cell (10⁹/L)**   |                   |                   |         |         |
|                                | 227.6±48.8        | 222.6±37.6        | 0.578   | 0.565   |
|                                | 231.3±45.6        | 220.8±47.1        | 1.152   | 0.252   |
| **Hematocrit (%)**             |                   |                   |         |         |
|                                | 6.58±1.72         | 6.73±1.69         | -0.422  | 0.674   |
|                                | 8.07±1.72         | 8.21±2.37         | -0.352  | 0.726   |
| **Eosinophil (10⁹/L)**         |                   |                   |         |         |
|                                | 0.126±0.084       | 0.264±0.393       | -2.040  | 0.045*  |
|                                | 0.126±0.090       | 0.115±0.098       | 0.610   | 0.543   |
| **Blood biochemistry**         |                   |                   |         |         |
| **Potassium (mmol/L)**         |                   |                   |         |         |
|                                | 4.13±0.30         | 4.11±0.30         | 0.317   | 0.752   |
|                                | 4.08±0.33         | 4.16±0.33         | -1.315  | 0.191   |
| **Magnesium (mmol/L)**         |                   |                   |         |         |
|                                | 0.88±0.05         | 0.88±0.05         | 0.000   | 1.000   |
|                                | 0.85±0.04         | 0.85±0.06         | 0.677   | 0.500   |
| **Chlorine (mmol/L)**          |                   |                   |         |         |
|                                | 99.8±2.81         | 98.8±2.40         | 1.855   | 0.067   |
|                                | 102.7±1.66        | 102.4±1.89        | 0.661   | 0.510   |
| **C-reactive protein (g/L)**   |                   |                   |         |         |
|                                | 0.109±0.082       | 0.109±0.053       | -0.030  | 0.976   |
|                                | 0.062±0.045       | 0.098±0.103       | -2.132  | 0.037†  |
| **Creatinine (mmol/L)**        |                   |                   |         |         |
|                                | 77.2±9.53         | 77.4±9.53         | -0.093  | 0.926   |
|                                | 77.7±11.2         | 85.1±12.9         | -3.162  | 0.002†  |
| **Uric acid (mmol/L)**         |                   |                   |         |         |
|                                | 345.4±64.4        | 361.4±65.9        | -1.254  | 0.213   |
|                                | 346.3±65.3        | 369.0±92.7        | -1.453  | 0.149   |
| **Alkaline phosphatase (U/L)** |                   |                   |         |         |
|                                | 70.7±19.7         | 66.5±13.7         | 1.288   | 0.201   |
|                                | 80.6±20.2         | 71.7±18.2         | 2.389   | 0.019†  |
| **Lactate dehydrogenase (U/L)**|                   |                   |         |         |
|                                | 189.1±54.4        | 179.8±27.2        | 1.104   | 0.272   |
|                                | 188.1±43.9        | 176.5±24.9        | 1.685   | 0.095   |
| **Aspartate aminotransferase (U/L)**|               |                   |         |         |
|                                | 17.6±5.37         | 19.8±6.74         | -1.858  | 0.066   |
|                                | 17.3±3.95         | 19.7±6.72         | -2.231  | 0.028†  |
| **Glucose (mmol/L)**           |                   |                   |         |         |
|                                | 4.93±0.44         | 4.87±0.41         | 0.526   | 0.600   |
|                                | 5.43±0.57         | 5.59±0.83         | -1.098  | 0.275   |

§: Plus-minus values are means±SD.

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

**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) \((t=-2.229, P=0.027)\) and heart rate variability (HRV) triangle index \((t=-2.271, P=0.027)\) were significantly higher in the AMS group at sea level compared with the non-AMS group, while the tricuspid annular plane systolic excursion (TAPSE) \((t=1.998, P=0.027)\) 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.

**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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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 | Altitude |
|--------------|-----------|----------|
| 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.

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 the 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 ($\beta=-0.033, R^2=0.042, P=0.043$), 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=$3.783+0.281\times$Eosinophil$–0.219\times$Alkaline phosphatase$+0.032\times$PNN50.

Table 3. Results of multiple regression analysis

| Variables          | Unstandardized coefficients | Standardized coefficients |
|--------------------|-----------------------------|---------------------------|
|                    | $\beta$ | Std. error | $\beta$ | $R^2$ | $P$ 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     |

**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 difference 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 was 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 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 eosinophilic production of vascular endothelial growth factor and other proinflammatory cytokines, 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.\textsuperscript{[12-14]}

HRV reflected the activity of cardiac autonomic nervous system. It can be used as a reliable index to study the function of cardiac autonomic nervous system. It is also an important index to evaluate the activity of sympathetic nerve and parasympathetic nerve activity and its balance.\textsuperscript{[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.\textsuperscript{[18]} This present study confirms that index 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 the 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.\textsuperscript{[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.\textsuperscript{[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 the autonomic nervous system are relatively balanced, which ensures the relative stability and the strain capacity of the heart rate. However, the balance of the autonomic nervous system will be changed from the adaptive regulation to the state of the hypobaric hypoxia. 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. 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 the 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 at an increased risk of cardiovascular disease. The level of aspartate aminotransferase is commonly measured clinically as biomarkers for liver health. The increased 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 damage.

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 AMS and non-AMS groups as the independent variable, prediction equation were established to estimate AMS. The equation may help us to identify people prone
to AMS in plains, therefore they can avoid travelling to high altitudes 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 interest statement**

The authors declare no conflict of interest.

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