The Relationship Between Baseline Exhaled Nitric Oxide Levels and Acute Mountain Sickness

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Abstract: *Background:* Acute mountain sickness (AMS) is a common disabling condition observed in people ascending to high altitudes. However, a simple predictive test for AMS is not known. The aim of this study was to assess the relationship between baseline exhaled nitric oxide (FENO) and AMS occurrence. *Methods:* Eighty healthy lowland Chinese adults were recruited for this study. FENO was measured at baseline, as well as 6 and 24 hours after arrival in Tibet. The standard Lake Louise Score (LLS) consensus symptoms questionnaire was used to assess the incidence and severity of AMS. *Results:* Individuals with a high LLS (>3) had higher FENO levels at baseline and after arrival in Tibet than people with a low LLS (≤3) (baseline: 22.9 ± 11.9 versus 16.7 ± 6.4; 6 hours: 26.2 ± 16.7 versus 17.9 ± 5.7; 24 hours: 24.9 ± 13.1 versus 16.3 ± 1.7; all $P < 0.01$). Evaluation of risk factors revealed that female gender, diabetes and not smoking were associated with a high AMS score (all $P < 0.05$), but that hypertension showed no association ($P > 0.05$). *Conclusions:* This prospective observational study suggests that baseline FENO levels may be positively correlated with AMS in healthy Chinese lowlanders.

Key Indexing Terms: Acute mountain sickness; exhaled nitric oxide; Lake Louise consensus symptoms questionnaire. **[Am J Med Sci 2015;349(6):467–471.]**

Acute mountain sickness (AMS) is a common disabling condition observed in nonacclimatized people ascending to high altitude. AMS can cause adverse health effects, in some cases severely impacting on physical function.[1,2] To date, it has proven difficult to predict individual susceptibility to AMS, and a number of different views and methods have been proposed.[3] A screening method should ideally be noninvasive, convenient, fast and of low cost, but no such method is currently available.

Nitric oxide (NO) is a gaseous signaling molecule responsible for a variety of physiological functions, including the regulation of airway vascular and smooth muscle relaxation.[4] The respiratory tract generates endogenous NO that can be detected in exhaled gas. Studies have shown that exhaled NO levels in a high-altitude pulmonary edema–susceptible population were significantly lower than those in controls, and that there was a negative correlation between NO levels and pulmonary artery pressure.[5–7] It has been assumed that NO production by pulmonary vascular endothelial cells and airway epithelial cells is downregulated after short-term exposure to high altitude and low pressure, and that this is one of the possible reasons for excessive hypoxic pulmonary hypertension.[5–7] However, Donnelly et al[8] found that although baseline exhaled nitric oxide (FENO) levels decreased and pulmonary artery pressure increased at high altitude, the FENO level did not decrease in normobaric hypoxia despite an increase in pulmonary artery pressure. Thus, the role of exhaled NO in AMS remains undetermined. However, several studies performed in different populations have suggested that baseline FENO levels may predict AMS occurrence, that is, that lower baseline FENO levels associate with a higher susceptibility to AMS.[3,5–7,9,10]

Taking into consideration the differing genetic and environmental factors between Chinese and white lowlanders, we hypothesized that FENO levels are associated with AMS occurrence in Chinese lowlanders. The aim of this study was to assess the relationship between baseline FENO leves and AMS occurrence. To achieve this, we measured FENO levels in a group of 80 healthy Chinese lowlanders at baseline, and 6 and 24 hours after their arrival in Tibet. The participants were divided into groups according to their Lake Louise Score (LLS).[11]

METHODS

Study Design

This was a prospective observational study. The participants underwent FENO measurements at baseline (in Beijing, at an altitude of 20–60 m, before taking the plane to Tibet), and 6 hours and 24 hours after arrival in Tibet (an altitude of 4,300 m). This study was approved by the ethical committee of the People's Liberation Army General Hospital and was registered in the Chinese clinical trials registration platform (ChiCTR-TRC-13003590). Each participant provided written informed consent before participation.

Participants

We selected 80 apparently healthy volunteers (aged 20–50 years). There were an equal number of men and women. All volunteers were Chinese individuals living in low-altitude regions, who had not visited any high-altitude regions in the year preceding their participation. The exclusion criteria were (1) coronary heart disease, (2) severe hypertension (systolic/diastolic blood pressure higher than 140/90 mm Hg), (3) uncontrolled diabetes, (4) anemia, (5) bronchial asthma, (6) chronic obstructive pulmonary disease, (7) liver or kidney dysfunction, (8) history of allergy or (9) a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) <70.

Protocol

Figure 1 shows the study protocol. On the day before departure, all volunteers were interviewed to provide a medical

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Submitted March 24, 2014; accepted in revised form July 30, 2014.

Supported by grants from Study of Early Warning and Intervention of Acute Heart and Lung Injury in Plateau.

The authors have no conflicts of interest to disclose

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history and received a physical examination that included measurements of vital signs, pulmonary function and FENO. On day 1, participants boarded the plane in Beijing at 8 AM and arrived in Lhasa at 2 PM Six hours after arrival (8 PM), FENO, heart rate, blood pressure and blood oxygen saturation were measured. From day 2 onward, LLS was assessed every morning. On the afternoon of day 2, the group took a bus journey to Nyingchi (an altitude of 3,100 m; the average altitude of the route was about 3,500 m). At 2 PM (or 24 hours after arrival), the FENO levels were measured. On day 3, the group traveled back to Lhasa by bus. On day 4, the group traveled by bus from Lhasa to Nam Co (an altitude of 4,300 m, with a peak at 5,018 m), before returning to Lhasa in the evening. The return flight to Beijing was on day 6.

Indicators and Assessments

The severity of AMS was assessed based on LLS,[11] including the occurrence of headaches in combination with at least one of the following symptoms: (1) gastrointestinal upset (loss of appetite, nausea and/or vomiting), (2) fatigue/weakness, (3) dizziness/light-headedness or (4) insomnia (more than usual).

Hemoglobin was determined using routine blood flow cytometry, and oxygen saturation was measured using a pulse oximeter (Radical-7; Masimo, Irvine, CA).

A chemiluminescence analyzer (Bedfont Scientific, Kent, United Kingdom) was used to measure FENO, in compliance with the current guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS). The measurement process using the chemiluminescence analyzer was repeated at least 3 times to ensure reproducibility (the correlation coefficient was 0.960, $P < 0.001$). The exhalation time for each participant was 12 seconds, with a flow of 50 mL/s.

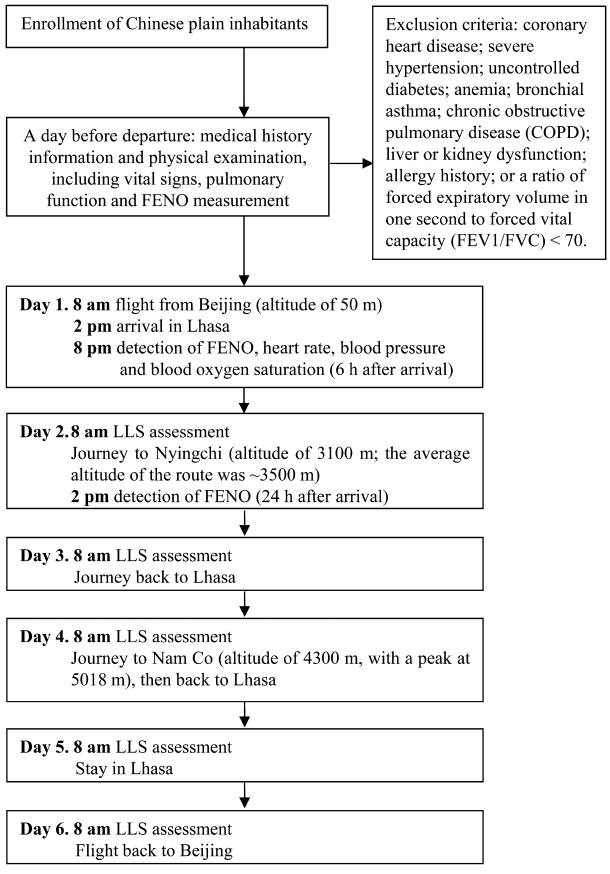

FIGURE 1. Study protocol.

The participants were assessed using a computerized spirometer (Chest Graph HI-701; Chest M.I. Inc, Hongo, Bunkyo-Ku-Tokyo, Japan). Information concerning the participant's age, gender, height and race was entered directly into the spirometer to calculate the predicted normal lung function value and to determine the percentage of the predicted value. Spirometer calibration was performed with a 3-L calibration pump before each testing session. The lung function parameters examined were FEV1 and FVC.

Blood pressure (systolic or diastolic) changes (%) were calculated as (blood pressure at 6 hours − baseline blood pressure)/baseline blood pressure. Changes in heart rate (%) were calculated as (heart rate at 6 hours − baseline heart rate)/baseline heart rate.

Data Analyses

Data were analyzed using SPSS 18.0 statistical software (SPSS Inc, Chicago, IL). The highest LLS of each participant during their stay at the plateau was recorded, and the participants were divided into a low LLS group (LLS ≤3) and a high LLS group (LLS >3). All data were compared using the 2-tailed Student's t test for paired or unpaired data, as appropriate, and are presented as mean ± standard deviation. Differences in proportions were evaluated using the Fisher's exact test or the χ^2 test, as appropriate. A P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Participants

Table 1 shows the baseline characteristics of the entire group (n = 80), the low LLS group (n = 45) and the high LLS group (n = 35). There were no significant differences in age, body mass index, heart rate, hemoglobin, oxygen saturation, FVC or FEV1 between the low LLS and high LLS groups at baseline (all $P > 0.05$). However, there were marked differences between the 2 groups in baseline systolic and diastolic blood pressures and baseline FENO level (at Beijing) (all $P < 0.01$).

Comparison of FENO Levels and Physiological Indices Between Participants With Low and High LLS After Arrival at the Plateau

Table 2 presents the FENO levels and physiological indices measured 6 or 24 hours after arrival in Lhasa. At 6 hours after arrival in Lhasa, participants in the high LLS group had a higher FENO level ($P = 0.008$), lower diastolic blood pressure ($P < 0.001$) and higher heart rate ($P < 0.001$), compared with the low LLS group. After 24 hours in Lhasa, the FENO levels were still elevated in participants in the high LLS group ($P < 0.001$), but there were no significant differences in the other indices between the 2 groups (all $P > 0.05$; Table 2).

Factors Associated With AMS Severity

Among the participants in the high LLS group, less were male (25.7% versus 48.9%, $P = 0.035$), more suffered from mild well-controlled type II diabetes (14.3% versus 0%, $P = 0.031$) and less were smokers (8.6% versus 28.9%, $P = 0.024$). Mild hypertension (systolic/diastolic blood pressure between 130/85 and 140/90 mm Hg) was not associated with LLS ($P = 0.453$; Table 3).

TABLE 1. Baseline demographic and physiological characteristics of participants in the low and high LLS groups

	Entire group (n = 80)	Score ≤3 (n = 45)	Score >3 (n = 35)	*P*
Age, yr	38.4 ± 9.9	38.6 ± 8.3	38.1 ± 11.8	0.829
Body mass index, kg/m^2	25.5 ± 3.8	26.2 ± 3.5	24.7 ± 3.9	0.069
Systolic blood pressure, mm Hg	118.8 ± 16.0	123.8 ± 14.9	112.3 ± 15.3	0.001
Diastolic blood pressure, mm Hg	78.6 ± 10.3	83.2 ± 9.0	72.7 ± 8.7	<0.001
Heart rate, bpm	79.3 ± 10.2	81.0 ± 8.6	77.1 ± 11.7	0.094
Hemoglobin, g/L	144.6 ± 11.2	145.3 ± 12.2	143.6 ± 9.7	0.517
Oxygen saturation, %	97.8 ± 0.4	97.73 ± 0.45	97.8 ± 0.4	0.308
FVC, L	4.2 ± 1.0	4.0 ± 0.8	4.3 ± 1.1	0.152
FEV1, L	3.1 ± 0.7	3.2 ± 0.7	3.0 ± 0.6	0.113
FENO in Beijing, ppb	19.4 ± 9.7	16.7 ± 6.4	22.9 ± 11.9	0.007

Data are presented as mean ± SD.

DISCUSSION

Very few previous studies have examined the relationship between the FENO level and AMS in Chinese lowlanders.[10] Therefore, the aim of this study was to assess the relationship between the FENO level and AMS occurrence in Chinese lowlanders. Our results showed that participants with a high AMS score had higher FENO levels at baseline and at high altitudes (above 3,500 m) than those with a low AMS score. Evaluation of risk factors revealed that female gender, mild well-controlled type II diabetes and nonsmoking status were associated with a high AMS score.

High-altitude illnesses encompass the pulmonary and cerebral syndromes that occur in nonacclimatized individuals shortly after rapid ascent to high altitude, the most common of which is AMS.[12] Previous studies have observed that being in a high-altitude environment is associated with adverse conditions such as cold temperature, low oxygen partial pressure and excessive ultraviolet radiation, leading to hyperfunction of the pituitary-adrenal medullary axis and the secretion of substantial quantities of catecholamines and other substances into the circulation. This causes an increase in the peripheral resistance and central circulation, as well as enhanced secretion of antidiuretic hormone and ketone aldehyde, resulting in water and sodium retention.[13–15]

In this study, the initial physiological responses we observed were decreased oxygen saturation, increased heart rate and elevated blood pressure. After analysis, we determined that blood pressure at baseline may not be a determining factor for AMS; although both groups of participants experienced an increase in blood pressure, there was no difference between the 2 groups in the blood pressure change. However, the heart rate increased significantly, especially in the high LLS group.

Some researchers have attempted to establish statistical models to predict the independent effects of hypoxia in AMS.[16] Measurement of FENO has been proposed as a noninvasive method for assessing airway inflammation in asthma. Studies have shown that this method is practical and comfortable for the patients and can be used as a diagnostic method.[17] NO is a gaseous signaling molecule with extensive physiological functions, such as relaxation of airway and vascular smooth muscle, and regulation of the ventilation-perfusion ratio.[4] Gustafsson et al[18] have reported that NO may also play a role in vascular regulation and host defense, both in physiological and pathological settings. NO exerts its biological effects through the activation of proteins and intracellular messengers involved in vasodilatation, such as cGMP.[19]

Our study found that the FENO level in Chinese subjects after exposure to high altitude differed from that at baseline. It has been reported previously that FENO decreases with altitude, but that this is not the main factor causing hypoxic pulmonary vasoconstriction.[20] Hemmingson and Linnarsson[21] showed that FENO during hypobaric hypoxia was significantly lower than that in the normobaric hypoxic state. Vinnikov et al[22] have observed that high-altitude miners exhibit a remarkable reduction in FENO but no obvious clinical symptoms, perhaps because these miners were already adapted to high-altitude hypoxia.[23] When subjects are rapidly

TABLE 2. FENO levels and physiological characteristics of participants in the low and high LLS groups within 24 hours of arrival in Lhasa

	Entire group (n = 80)	Score ≤ 3 (n = 45)	Score > 3 (n = 35)	*P*
FENO 6 hr after arrival in Lhasa, ppb	21.5 ± 12.5	17.9 ± 5.7	26.0 ± 16.7	0.008
FENO 24 hr after arrival in Lhasa, ppb	20.1 ± 9.7	16.3 ± 1.7	24.9 ± 13.1	<0.001
Systolic blood pressure 6 hr after arrival in Lhasa, mm Hg	129.1 ± 23.1	133.0 ± 29.0	124.1 ± 10.1	0.062
Diastolic blood pressure 6 hr after arrival in Lhasa, mm Hg	81.4 ± 11.8	85.4 ± 10.4	76.3 ± 11.5	<0.001
Heart rate 6 hr after arrival in Lhasa, bpm	93.0 ± 10.8	89.2 ± 9.6	98.0 ± 10.3	<0.001
Oxygen saturation 6 hr after arrival in Lhasa, %	84.0 ± 5.2	84.8 ± 5.4	82.9 ± 4.8	0.097
Systolic blood pressure change, %	—	6.9 ± 15.0	12.1 ± 14.2	0.122
Diastolic blood pressure change, %	—	3.5 ± 15.1	5.4 ± 14.2	0.563
Heart rate change, %	—	11.4 ± 16.9	30.3 ± 27.0	0.001

Data are presented as mean ± SD.

TABLE 3. Demographic and clinical factors associated with AMS severity

	LLS ≤3 (n = 45)	LLS >3 (n = 35)	*P*
Male gender	22 (48.9)	9 (25.7)	0.035
Mild diabetes	0	5 (14.3)	0.031
Mild hypertension	6 (13.3)	2 (5.7)	0.453
Smoker	13 (28.9)	3 (8.6)	0.024

Data are presented as n (%). Mild hypertension was defined as systolic/diastolic blood pressure between 130/85 and 140/90 mm Hg. Smokers were defined as those who had ever smoked more than 100 cigarettes and were smoking currently.

exposed to high altitudes without an adaptation period, hypoxia-related diseases may appear. Some studies have suggested that individual susceptibility, the rate of ascent and pre-exposure are major independent factors for AMS.[24] In this study, we did not assess individual susceptibility, and the subjects were exposed rapidly to high altitude without an adaptation period. These factors could explain the differences observed between previous investigations[10] and this study.

Studies of patients with asthma have demonstrated that a persistent expression of endothelial NO synthase in epithelial cells plays an important role in determining the measured FENO levels.[25] NO is an important factor in chronic airway inflammation and airway reactivity in asthma.[26] However, a previous investigation has reported no significant correlation between FENO and AMS, based on self-reported symptoms during short-term exposure to high altitudes.[9] Our results show that lower baseline FENO levels do not indicate an adaptation to a high-altitude environment, but that high FENO levels are associated with high AMS scores. Thus, a high FENO level is associated with AMS susceptibility, a finding that differs from previous investigations.[3]

The study of gene polymorphisms in high-altitude residents has revealed that variation in the gene for NO synthase is a risk factor for AMS development.[27–29] The influence of smoking status also needs consideration, in addition to the roles of hypoxia, fatigue and insufficient energy intake. In this study, the high LLS group had fewer smokers than the low LLS group. Consistent with this, previous research has demonstrated that smoking slightly reduced AMS risk but impaired lung function during long-term adaptation to high altitude.[30,31] However, Beidleman et al[32] have reported that smoking status is not significantly associated with AMS but may decrease the FENO level.[33,34] Our study yielded similar results; there were more smokers in the low LLS group, which exhibited relatively lower FENO levels. In the future, studies based on genome-wide associations and genetic analysis will help us to better understand the complex genomic interactions that contribute to the rapid and effective adaptation to a high-altitude hypoxic environment.[35]

One limitation of our study design was the control of the duration of hypoxia. Indeed, the participants were exposed only to short-time hypoxia, but it remains possible that some of them may have developed symptoms of AMS only in the mid or long term. Therefore, further research using longer exposures to hypoxia are necessary; these will help to explain the underlying etiology of AMS and provide more effective tools to evaluate the ability of an individual to tolerate hypoxia. In addition, this study included only healthy volunteers, and comorbidities could affect tolerance to high altitudes.

CONCLUSIONS

Baseline FENO levels seem to be related to AMS risk. However, these results need to be confirmed in larger studies.

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