National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

A study of autonomic cardiovascular regulation in subjects with acute mountain sickness

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Received: December 25, 2016; **Accepted:** January 15, 2017

ABSTRACT

Background: Increased sympathetic activity is a part of the integrated physiological response to a hypoxic stimulus but it is not clear if it plays a role in the genesis of acute mountain sickness (AMS). **Aims and Objectives:** This study was conducted to evaluate the role of the autonomic nervous system in AMS during the initial phase of acute high-altitude exposure. **Materials and Methods:** The study was conducted on 42 lowlanders ascended at an altitude of 3500 m by airplane. Autonomic function tests of 20 subjects who suffered from AMS were studied, and the results were compared with 22 healthy individuals. AMS was diagnosed using the Lake Louise score, and autonomic cardiovascular functions were evaluated using non-invasive cardiovascular reflex tests. **Results:** At high-altitude, the diastolic blood pressure (DBP) rise in response to sustained handgrip was higher in AMS subjects than the control group. The rise in DBP in cold pressor test was higher in AMS subjects than controls. The valsalva ratio was also significantly higher in AMS patients than controls. **Conclusion:** Sympathetic hyperactivity on induction to high altitude is positively associated with the development of AMS.

KEY WORDS: High Altitude; Autonomic Nervous System; Acute Mountain Sickness

INTRODUCTION

A large number of people travel to high-altitude region all over the world for various reasons such as pilgrimage, trekking, mining or defense service requirements. The decreasing barometric pressure and ambient temperature are very important limiting factors for the travels to high altitude. The individuals who fail to adapt to these adversities may develop acute mountain sickness (AMS) or high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE).[1]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0100115012017	

AMS is a non-specific syndrome complex characterized by headache, weakness, insomnia, gastrointestinal symptoms, and neurological signs such as changes in mental status and ataxia.[1-3] AMS is relatively very common and may occur in subjects ascending to an altitude of >2500 m and is reported in 42% of those at >3000 m altitude.[3-5] AMS is generally harmless and transient but may occasionally progress to the more serious life-threatening HACE and HAPE.

The exact mechanism causing AMS is not clear, although the prevailing hypothesis points to the decreased parasympathetic activity and increased sympathetic activity.[6-10] Whether autonomic hyperactivation plays a role in the genesis of AMS is not known. There is a scarcity of data regarding the role of autonomic nervous system (ANS) in the development of AMS, especially from Indian subcontinent. Hence, this study was conducted to elucidate the role of the ANS in AMS during the initial phase at acute high-altitude exposure.

MATERIALS AND METHODS

This is a cross-sectional study conducted at city of Leh situated at an altitude of 3500 m above sea level. The study was performed on 42 healthy lowlanders, who ascended rapidly to an altitude of 3500 m, by airplane. Written informed consent was obtained from all subjects before the study. All the subjects were evaluated for AMS by Lake Louise scores. The detailed history and clinical examination was carried out on all the subjects. They were in the age group of 20-30 years.

All subjects were evaluated on the 5th day of arrival at high altitude as subjects with AMS became asymptomatic by 5th day. After recording baseline heart rate (HR) and blood pressure (BP), all subjects underwent four simple non-invasive cardiovascular reflex tests, namely, (a) HR response to deep breathing, (b) valsalva manoeuvre, (c) BP response to sustained handgrip, and (d) cold pressor test (CPT). The tests were performed in thermo-neutral environment of the laboratory.

The deep breathing test was performed with subject sitting quietly and then breathing deeply and evenly at six breaths per min. Inspiration and expiration of five seconds each was optimized using a metronome. An electrocardiograph lead II was recorded throughout the period of deep breathing and the operator marked the onset of each inspiration and expiration. The E:I was calculated, which is the ratio of the mean of the longest R-R intervals during deep expiration to the mean of the shortest R-R intervals during deep inspiration. The change in HR was calculated as the difference in beats per min between the shortest and the longest R-R interval.

The standard valsalva manoeuvre was carried out in supine position. The subjects forcibly exhaled for 15 s against a fixed resistance with an open glottis into tubing of mercury sphygmomanometer. The subjects were asked to maintain constant pressure at 40 mm of Hg over the 15 s, imitating cough act without permitting the escape of air from the nose and mouth. The valsalva ratio was calculated as the longest R-R divided by the shortest R-R occurring within 45 s of peak HR and is indicative of the overall condition of the parasympathetic and sympathetic fibers.

To ascertain BP response to sustained handgrip test, the subject was asked to grip the inflated BP cuff maximally with his dominant hand for 5 s, which was called as maximum voluntary contraction (MVC). Thereafter, the subject was instructed to maintain the hand grip at 30% MVC for 5 min. The diastolic BP (DBP) was recorded in non-exercising arm after exercise.

CPT was carried out by immersing the right hand of subject in cold water bath. The water bath had a 6 L water capacity and maintained a temperature of 1-3°C. The HR, systolic BP (SBP), DBP and mean arterial pressure (MAP) were recorded before and after 1min of cold stimulus.

Statistical Analysis

Biological values of all study participants were expressed as mean ± standard deviation. Differences between the two groups of subjects with and without AMS were compared by Mann–Whitney *U*-test. $P < 0.05$ was considered significant.

RESULTS

All 42 subjects successfully completed autonomic function tests at high altitude following 5th day of ascent to an altitude of 3500 m above sea level. 20 subjects had AMS, as indicated by a Lake Louise score ≥3 (range 3-8). Headache (85%) was the most common symptoms followed by difficulty in sleep (75%), nausea (60%), giddiness (60%), and easy fatigability (40%). On the day of the test, all AMS patients were asymptomatic.

Age, height, weight distribution, and the baseline cardiovascular parameters of normal healthy individuals and subjects with AMS are shown in Table 1. Subjects with AMS were older and none of them had a prior history of AMS. The resting HR was higher in AMS subjects than the control group. The basal SBP and DBP were significantly lower in AMS subjects than normal subjects (*P* value 0.001 and 0.002).

Deep Breathing Test

The mean HR variability (HRV-difference between maximum and minimum HR) for AMS subjects and healthy subjects

Table 1: Age, height, weight distribution and baseline cardiovascular parameters of normal healthy individuals and subjects with AMS

Baseline parameters	Mean±SD		"*P*" value
	Non AMS (*n*=22)	AMS (*n*=20)	
Mean age (years)	25.18±2.93	27.15±3.66	0.09
Height (cm)	173.45±4.51	176.25±5.01	0.05
Weight (kg)	74.45±6.75	75.20±4.85	0.75
Basal heart rate	70.82±9.97	73.55±11.19	0.21
Basal DBP	81.50±6.23	74.65±6.93	≤0.001
Basal systolic BP	125.05±9.35	116.25±8.57	≤0.001
MAP	96.09±8.11	88.70±6.52	≤0.001
SPO_2	92.41±1.46	90.65±2.08	≤0.001
Respiratory rate	21.18±2.55	22.20±2.58	0.15
Lake Louise score	NA	8.00±2.29	-

AMS: Acute mountain sickness, SD: Standard deviation, BP: Blood pressure, MAP: Mean arterial pressure

were 25 ± 9 beats/min and 29 ± 9 beats/min, respectively. The HRV was lower in AMS patients than the mean HRV for normal healthy subjects, but the difference was not significant (*P* value 0.2). E:I ratio for AMS subjects was higher than normal healthy subjects (AMS: 2.21 ± 3.76, non-AMS: 1.43 ± 0.17), but the difference was not significant (*P* value 0.48).

Valsalva Manoeuvre

In our study, the valsalva ratio for AMS subjects was 2 ± 0.47 which was significantly higher than normal healthy individuals 1.66 ± 0.55 (*P* = 0.04) as shown in Table 2.

Sustained Handgrip Exercise

The average DBP at rest for AMS patients 75.65 ± 6.83 mm of Hg) was lower than that of the control group (82.05 ± 5.57 mm of Hg). The DPB rise for healthy individuals was 9.00 ± 7.21 mm of Hg and DBP rise for AMS subjects was 19.35 ± 9.72 mm of Hg, indicating highly significant change between AMS and non-AMS subjects (*P* ≤ 0.001).

CPT

Reduction in HR was observed in AMS subjects after 1 min of CPT by 1.30 ± 5.35 beats/min while there was increase in HR in non-AMS subjects by 2.59 ± 4.47 beats/min. This change was significant (*P* ≤ 0.001). The peak increase in DBP from rest was higher in AMS subjects than non-AMS subjects (AMS: 14.40 ± 4.30 mm of Hg; non-AMS: 10.36 ± 6.26 mm of Hg), and the change was significant (*P* ≤ 0.001). The peak increase in SBP from rest was higher in AMS subjects than non-AMS subjects (AMS: 13.15 ± 8.20 mm of Hg; non-AMS: 11.00 ± 6.23 mm of Hg) but the change was not significant (*P* = 0.36). The peak increase in MAP from rest was higher in AMS subjects than non-AMS subjects (AMS: 13.70 ± 5.48 mm of Hg; non-AMS: 10.73 ± 6.65 mm of Hg) but the change was not significant (*P* = 0.07) as shown in Figure 1.

DISCUSSION

The effect of high altitude on the cardiovascular and respiratory systems is complex and not fully understood. Although increased sympathetic activity is a part of the integrated physiological response to a hypoxic stimulus,[2,11,12] its role in Indian population is not explored. In this study, we investigated the autonomic response in lowlanders following rapid ascent to high-altitude area using simple non-invasive tests.

In our study, all the BP parameters were lower in subjects with AMS, indicating that AMS subjects have blunted sympathetic activity at rest and hyperactivity is obvious only after stress. Our study revealed that during deep breathing test there was no significant differences in HRV and E:I ratio of AMS subjects when compared with non-AMS group. The metronomic deep breathing test is an autonomic test that attempts to standardize respiratory changes and their relation to HR, hence to vagal activity.[13] Beat-to-beat variation in HR with respiration depends on parasympathetic innervations.[14] This means there is no significant difference in parasympathetic activity in AMS subjects and normal healthy individuals.

Table 2: The parameters in valsalva manoeuvre in AMS and non AMS group

Groups	Longest RR	Shortest RR	Valsalva ratio
Non AMS group	24.86±4.85	15.64±3.52	1.66±0.55
AMS group	29.20±5.13	15.15±3.82	2.00±0.47
P value	≤0.001	0.47	0.04

AMS: Acute mountain sickness

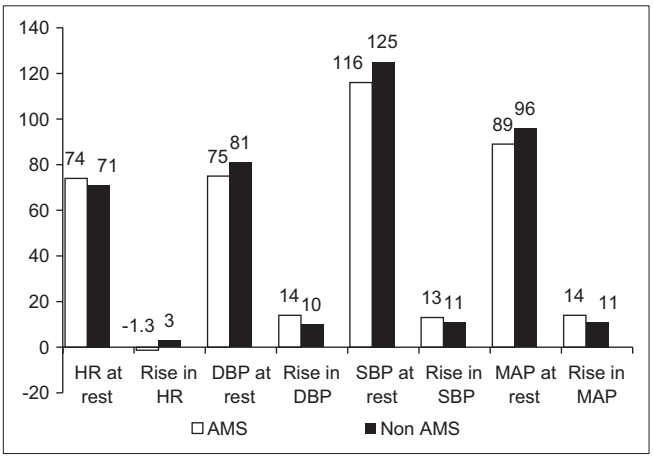

Figure 1: Heart rate, diastolic blood pressure, systolic blood pressure, and mean arterial pressure responses during cold pressor test compared with baseline in subjects with and without acute mountain sickness

In valsalva manoeuvre, HR response is modified by changes in BP.[15] In our study, valsalva ratio was significantly higher in AMS patients than non-AMS subjects which point toward sympathetic hyperactivation. Isometric handgrip is a specific, sensitive, reproducible, simple, and non-invasive test of sympathetic function with relatively well-studied reflex pathways.[16] In our study, we noted a significant increase in DBP in AMS subjects as compared to non-AMS group indicating sympathetic over activity in AMS subjects.

The CPT is used to activate pain and temperature fibers by immersing one hand in ice-cold water (0-4°C) for 40-180 s. The sympathetic nervous system is activated through the spinothalamic tract, inducing an increase in BP and HR.[17] The DBP is a better indicator of sympathetic activity. As after 1 min of cold stimulus, the increase in DBP in subjects with AMS was higher than healthy individuals, we conclude that there was sympathetic over-activity in subjects with AMS.

A prior study by L Min et al. did not show any significant change on CPT in AMS patients but showed significant sympathetic over-activity in AMS patients than healthy individuals by spectral analysis of HRV.[18] The significant increase in diastolic pressure in sustained handgrip test and CPT and higher valsalva ratio in AMS subjects may reflect an overall enhanced vascular sympathetic response in this condition. The insignificant change in E:I ratio in deep breathing test indicates that there is no significant difference in parasympathetic activity of patients of AMS patients and healthy individuals.

In healthy individuals, sympathetic nervous activity increases with the increase in altitude. The increase in sympathetic discharge and down-regulation of the β-adrenergic receptor system is a phenomenon observed during high-altitude acclimatization. This alteration is considered to be beneficial in protecting organs, including the heart, from long-term sympathetic stimulation at high altitude.[1] There are reports describing alterations in activity of the ANS on ascent to high-altitude.[6,9-12] Hughson and colleagues studied the effect of long-term exposure to an altitude above 4000 m and the role of the β-adrenergic system in high-altitude acclimatization.[11] They observed increased sympathetic discharge and decreased parasympathetic discharge in the early phase of acclimatization. Farinelli et al. reported alterations in HRV during a long-term stay above 5000 m. This study demonstrated that the sympathetic system is dominant compared to the parasympathetic at a high altitude.[8]

Most of the prior studies have shown increased sympathetic activity on acute exposure to high altitude by analyzing HRV with spectral analysis. There is a scarcity of Indian studies, which have utilized non-invasive tests such as deep breathing test, valsalva manoeuvre, sustained handgrip test, and CPT to assess cardiovascular autonomic function in patients of AMS. We have attempted to address that issue in lowlanders recently inducted to high altitude.

AMS is related to cerebral edema due to hypoxic cerebral vasodilation and elevated cerebral capillary hydrostatic pressure. Increase in HR and mean diastolic pressure indicates augmentation of beta-adrenergic tone as a result of significant elevation of sympathetic activity in AMS. The BP response to hypoxia results from the complex interaction between several factors, including the effects of chemoreflexes (vasoconstriction), hyperventilation (vasodilation), and central and peripheral contrasting effects of hypoxia and hypocapnia.[12,19] Sympathetic nervous system activation caused by cold and hypoxia may also cause platelet activation and trigger acute coronary syndrome.[20] It could be possible that subjects with AMS have blunted sympathetic cardiac modulation at rest and the sympathetic over-activity observed after cardiovascular autonomic function tests are secondary to established mountain sickness. Although our study is limited by sample size, it is suggested that an exaggerated sympathetic vascular response may be responsible for genesis of AMS. Thus, a higher vasomotor response to hypoxia could identify subjects who are prone to develop AMS. However, it is debatable whether sympathetic over-activity is the cause or effect of AMS.

CONCLUSION

We conclude that autonomic cardiovascular function is altered in subjects with AMS with predominant sympathetic over-activity. The autonomic derangement that accompanies AMS could potentially increase the risk of life-threatening arrhythmias in predisposed subjects. Morbidity is significant among visitors to high altitude due to AMS. The autonomic cardiovascular response to short-term hypoxia could represent a low-cost noninvasive test to help identify those subjects who are at risk for AMS.

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How to cite this article: Jaipurkar R, Bajaj R, Mohan L, Bobdey S. A study of autonomic cardiovascular regulation in subjects with acute mountain sickness. Natl J Physiol Pharm Pharmacol 2017;7(5):533-537.

Source of Support: Nil, **Conflict of Interest:** None declared.