Prediction of acute mountain sickness and sleep apnea in subjects travelling to and training at altitude

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EXECUTIVE SUMMARY

Acute mountain sickness (AMS) is a debilitating health problem that affects a number of subjects when ascending to high altitude. Symptoms can include headache, nausea, lethargy, fatigue and subsequent loss of sleep and performance, however if susceptible subjects could be identified early precautionary measures could be put in place to reduce or eliminate AMS. The aim of this study was to determine if physiological variables measured at sea level could predict AMS (as measured by the Lake Louise score) at real altitude. A series of physiological measures were taken at rest at sea level (Dunedin, New Zealand) and again at 5050m (Pyramid Research Laboratory, Nepal). Measures included oxyhaemoglobin saturation, haematocrit, haemoglobin concentration, blood pressure, heart rate, cerebral blood flow and a number of ventilatory measures. We found that sea-level cerebral blood flow (R = 0.47), and haematocrit (R= -0.50) were strongly correlated with AMS, however using multiple linear regression results indicated that sea-level mean blood pressure was the only statistically significant predictor of AMS at altitude (p < 0.01). This analysis indicated that sea-level mean blood pressure accounted for 45% of the prediction of AMS at altitude. In conclusion, while sea-level mean blood pressure is a useful predictor of AMS at altitude, clearly other factors account for the remaining 55% of AMS at altitude, and further research is required to uncover these remaining factors.

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INTRODUCTION

The occurrence of acute mountain sickness (AMS) is a public health concern as about half of lowlanders develop symptoms after rapid ascent to altitude > 2500 m [1]. These symptoms, including headache, nausea, vomiting, anorexia, lethargy, fatigue, dizziness and insomnia, can be experienced to differing degrees with onset occurring between 6-10 h after arrival [1]. Knowledge of predictive factors responsible for this large inter-individual variation in AMS susceptibility would enable preventative strategies to be implicated.

The occurrence of AMS has been shown to be related to previous acclimatisation to high altitude, rate of ascent and individual susceptibility [2-4]. The physiological responses which determine an individual's susceptibility, however, remain debateable. A wide range of ventilatory, cardiovascular and cerebral variables have been recorded for the prediction of susceptibility to acute mountain sickness, however, as yet, no clear conclusion can be drawn [5, 6]. Moore et al. (1986) found individuals who develop AMS symptoms to simulated altitude (4,800 m for 4.5 h) have a lower hypoxic ventilatory response (HVR) compared with those that are asymptomatic. Further research, however, has been unable to replicate this finding [7-11]. The majority of the literature, involving both simulated [12-15] and real [16-19] altitude exposures, of both prospective and retrospective design, suggest lowered SaO_2 to be a good predictor of AMS susceptibility and AMS progression (reviewed in [5]). Several studies, however, have found no predictability of AMS susceptibility by SaO_2 levels [20-22], although trends suggested greater O_2 desaturation in subjects exhibiting AMS [21, 22]. Further, Grant et al. (2002) found a

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fairly poor correlation between SaO_2 levels at simulated altitude (in the laboratory) and those found at a comparable real altitude. This finding would suggest correlations between SaO_2 at simulated altitude and AMS may not necessarily occur upon ascent to real altitude.

In addition to HVR and SaO_2, physiological variables such as fluid retention [23], elevated intracranial pressure [24-26], elevated cerebral blood flow (CBF) [18], and impaired regulation of cerebral circulation [22] have been suggested to be related to the development of AMS. Further studies at simulated altitude (3800 – 4600 m), however, have reported no relationship between CBF and AMS susceptibility [12, 27-29].

The majority of research on AMS susceptibility has focused on physiological responses upon exposure to simulated altitude (≤ 4600m) for short durations (30 min – 6 h). As AMS symptoms may take longer to fully develop, and responses to simulated altitude may differ to those at real altitude, the current research aimed to identify physiological variables involved in the development of AMS upon ascent to the pyramid research laboratory, (5050 m), 4 km from Mt Everest base camp, Nepal.

Aim of Study

To determine if the symptoms of acute mountain sickness and the development of sleep apnea while breathing low levels of oxygen at sea-level can predict the extent of these symptoms at high altitude.

METHODOLOGY

Subjects

Seventeen (11 males, 6 females) active, healthy individuals volunteered to participate in this study (Table 1), which was approved by the Lower South Otago Regional Ethics Committee and the Nepalese Research Council, and conformed to the standards set by the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks involved in the study and written informed consent was obtained. Subjects had no history of cardiovascular, cerebrovascular or respiratory disease, were not taking medication and were non-smokers. All subjects were sea-level residents and had not spent time at altitude in the preceding 6 months.

Table 1
Subject characteristics and LLAMS scores

	Males	Females	All Subjects
N	11	6	17
Age (yr)	32±10	30±8	31±9
Height (cm)	176.3±6.8	168.0±7.1	173.4±7.8
Body Mass (kg)	72.3±7.8	61.8±5.9	68.6±8.7
LLAMS score	2.9±3.4	4.5±1.4	3.5±2.2

Experimental design

In Dunedin, New Zealand, sea-level respiratory, cardiovascular and cerebrovascular measurements were obtained in normoxia (Partial Pressure of inspired O_2 (P_IO_2) = 140 mmHg) while resting in a reclined position. On arrival to Kathmandu, Nepal, the team of researchers and subjects ascended to the Pyramid Laboratory (5,050 m; P_IO_2

~74 mmHg) in the Khumbu Valley (4 km from Everest Base Camp). At the Pyramid Laboratory, the same measurements as were conducted at sea-level were repeated within 1-3 days of arrival. In addition, subjects completed the self-assessment section of the Lake Louise Consensus Altitude Mountain Sickness Scoring questionnaire (LLAMS) [30] regarding the occurrence of AMS symptoms.

Respiratory measurements

Tidal volume (V_T), minute volume (V_E) and respiratory frequency were measured with BREEZE Ex v3.06, Medical Graphics CPX/D Metabolic Cart (Medical Graphics, St. Paul, Minnesota, USA).

CBF velocity, arterial BP and HR measurements

CBF velocity was estimated by the measurement of middle cerebral artery blood flow velocity (MCAV) with a 2-MHz pulsed Doppler ultrasound system (DLW Doppler, Sterling, VA) and search techniques described elsewhere [31]. Beat-to-beat arterial BP was monitored with finger photoplethysmography (Finometer, TNO-TPD Biomedical Instrumentation) and mean arterial blood pressure (MBP) was calculated by [(2×diastolic)+systolic]/3. Cerebrovascular conductance (mean MCAV/MBP) and resistance (MBP/mean MCAV) were calculated. Heart rate was calculated from the BP waveform. All data were acquired continuously at 200 Hz with an analog-to-digital converter (Powerlab/16SP ML795; ADInstruments).

Arterial blood measurements

An arterial line was inserted into the radial artery and upon sampling, blood was immediately analysed ($PaCO_2$, PaO_2, SaO_2, Hb, Hct, pH, $HCO3^-$) with a previously calibrated blood gas analyser (Radiometer ABL 500, Copenhagen, Denmark).

Hypoxic responses

Hypoxic ventilatory, cardiac and cerebral responses were calculated using the change in variables from SL to high altitude (day 1-3) as follows:

Hypoxic ventilatory response (HVR) = $\Delta VE/\Delta SaO_2$

Hypoxic cardiac response (HCR) = $\Delta HR/\Delta SaO_2$

Cerebrovascular Response = $\Delta CBF/\Delta P_aCO_2$

Statistical Analyses

Data are presented as mean ± SD and analyses were conducted on SPSS (Version 15). Physiological changes from sea-level to altitude were analysed by paired t-tests. Simple linear regression was computed to locate variables most related to LLAMS score and the correlation matrix was studied for correlation between independent variables. This process resulted in the selection of 4 variables for further analyses. A multiple regression analysis, using a backwards elimination process, including quadratic transformation for the independent variable, was performed to determine the best subset of predictors of LLAMS score. Box-plots of these variable distributions were viewed for data normality. Log_{10} transformation of the dependent variable (LLAMS) resulted in no improvement of model fit.

RESULTS

Residence at high altitude (5,050 m) for 1-3 days significantly affected many systemic and cerebral variables compared to sea-level values (Table 2). HR and MBP were elevated at altitude compared with sea-level. V_E was increased despite no significant change in either V_T or Bf. An increase in CBF was found despite hyperventilatory induced hypocapnia (decreased respiratory and arterial CO_2).

Table 2
Cardiovascular, cerebral, respiratory and blood gas variables measured at sea-level and at altitude (5,050 m)

	Sea-level	*Altitude*	*P*
HR (beats·min^{-1})	69±10	80±10	< 0.01
MBP (mmHg)	78.5±14.0	89.8±15.0	<0.05
CBF (cm·s^{-1})	66.3±10.9	84.1±16.0	<0.001
CVC (cm·s^{-1}·mmHg^{-1})	0.880±0.242	0.962±0.176	NS
CVR (mmHg·cm^{-1}·s^{-1})	1.233±0.382	1.096±0.260	NS
V_E (L·min^{-1})	13.7±2.5	16.3±4.2	<0.05
Vt (L)	1.0±0.3	1.0±0.3	NS
Bf (breaths·min^{-1})	15.3±4.2	17.2±4.3	NS
PO$_2$ (mmHg)	108.7±8.1	47.2±5.8	<0.001
PCO$_2$ (mmHg)	40.8±4.5	25.6±2.9	<0.001
SaO$_2$ (%)	98.4±0.5	79.9±3.4	<0.001
PaO$_2$ (mmHg)	105.1±10.8	43.9±2.8	<0.001
PaCO$_2$ (mmHg)	41.5±3.1	29.2±2.6	<0.001
pH	7.45±0.04	7.47±0.03	<0.05
HCO3$^-$ (units??)	28.6±3.1	21.3±2.4	<0.001
Hct (%)	43.7±4.0	45.7±3.9	<0.01
Hb (g·dL^{-1}??)	14.6±1.2	14.9±1.3	NS

Data are mean±SD. *P* indicates statistically different between sea-level and altitude measurements.

The increases in both MBP and CBF at altitude resulted in no change in CVC or CVR. A fall in SaO_2 within the first few days at altitude accompanied the reduction in O_2 partial pressures (respiratory and arterial). Elevated arterial blood Hct at high altitude was not reflected by a change in Hb concentration. An increase in arterial pH with altitude exposure was found alongside a fall in arterial $HCO3^-$. Altitude exposure for 1-3 days resulted in the development of AMS of varying degrees in the majority of participants, with only two individuals reporting no symptoms (range $0 - 7.5$). Average LLAMS scores are reported in Table 1. Participant age and LLAMS score were not correlated. The LLAMS score was not related to CV response, HVR or plasma volume change, but was significantly correlated with HCR (R = -0.58, *P* = 0.015). Of the sea-level measurements, MBP (Figure 1), CBF, CVC, CVR and Hct were found to be significantly correlated with LLAMS score (Table 3).
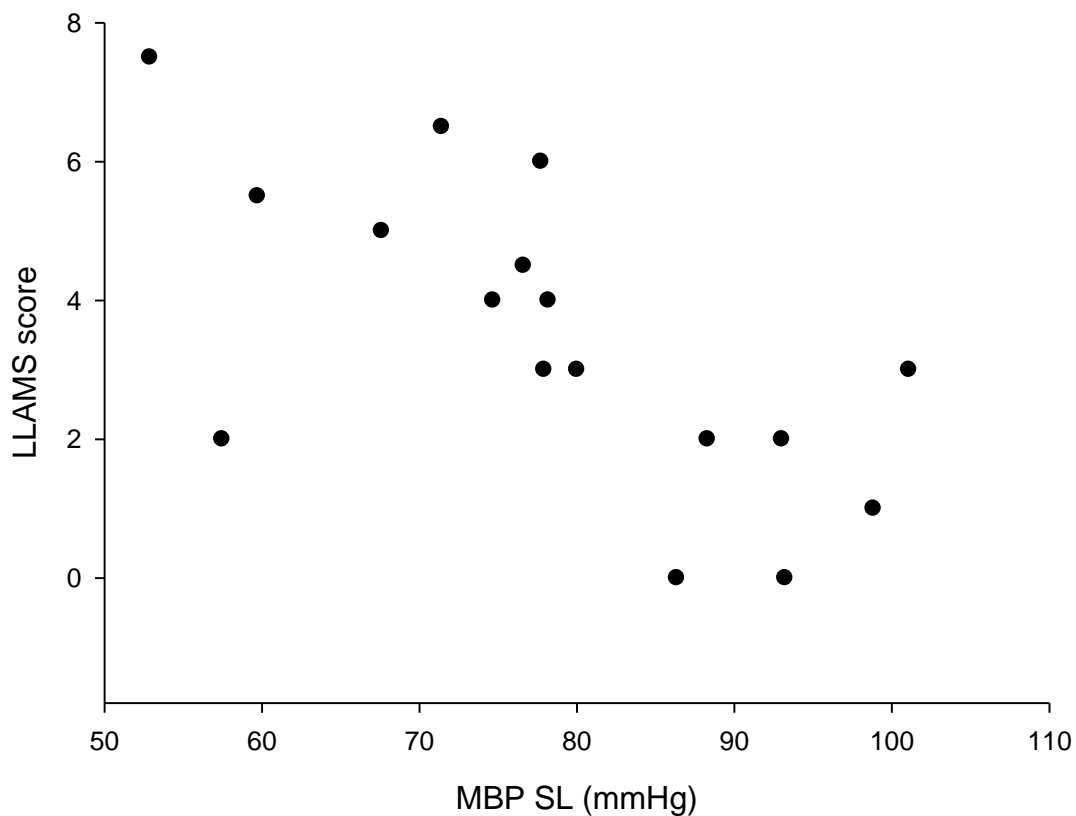
Table 3
Variables significantly correlated with LLAMS score selected for multiple linear regression and their correlation with LLAMS score (R)

	Pearson Correlation R
HCR	-0.58*
MBP (SL)	-0.67**
CBF (SL)	0.47*
CVC (SL)	0.71**
CVR (SL)	-0.66**
Hct (SL)	-0.50*

P < 0.05*, 0.01**, SL = sea-level

As CVC and CVR were also highly correlated with both CBF (R = 0.77, -0.81, respectively) and MBP (R = -0.89, 0.86, respectively) at sea-level, these variables were removed from the multiple regression model to reduce collinearity. No variables measured at altitude were correlated with LLAMS score. Simple linear regression, therefore, identified the following variables as being highly correlated with LLAMS score and were chosen for the subsequent multiple regression analysis; HCR, CBF SL, MBP SL and Hct SL.

Figure 1
Relationship between AMS score and MBP at sea-level (SL)

The backward procedure isolated MBP SL as the only significant predictor of LLAMS score (Table 4). A quadratic transformation of MBP SL had little effect on the model

fit and was hence not included in the final analysis. MBP SL accounted for 45 % ($R^2 = 0.448$) of the prediction of LLAMS score.

Table 4
Multiple linear regression analysis of variables as predictors of LLAMS score

	Variables	Coefficient	SE	*P*
Multiple Regression	HCR	-0.622	0.642	0.352
(all variables)	CBF SL	0.037	0.041	0.384
	MBP SL	-0.061	0.035	0.105
	Hct SL	-0.159	0.106	0.161
Backwards Analysis	MBP SL	-0.105	0.030	**0.003**
(best fit)				

P indicates significance of *t* tests of regression coefficients against 0. SL = sea-level.

DISCUSSION

Exposure to high altitude (5,050 m) for 1-3 days was found to affect several physiological variables and result in the development of AMS symptoms to varying degrees in the majority of subjects. The severity of AMS, as determined by the Lake Louise AMS scoring system, was best predicted by the measurement of MBP at sea-level which accounted for 45 % of the prediction of AMS score.

Exposure to high altitude for 1-3 days elevated both HR and MBP, with an increased sympathetic activity likely responsible for these changes. Although elevated HR at altitude is well documented [12, 13, 22, 27, 28, 32-35], few have concurrently reported an enhanced MBP [33, 34]. MBP appears to remain unchanged at altitude in the majority of studies [12, 22, 27, 28, 36]. Contrasting findings within the literature are potentially related to differing methodologies, including factors such as real versus simulated altitude, magnitude of elevation (m), rate of ascent and duration at altitude. Although a simulated altitude protocol was utilised by Sevre et al. (2001), the fact that they also reported elevated BP with increased altitude is potentially due to the stepwise increment in altitude over 3 days to an elevation of 4500 m, similar to the real elevation in altitude in the present study. The other aforementioned studies either exposed subjects immediately to altitude (simulated) [12, 27, 28, 37] or ascent occurred faster than the present study (~ 1.5 days, [22]). A gradual rate of ascent has previously been shown to elevate HR to a greater level than an abrupt ascent (Vogel et al. 1967 – reviewed in [38]), a similar BP response may potentially occur.

Sea-level MBP was negatively correlated with AMS severity (R = -0.67, P < 0.01) and was the only significant predictor of AMS score. In contrast to the present finding, a significantly higher resting MBP at low altitude has been found in individuals susceptible to AMS (R = 0.5, *P* = 0.03) [21]. As the occurrence of AMS is well known to be influenced by the rate of ascent to altitude [4], with symptoms generally developing from 6 h of exposure [1], these differing findings may be due to a combination of slower rate of ascent and delayed recording of AMS symptoms (1-3 days versus 2-4 h) upon arrival at altitude in the present study. A further possibility is that in the present study, AMS score was obtained from the self-reported section of the Lake Louise questionnaire, whereas, Lanfranchi et al. (2005) combined the self-reported and clinical assessment sections. Although sea-level MBP was detected as the best predictor for AMS severity, it only accounted for ~ 45 % of AMS score, hence it is clear there are other factors involved in AMS susceptibility.

AMS severity was not related to either sea-level or altitude HR or SaO$_2$ values, however, when the fall in SaO$_2$ at altitude was simultaneously considered with the change in HR, the hypoxic cardiac response was significantly correlated with AMS score (R = -0.58, *P* < 0.01), although it was not a significant predictor of AMS. In contrast, Leoppky et al. (2008) found HR at altitude (12 h at simulated altitude 4880m) to be greater in those with the highest Lake Louise AMS scores compared with those with the lowest scores. Differing methodology between the two studies; real vs simulated altitude, rate of ascent to altitude, duration at altitude (24-72 h vs 12 h); may explain these conflicting findings. Although the fall in SaO$_2$ at altitude has previously been suggested to be the most useful predictor of AMS susceptibility [5,

12, 13], this is not supported by the current research or several earlier studies [20-22]. This suggests that some factor other than the extent of hypoxaemia is responsible for the development of AMS.

Resting CBF was elevated by 35.7% following 1-3 days exposure to high altitude ($P < 0.001$). This elevation falls within the range reported (30-60%) upon acute ascent to ~ 4000 m altitude [39], and is supported by many studies which have found an increase in CBF at altitude [28, 40]. There are, however, several reports of no change in CBF upon exposure to simulated [12, 27, 33] or real [22, 41] altitude. CBF change is dependent upon the sensitivity of the individual to hypoxic cerebral vasodilation and hypocapnic cerebral vasoconstriction, potentially explaining the varied CBF responses to altitude [39]. The elevation of MBP and CBF at altitude in the present study resulted in no change in either CVC or CVR upon altitude exposure.

Resting CBF at sea-level was significantly correlated to AMS score ($P < 0.05$). This supports a previous finding that subjects exhibiting AMS symptoms (≥3 Lake Louise AMS scoring system) had a significantly higher resting CBF than those without AMS (0-2 Lake Louise score) [18]. Following further analysis (multiple regression with backward process), however, it became clear that, in the present study, CBF at sea-level was not a significant predictor of AMS score. Altitude CBF was not related to severity of AMS, supportive of several publications [12, 22, 27, 29]. With the recent publication of data from 1985 [26], when Brian Cummins directly measured intracranial pressure at high altitude (5,030 m), it appears that the development of AMS may be dependent upon the compliance of the CBF systems and subsequent

accommodation of increased intracranial pressure upon exposure to high altitude. Less invasive research has recently supported the role of intracranial pressure in the development and severity of AMS by utilising the measurement of optic sheath diameter [24, 25]. The elevated CBF at altitude, therefore, appears to not be a predictor of AMS itself, but rather how the brain copes with the resulting increased intracranial pressure. In addition, impaired dynamic autoregulation of cerebral circulation has been found at real altitude [22, 41], which has been reported to be the only significant independent predictor of AMS severity (Environmental Symptom Questionnaire) [22].

A disturbance in plasma volume has previously been suggested to be related to AMS susceptibility (Ward et al. 2000 – In [42]). This is not supported by the current research where no change in PV was found, as determined by Hb and Hct data. The estimation of PV change in the present study, however, may not be as precise as the method adopted by Ward et al. (2000) (In [42]).

The hyperventilatory-induced hypocapnia experienced during the first few days at high altitude was accompanied by a reduction in bicarbonate levels. This relationship has previously been reported [43], with an enhanced removal of excess base potentially occurring as a result of diuresis [44]. As the percentage fall in $PaCO_2$ was greater than that of $HCO3^-$, supportive of a previous finding [43], pH was increased at altitude, supportive of the literature [35].

Despite a wide age range in our subjects (19 – 57yr), no correlation was found between AMS score and age, potentially due to our relatively low subject numbers. Conflicting results regarding the relationship between AMS score and age are presented in the literature. Lanfranchi et al. (2005) found older subjects to be more symptomatic, whereas Wagner et al. (2008) reported a negative correlation between age and AMS score, potentially due to brain atrophy and hence larger ventricles in the older individual allowing for improved protection upon increased intracranial pressure (reviewed in [26]).

CONCLUSIONS

In summary, exposure to high altitude for 1-3 days affected many cardiorespiratory and cerebrovascular variables. Sea-level MBP, CBF and Hct, and HCR were strongly correlated with AMS score, however, sea-level MBP was the only significant predictor of AMS score (R^2 = 0.448, P < 0.01). As the majority of the AMS score remained unpredicted, it is clear other variables, as not measured in the current research, are involved in the prediction of AMS susceptibility. Factors such as intracranial pressure and dynamic cerebral autoregulation may potentially be involved in the development of AMS at altitude. The measurement of these factors, however, involves specialised equipment and experienced individuals, and are, therefore not practical for AMS prediction for the general population ascending to altitude.

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