Heart rate variability changes at 2400 m altitude predicts acute mountain sickness on further ascent at 3000-4300 m altitudes

Karinen, Heikki M.

2012


http://hdl.handle.net/10138/166784
https://doi.org/10.3389/fphys.2012.00336

Downloaded from Helda, University of Helsinki institutional repository.
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.
Heart rate variability changes at 2400 m altitude predicts acute mountain sickness on further ascent at 3000–4300 m altitudes

Heikki M. Karinen1,2*, Arja Usitalo2, Henri Väähä-Ypyä3, Mika Kähönen4, Juha E. Peltonen2,7, Phyllis K. Stein6, Jani Viik6 and Heikki O. Tikkonen2,7

1 Unit for Occupational Health, Department of Health Sciences, University of Tampere, Tampere, Finland
2 Department of Sports and Exercise Medicine, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland
3 Department of Biology of Physical Activity, University of Jyväskylä, Jyväskylä, Finland
4 Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, Finland
5 Division of Cardiology, Washington University School of Medicine, St. Louis, MO, USA
6 Department of Biomedical Engineering, Tampere University of Technology, Tampere, Finland
7 Clinic for Sports and Exercise Medicine, Foundation for Sports and Exercise Medicine, Helsinki, Finland

**Objective:** If the body fails to acclimatize at high altitude, acute mountain sickness (AMS) may result. For the early detection of AMS, changes in cardiac autonomic function measured by heart rate variability (HRV) may be more sensitive than clinical symptoms alone. The purpose of this study was to ascertain if the changes in HRV during ascent are related to AMS. **Methods:** We followed Lake Louise Score (LLS), arterial oxygen saturation at rest (R-SpO2) and exercise (Ex-SpO2) and HRV parameters daily in 36 different healthy climbers ascending from 2400 m to 6300 m altitudes during five different expeditions. **Results:** After an ascent to 2400 m, root mean square successive differences, high-frequency power (HF2min) of HRV were 17–51% and Ex-SpO2 was 3% lower in those climbers who suffered from AMS at 3000 to 4300 m than in those only developing AMS later (≥5000 m) or not at all (all p < 0.01). At the altitude of 2400 m RMSSD2min ≤ 30 ms and Ex-SpO2 ≤ 91% both had 92% sensitivity for AMS if ascent continued without extra acclimatization days. **Conclusions:** Changes in supine HRV parameters at 2400 m were related to AMS at 3000–4300 m Thus, analyses of HRV could offer potential markers for identifying the climbers at risk for AMS.

**Keywords:** extreme altitude, altitude illness, heart rate variation, mountaineering

**INTRODUCTION**

When ascending to high altitude, the body needs to acclimatize to low atmospheric pressure and hypoxic hypoxia (Hackett and Roach, 2001). If the adaptation process fails due to too rapid ascent rate or susceptibility of the climber, one or more of three illnesses may result: acute mountain sickness (AMS), high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE). AMS is the most common of these problems affecting 25% of those who ascend to altitudes of 1850–2750 m (Honigman et al., 1993), 42% at altitudes of 3000 m (Hackett and Roach, 2001) and as many as 75% among those attempting Mount Kilimanjaro (5984 m) (Karinen et al., 2008). AMS is a non-specific syndrome characterized by the presence of headache and at least one of the following: gastrointestinal symptoms (loss of appetite, nausea, and vomiting), insomnia, dizziness, and weakness or fatigue. It is a self-limiting syndrome, which usually resolves in 1–2 days if properly treated (rest, descent to lower altitude, medication etc.) but may sometimes progress to more serious altitude illnesses such as HAPE and HACE (Hackett and Roach, 2001; Imray et al., 2011).

The exact mechanism causing AMS is unknown, but a marked increase in peripheral sympathetic activity is a common feature of AMS (Kamimori et al., 2009) and may be involved in the pathogenesis of HAPE (Mazzeo et al., 1998; Duplain et al., 1999; West, 2004). Heart rate variability (HRV) reflects sympathetic and parasympathetic cardiac autonomic nervous system regulation. Several studies have shown a transient reduction in parasympathetic and increased sympathetic activity during acute exposure to hypobaric hypoxia (Zuzewicz et al., 1999; Sevre et al., 2001; Saito et al., 2005; Hainsworth et al., 2007) which tended to be reversed with acclimatization (Cornolo et al., 2004).

There is a need for a non-invasive, specific and convenient method under field conditions for the detection of inadequate acclimatization and impending AMS. The arterial oxygen saturation (SpO2) measurement is useful in anticipating AMS (Roach et al., 1998; Karinen et al., 2010) but use of pulse oximetry under field conditions is susceptible to many disruptive factors e.g., temperature (Luks and Swenson, 2011). Reduction in parasympathetic and increased sympathetic activity during acclimatization and AMS at 3180–4559 m altitudes have been shown in several studies (Loeppky et al., 2003; Lanfranchi et al., 2005; Chen et al., 2008; Huang et al., 2010). To the best of our knowledge, studies on HRV conducted in the field at extreme altitudes (>5000 m) are still lacking, despite two studies at simulated altitude (Yamamoto...
et al., 1993; Wille et al., 2004). Therefore the purpose of this study was to evaluate whether HRV is related to AMS during ascent and provides new information on the changes in cardiac autonomic function as measured by HRV and not limited to altitudes between 2400 and 5000 m, which are most frequent among climbers, but also at extreme altitudes above 5000 m under field conditions.

**MATERIALS AND METHODS**

The study group consisted of participants in four different expeditions to Denali (Denali 1, Denali 2), Shisha Pangma and Mount Everest. All subjects were informed about the objective of the study and the experimental protocol. The Ethics Committee of Tampere University Hospital, Finland, approved the study protocol, and all subjects gave informed consent prior to the measurements, as stipulated in the Declaration of Helsinki. Thirty six healthy volunteers (2 women and 34 men) with an age range of 24–45 years participated in this study. Subjects’ mean age was 32 (SD 6) years, body mass index (BMI) 25 (3) kg/m² and maximal oxygen uptake (VO₂max) 59 (7) ml/kg/min. None of the subjects had been exposed to an altitude above 1000 m within the 6 months prior to this study. They were all lowland dwellers and recreational mountaineers, and during the expeditions none had taken acetazolamide as an AMS prophylaxis. Two climbers were taking regular medication for asthma but no one was using oral steroids, salmeterol, sildenafil or nifedipin. All expeditions were organized in April-May. Ascent profiles were similar at sleeping altitudes, but three expeditions had faster and two slower ascent rate. Before the expeditions, all members underwent a medical examination including resting ECG and flow volume spirometry. To examine their exercise responses and to measure maximal oxygen uptake (VO₂max), they performed an incremental clinical exercise test on a cycle ergometer (Ergoline 800S, Ergoline GmbH, Bitz, Germany). They started cycling at 20 W and work rate was increased stepwise 20 W/min up to volitional fatigue. A 12-lead ECG was obtained at rest before the exercise, and during the exercise test. All subjects had a normal EKG and none developed arrhythmias during the exercise test.

**DATA COLLECTION DURING ASCENT**

Autonomic cardiac function was assessed by analysis of R-R intervals (RRI). In power spectral analysis of HRV total variability of RRI is divided into low and high frequency bands. High frequency power (HF power, 0.15–0.40 Hz) reflects cardiac parasympathetic modulation and is influenced by respiration. Low frequency power (LF power, 0.04–0.15 Hz) reflects both cardiac sympathetic and parasympathetic modulation. The ratio of LF and HF powers (LF/HF) has been reported to reflect sympathetic and parasympathetic modulation. The ratio of LF/HF has been reported to reflect sympathovagal balance. RMSSD is the square root of the mean squared differences of successive RRI and it is considered to be an index of cardiac parasympathetic modulation (Task Force, 1996). Data processing and analysis were performed after the expeditions by Polar Precision Performance software (version 3.02.007) and Kubios software (version 2.0) (Niskanen et al., 2004). Areas of ectopy or artifact were identified and fixed by manual or automatic error correction. Corrected segments were less than 5% of the analyzed data. Analysis of HRV was done for stationary 2 min data segments. The power spectra were quantified by measuring the area in two frequency bands. The HF₂min power was calculated for frequency band 0.15–0.40 Hz and LF₂min power for frequency band 0.04–0.15 Hz.

After the HRV and SpO₂ measurements subjects were scored according to the Lake Louise scoring (LLS) AMS system, which include a self-report questionnaire related to the presence and severity of symptoms and a clinical assessment (Hackett and Oelz, 1992). The LLS was obtained by adding the score of the clinical section to the self-report questionnaire. AMS was diagnosed
Figures 1 A: Ascent profiles of different expeditions and number of AMS cases at different altitudes. Three climbers descended after 4300 m because of AMS. Measurements were made daily up to 5300 m except on Shisha Pangma, where measurements were made up to 5600 m. AMS, Acute Mountain Sickness; AMS*, AMS at this altitude; AMS**, AMS at some other altitude.

AMS= Acute Mountain Sickness, AMS*= AMS at this altitude, AMS**= AMS at some other altitude

According to a recent gain in altitude, the presence of headaches and at least one of the following symptoms: gastrointestinal (GI) upset, fatigue, dizziness or insomnia. To study retrospectively, whether HRV changes could have predicted AMS at higher altitudes, we divided the study group into two groups: (1) If the LLS was $\geq 3$ at any altitude the subject was assigned to the AMS group, and (2) If the LLS was $\leq 2$ at every altitude measured, the subject was assigned to the no-AMS group.
STATISTICAL ANALYSIS
Continuous values are presented as means ± standard deviation (SD). The frequency of parameters was assessed by χ² tests with Yates’ correction. Differences between AMS and no-AMS groups were compared by nonparametric t-test. Correlations between the LLS and clinical and autonomic variables were assessed by Pearson’s correlation. In all tests p ≤ 0.05 was considered significant.

RESULTS
In total, 36 subjects were studied up to the altitude of 4300 m. Three discontinued because of AMS and the remaining 33 continued up to 5000 and 5300 m altitudes. Five made all measurements at 5600 and one at 6300 m altitude. The Denali 1 and Shisha expeditions reached the altitude of 5000 m in 7 days (n = 16) and the Denali 2 and Everest expeditions took 11–17 days to reach the same altitude (n = 20) (Figure 1). Acute mountain sickness developed in 24 out of 36 (66%) subjects at some altitude between 3000 and 5600 m, including both women and 22 of 34 men, while 12 men (34%) did not get AMS at any altitude (no-AMS group). There were 11 AMS cases in the faster group and 13 AMS cases in the slower group. The groups did not differ in age, BMI or VO₂max. The descriptive data of participants and ascents for each expedition are presented in Table 1 and Figure 1.

During this study, the daily ascent rates were mostly higher than what is generally recommended (300 m/day) but quite common for these mountains (range 400–1500 m). In the no-AMS group, RMSSD_{2 min}, LF_{2 min} and HF_{2 min} increased in the first few days of the ascent. Above 3500 m all HRV parameters decreased while HR increased.

The number of AMS cases at different altitudes is presented in Figure 1. Among those who suffered from AMS, LLS scores varied between 3 and 8. Most of the AMS cases occurred at 5300 m (n = 12) or not at all (n = 12) (Figure 1). Headache and difficulty in sleeping were the most frequent symptoms of AMS followed by GI symptoms, fatigue, and dizziness.

At 2400 m altitude, RMSSD_{2 min} and HF_{2 min} were lower among those climbers who got AMS at lower altitudes (3000–4300 m) (n = 12) than in those who got AMS 3–7 days later at higher altitude (≥5000 m) (n = 12) or not at all (n = 12) (Table 2). HR_{2 min}, lnHF_{2 min} and RMSSD_{2 min} at 2400 m correlated with the lowest altitude at which a climber suffered AMS (AMS altitude) (Figure 2). There were no differences between R-SpO₂ at 2400 m and later onset of AMS, but Ex-SpO₂ was statistically higher in the no-AMS than the AMS group at 3000–4300 m (p < 0.01) (95% CI 3 (1–5) and in the AMS at ≥ 5000 m group (p < 0.05). However, Ex-SpO₂ did not correlate with the AMS altitude (r = −0.028). At the altitude of 2400 m RMSSD_{2 min} ≤ 30 ms and Ex-SpO₂ ≤ 91% both had 92% sensitivity for AMS at 3000–4300 m if the ascent continued without extra acclimatization days (Figure 3). The sensitivity, specificity, positive, and negative predicative values for chosen cut-off values are presented in Table 3.

DISCUSSION
Our most important finding was that subjects susceptible to AMS had lower HRV before the clinical manifestations of AMS than those who acclimatized well and did not get AMS. This is a new finding and offers fascinating options for predicting AMS at high altitude in field conditions.

The diagnosis of AMS is clinical, but some specific changes in cardiac autonomic function measured by HRV have been estimated to be more sensitive in the detection of the early signs of AMS than clinical symptoms alone at high altitudes (Saito et al., 2005). HRV is reported to decrease in absolute units (Hughson et al., 1994; Bernardi et al., 1998; Kanai et al., 2001) and LF/HF mostly increased when subject got AMS (Loepky et al., 2003; Lanfranchi et al., 2005; Chen et al., 2008; Huang et al., 2010). There are, however, also opposite findings reported about HRV (Koehle et al., 2010). However, studies conducted in the field at high and extreme altitudes (>5000 m) are still lacking.

During mild sympathetic activation, the observed increase in HR has been reported to be associated with an increase in LF power (Elghozi and Julien, 2007). However, with more intense sympathetic stimulation, the increase in HR was reported to be associated with an overall decrease in HRV, including its LF component. Our present findings on changes in HRV values at extremely high altitudes support this concept.

Table 1 | Demographic data (age, BMI, and VO₂max) of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>no-AMS (n = 12)</th>
<th>AMS at some altitude (n = 24)</th>
<th>All (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>30 ± 5</td>
<td>33 ± 7</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 1</td>
<td>25 ± 4</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>VO₂max (mL/kg/min)</td>
<td>60 ± 4</td>
<td>60 ± 9</td>
<td>59 ± 7</td>
</tr>
</tbody>
</table>

There were no statistically significant differences in the basic characteristics between no-AMS and AMS groups.

Values are mean ± SD. BMI, body mass index; VO₂max, maximal oxygen uptake.

Table 2 | Resting heart rate (HR) and HRV parameters at 2400 m among the climbers who subsequently developed AMS at two different altitude ranges, and those who had no subsequent AMS.

<table>
<thead>
<tr>
<th></th>
<th>no-AMS (n = 12)</th>
<th>AMS at 3000–4300 m (n = 12)</th>
<th>AMS at ≥ 5000 m (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>70 ± 9</td>
<td>82 ± 15*</td>
<td>62 ± 8*†</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>43 ± 25</td>
<td>21 ± 13*</td>
<td>48 ± 32†</td>
</tr>
<tr>
<td>InLF (ms²)</td>
<td>7 ± 1</td>
<td>6 ± 1†</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>InHF (ms²)</td>
<td>6 ± 1</td>
<td>5 ± 2*</td>
<td>7 ± 2†</td>
</tr>
<tr>
<td>LF/HF</td>
<td>5 ± 4</td>
<td>6 ± 6</td>
<td>1.2 ± 1.1†</td>
</tr>
<tr>
<td>R-SpO₂</td>
<td>94 ± 1</td>
<td>93 ± 2</td>
<td>94 ± 2</td>
</tr>
<tr>
<td>Ex-SpO₂</td>
<td>91 ± 2</td>
<td>88 ± 3‡</td>
<td>89 ± 3*</td>
</tr>
</tbody>
</table>

Values are presented in mean ± SD. †p < 0.05, ‡p < 0.01, difference between AMS 3500–4300 m vs. no-AMS groups and AMS ≥ 5000 m vs. no-AMS groups, †p < 0.05, difference between AMS 3500–4300 m vs. AMS ≥ 5000 m.
FIGURE 2 | Negative correlation between HR and positive correlation between lnHF, lnLF, and RMSSD at 2400 m altitude and the lowest altitude at which a climber got AMS (HR $r = -0.743$, $p < 0.01$; lnHF $r = 0.558$, $p < 0.05$, lnLF $r = 0.302$, $p < 0.05$, RMSSD $r = 0.495$, $p < 0.05$). No-AMS subjects datapoints are added at 5600 m level.

FIGURE 3 | Scattergram showing the distribution of values of RMSSD and Ex-SpO2 measured in 24 study subjects at 2400 m in AMS and no-AMS. The cut-off lines RMSSD$_{2\text{min}} \leq 30$ ms and Ex-SpO2 $\leq 91\%$ are for 92% sensitivity for AMS.

At 2400 m the no-AMS group had higher HRV and lower HR$_{2\text{min}}$ than the AMS group. The differences are not related to differences in physical fitness in the AMS and no-AMS groups because the basic maximum oxygen uptake did not differ significantly between the groups (59 ± 11 vs. 60 ± 4, $p > 0.05$). Furthermore, clear changes did not come in connection with the ascent. However, in the no-AMS group HF$_{2\text{min}}$ tended to be lower, while LF$_{2\text{min}}$ tended to be higher than in the AMS group.
The physiologic significance of these findings remains uncertain, but they do not directly support the earlier assumption that AMS is simply connected with higher cardiac sympathetic activity. Rather, it seemed that a rise in cardiac sympathetic activity would have been a protective phenomenon against altitude illness. However, altitude illness is a dynamic process. It may be that as the AMS proceeds, HRV could further decrease. In other words, changes in HRV were related to higher altitudes in all climbers, but also notably to acclimatization and especially to failure to acclimatize.

The present findings are still generally in agreement with those of earlier studies and provide further insights into the usefulness of HRV in the prediction of AMS under field conditions. Several studies have shown that of SpO2 measurements at rest (R-SpO2) and immediately after exercise (Ex-SpO2) are predictors of AMS (Roach et al., 1998; Saito et al., 2005; Burtscher et al., 2008; Karinen et al., 2010). Our study supports this. At 2400 m altitude the Ex-SpO2 was statistically higher in no-AMS group than AMS 3000–4300 group (p < 0.01) and AMS ≥ 5000 m group (p < 0.05). However, the SpO2 measurements made by pulse oximetry under field conditions may be susceptible to many disruptive factors (temperature, bright light, cold fingers etc.) (Luks and Swenson, 2011). Therefore, it is desirable to have another parameter(s) to follow-up for AMS susceptibility. Our findings support the possibility that HRV could be used along with commonly measured physiological parameters, HR and SpO2, clinical status and Lake Louise questionnaire for AMS prediction in the short time period at moderate altitudes. The altitude of 5000 m was reached mainly during the sleep, but also in some extent during wake (Insalaco et al., 1996; Fans et al., 2012). Because the breathing frequency was not measured in our study, we cannot exclude it totally. Unfortunately, we do not have sea-level HRV data for all subjects, so we cannot estimate whether those climbers whose basic level of HF is higher could acclimatize better than those whose HF level is lower at sea-level.

Periodic breathing has reported to exist at high altitude mainly during the sleep, but also in some extent during wake (Insalaco et al., 1996; Fans et al., 2012). Because the breathing frequency was not measured in our study, we cannot exclude it totally. McMullen et al., 2012. However, the visual analysis of RRI tachograms, AR spectrum and Poincare plots do not support the existence of periodic breathing during the measurements. The measurement periods were 2 min so we can assume that any significant periodic breathing was not seen when lying down during this measurement period.

The strengths of the present study are that the rate of ascent, altitude of origin and time of day of testing were known. Also, within each group every climber had a similar diet, they were relatively homogenous in their exercise capacity and they climbed the same route on mountains over a short period of time with essentially the same snow and weather conditions. Barometric pressure varied from day to day but during measurements it was stable.

In conclusion, at 2400 m decreased RMSSD2min and HF2min both predicted AMS in a few days if the ascent continued without rest days. Autonomic cardiac response to increasing altitude could be a low-cost non-invasive test to predict impending AMS and to help distinguish those who are at risk for AMS and those who are acclimatizing well. The trigger values typical for impending AMS await further studies.
REFERENCES


Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 10 February 2012; paper pending 21 March 2012, accepted: 31 July 2012; published online: 30 August 2012.


This article was submitted to Frontiers in Clinical and Translational Physiology, a specialty of Frontiers in Physiology.

Copyright © 2012 Karinen, Uusitalo, Vähä-Yppä, Kähönen, Peltonen, Stein, Viik and Tikkanen. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and subject to any copyright notices concerning any third-party graphics etc.