

PREDICTABILITY OF ACUTE MOUNTAIN SICKNESS

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Abstract

Introduction: Acute mountain sickness (AMS) is a common phenomenon during exposure to high altitude. Since there are growing numbers of tourists in the mountains, the prevention of or at least the development of predictive models for AMS is very important. Hence, the aim of the present study was to predict AMS.

Material and methods: 31 subjects (45% men, 55% women, age: 38 ± 12 years, BMI: $23 \pm 3 \text{ kg/m}^2$) have been tested in a prospective field study design. Tests in normoxia and exposure to natural high altitude (3650m, 45 hours) were parts of the study. The main parameter was the prevalence of AMS. Multivariate logistic regression analyses were conducted to detect possible predictors for AMS.

Results: The predictors “physical activity” and “arterial oxygen saturation in normoxia” showed the best regression model for the prevalence of AMS (percentage of correctly predicted cases: 90%, $R^2 = 59\%$). Higher physical activity and lower oxygen saturation were negatively related to the probability to develop AMS.

Conclusions: The prediction model for the prevalence of AMS showed very good values and represents a reliable alternative to existing predictions models. Additionally, physical activity and arterial oxygen saturation are parameters which can be determined easily and without simulated altitude. On the basis of the current results, physical activity deserves further attention when predicting AMS. Future studies should evaluate the influence of physical activity on AMS at different exercise intensities at high altitude.

Keywords: *Altitude sickness, oxygen saturation, prediction, physical activity*

Introduction

In the last decades, sport practice in the mountains such as hiking, climbing, ski mountaineering, and similar disciplines have shown increasing numbers of participants. According to recent estimates, there are 40 million of mountain tourists per year in the entire Alps [1]. However, sport and tourism are not the only reasons for sojourns at high altitude. Professional categories like scientists, miners, and soldiers (e.g. in Afghanistan) are often exposed to high altitude [2, 3]. Exposures to high altitude are associated with a decrease in endurance performance [4] and with the risk of high altitude diseases, out of which acute mountain sickness (AMS) is the most common [5].

AMS is defined as a usually self-limiting condition which impairs previously healthy people on fast ascents above 2300m [6]. Headache, gastrointestinal symptoms, weakness, dizziness, and sleeping disorders are parts of the symptom complex [7]. In general, the culmination of complaints manifests 24 to 48 hours after altitude exposure [6, 8]. The prevalence of acute mountain sickness mainly depends on the achieved altitude and varies between 9% on 2850m, 53% on ca. 4500m [9], and over 70% on nearly 6000m altitude [10]. Other contributing factors to the development of AMS are the ascent rate and acclimatization status [8]. Additionally, an individual susceptibility seems to be an independent risk factor for AMS development [11]. The detailed mechanisms of AMS development remain unclear, however, the decreased

arterial blood oxygenation seems to be a key factor for the development of AMS [6].

Several attempts to predict individual risk for AMS were conducted in the past [7, 12-15]. This knowledge would allow susceptible individuals to plan mountain tours adequately (e.g. slower ascent rate, pre-acclimatization, medicinal prophylaxis) or to abstain completely from certain tours. However, prediction of AMS is compounded by the large inter- and intra-individual variability in AMS prevalence [7]. Until now, the strongest predictor is “occurrence of severe AMS in prior exposures to high altitude” [15]. This prediction model can even be improved by the additional consideration of the predictors “high desaturation at exercise” and “low ventilatory response to hypoxia at exercise” [15]. However, experiences of previous exposures to altitude are missing or often heterogeneous. Another prediction model was developed on the basis of the results of an exercise test in altitude (“time needed for the test” and “desaturation during the test”) [12]. The authors wanted to predict, at which time an individual is able to ascend further without the risk of developing AMS. Other authors merely propose “arterial blood oxygenation in hypoxia” as a predictor [13, 14]. However, all these prediction procedures need a prior exposure to simulated or real high altitude.

Hence, the main purpose of this study was to predict the incidence of acute mountain sickness in natural high altitude by normoxic parameters in susceptible individuals.

Methods

Study design

The present study was part of a larger high altitude project and showed a prospective field study design with 2 different study blocks. Each block contained the measurement of potential predictors (Innsbruck, Austria, 590m) and the exposure to natural altitude (Mönchsloch hut, Switzerland, 3650m). The study was approved by the review board of the Department of Sport Science of the University of Innsbruck (Austria). The investigation was carried out in conformity with the ethical standards laid down in the 1964 Declaration of Helsinki.

Procedure

Potential study participants were recruited by public announcements. Persons who responded to the study announcements were invited to a pre-participation testing to determine inclusion and possible exclusion criteria. Inclusion criteria were age between 18 and 60 years, at least 2 previous exposures to high altitude > 3000m, and susceptibility for AMS which was determined retrospectively according to Schneider et al. [16]: participants were asked whether each of the 5 AMS symptom complexes (headache, gastro-intestinal symptoms, fatigue/weakness, dizziness/light-headedness, and difficulty of sleeping) occurred during prior high altitude exposures never (= 0), seldom (= 1), often (= 2), or regularly (= 3). Persons with AMS susceptibility were defined as suffering often or regularly from headache (score ≥ 2) and with a total score ≥ 4 .

Exclusion criteria were the followings: pregnancy (according to pregnancy test), breast-feeding, chronic or acute diseases (already existing or diagnosed during the study), migraine, smoking (more than 5 cigarettes per day), habitual residence > 1000m, and overnight stay > 2500m in the last 4 weeks. Subsequently, a health-related history and clinical routine examination were conducted including the measurement of resting blood pressure (M4 Plus, Omron, Germany) and lung function (SP 200, Schiller, Austria).

The first consecutive 33 persons with AMS susceptibility and without exclusion criteria comprised the study population. Written consent was obtained from all individuals after they were informed about the experimental procedures and possible risks associated with participation. Two potential subjects had to be excluded (reasons: injury occurred at the beginning of the exposure to high altitude, measurement error). Therefore, data of 31 participants (45.2% males; 54.8% females; age: 37.6 ± 11.7 years; height: $1.75 \pm .09$ m; body mass: 70.3 ± 11.3 kg; body mass index: 22.8 ± 2.5 kg/m²) were included into the analyses.

Anthropometric data and physical activity (hours/week) were assessed by interview. Physiological resting parameters in normoxia were determined in a seden-

tary position after at least 5 minutes rest. Respiratory parameters (ventilation, tidal volume, breathing frequency) were measured using an open spirometric system (MetaLyzer 3B, Cortex, Germany). Capillary blood samples were collected from the hyperemized earlobe to determine hematological parameters (pH, arterial partial pressure of oxygen and carbon dioxide, oxygen saturation, hematocrit, hemoglobin, and bicarbonate concentration) (ABL80 FLEX Co-Ox, Radiometer, Denmark).

The exposure to high altitude took place 7 to 10 days after the measurements described above. The participants were transferred to Interlaken, Switzerland (570m), where they stayed overnight. On the next day, the subjects travelled by train and cog railway to the Jungfrauoch (3450m) and hiked about 1 hour on a marked and prepared glacier path to the Mönchsloch hut (3650m), where the 45-hour high altitude sojourn took place. At the first day of the high altitude exposure, mountain guides instructed the participants in mountaineering skills (e.g. rope techniques at the glacier) between the measurements. No physical activities were planned at the first day of the high altitude exposure. At the second day, a glacier trek of about 5 hours was led by the mountain guides. Participants were instructed to choose moderate exercise intensity in all activities, according to a rating of perceived exertion ≤ 13 at the Borg's rate of perceived exertion scale [17], because heavy exertion would be a trigger for AMS [18]. Rate of perceived exertion was assessed retrospectively in the evening of the first and the second day. Participants were instructed to drink regularly (water ad libitum), but alcoholics were not allowed, because low fluid intake and alcohol may favor AMS development [18]. AMS was evaluated at regular intervals (3, 6, 9, 21, 30, and 45 hours after arriving at the Mönchsloch hut) according to the questionnaire of the Lake Louise Scoring (LLS) system [19]. AMS was defined as "developed" when the total score of the LLS was ≥ 4 and the item headache was ≥ 2 at one or more evaluation moments [20].

The complete high altitude sojourn was medically supervised by a physician, experienced in high altitude medicine, and not involved in any measurements. When AMS was developed, the symptoms were treated with NSAIDs (Ibuprofen) when requested by the subjects. After the conclusion of the 45 hours of exposure to high altitude, all participants descended and started the homeward journey.

Statistics

Statistical analyses were performed with SPSS Statistics 21.0 (IBM, Chicago, USA). Results were presented as frequencies (AMS prevalence) or means $\pm$ standard deviations.

To detect potential predictors for AMS prevalence, all items were tested for group differences between

“AMS developed” (AMS+) and “AMS not developed” (AMS-). T-Test for independent samples was used for normally distributed data, Mann-Whitney-U-Test for non-normally distributed data. Additionally, a correlation analysis (contingency coefficient C) between prevalence of AMS and all other items was conducted for further detection of possible predictors.

Uni- and multivariate binary logistic regression analyses were calculated for items showing significant group differences or a significant correlation with the prevalence of AMS. Nagelkerkes R^2 , sensitivity, specificity, and percentage of correctly predicted cases were stated for significant predictors. For significant univariate results, a power analysis was performed a posteriori using G*Power 3.1 (University of Düsseldorf, Germany) [21] and the methods for logistic regression analysis according to Faul et al. [22].

The level of significance was set at $p < .05$ (two-tailed).

Results

Overall, 21 participants (68%) developed AMS (AMS+) during the high altitude exposure, whereas ten participants (32%) did not develop AMS (AMS-). AMS prevalence at different evaluation times reached the maximum with 53% at 21 hours after exposure to high altitude and then declined continuously. For detailed results refer to Figure 1.

Participants developing AMS during the high altitude exposure reported a lower amount of physical activity, a lower functional vital capacity, a higher arterial oxygen saturation in normoxia, and a higher rate of perceived exertion at the first day compared to participants who did not develop AMS (see Table 1).

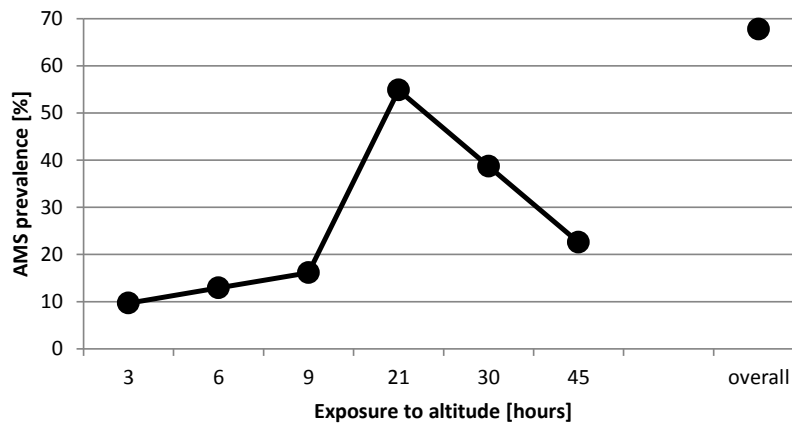


Figure 1. Prevalence of acute mountain sickness (AMS) during altitude exposure

Table 1. Test parameters for participants with (AMS+) and without (AMS-) development of acute mountain sickness

	AMS+ (n=21)	AMS- (n=10)	p
BMI [kg/m ²]	23.3 ± 2.8	21.8 ± 1.6	0.124
Age [years]	39 ± 12	34 ± 11	0.348
Physical activity [hours/week]	6 ± 2	13 ± 6	0.005*
Blood pressure systolic [mmHg]	134 ± 16	127 ± 9	0.254
Blood pressure diastolic [mmHg]	83 ± 8	78 ± 6	0.099
Functional vital capacity [l]	4.6 ± 0.9	5.5 ± 1.2	0.034*
SaO ₂ [%]	96.7 ± 0.9	95.9 ± 0.7	0.023*
pH	7.43 ± 0.02	7.42 ± 0.02	0.242
pCO ₂ [mmHg]	33.5 ± 3.6	31.5 ± 3.4	0.201
pO ₂ [mmHg]	84.3 ± 7.1	80.6 ± 6.0	0.166
Ventilation [l/min]	9.6 ± 2.3	9.8 ± 2.2	0.633
Tidal volume [l]	0.9 ± 0.3	0.9 ± 0.3	0.663
Breathing frequency [1/min]	11.9 ± 2.6	11.3 ± 2.9	0.595
RPE 1. day	13 ± 2	11 ± 2	0.007*
RPE 2. day	13 ± 2	12 ± 2	0.100

BMI: body mass index, SaO₂: arterial oxygen saturation, pCO₂: partial pressure of carbon dioxide, pO₂: partial pressure of oxygen, RPE: rate of perceived exertion. Data are presented as mean ± standard deviation.

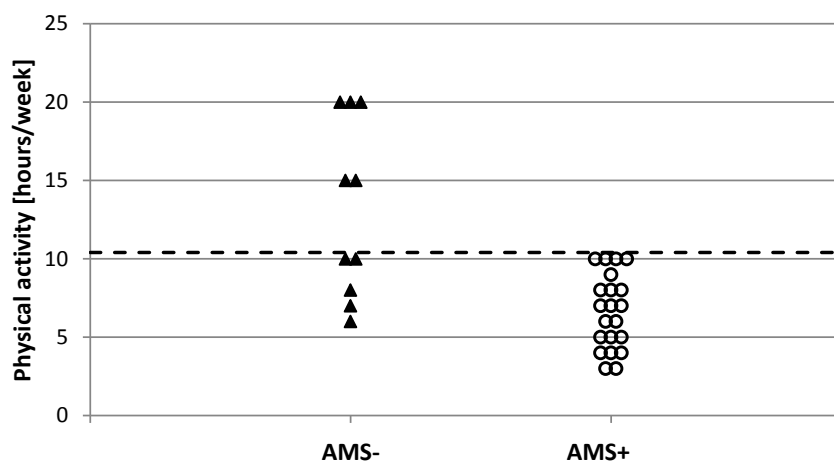


Figure 2. Actual and predicted development of acute mountain sickness (AMS) on the basis of physical activity

▲: AMS+: acute mountain sickness actually developed (n=21), ○: AMS-: acute mountain sickness actually not developed (n=10), broken line: predicted probability for AMS development: 50%

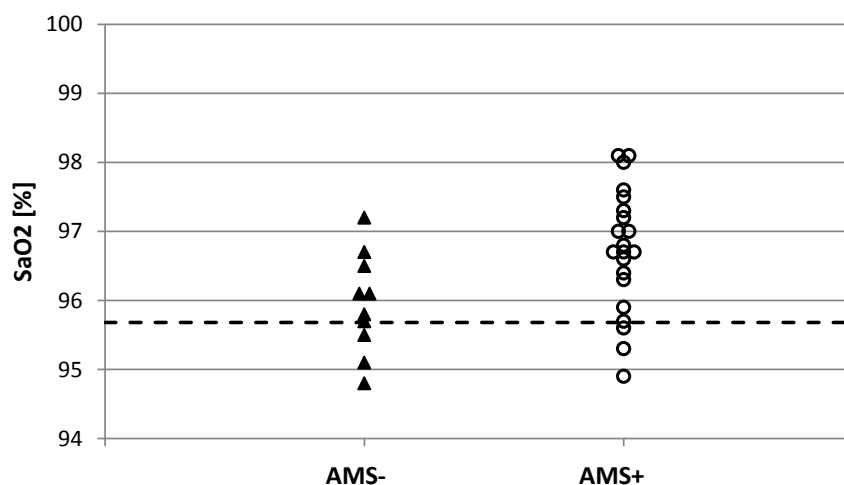


Figure 3. Actual and predicted development of acute mountain sickness (AMS) on the basis of arterial oxygen saturation in normoxia

SaO₂: arterial oxygen saturation in normoxia, ▲: AMS+: acute mountain sickness actually developed (n=21), ○: AMS-: acute mountain sickness actually not developed (n=10), broken line: predicted probability for AMS development: 50%

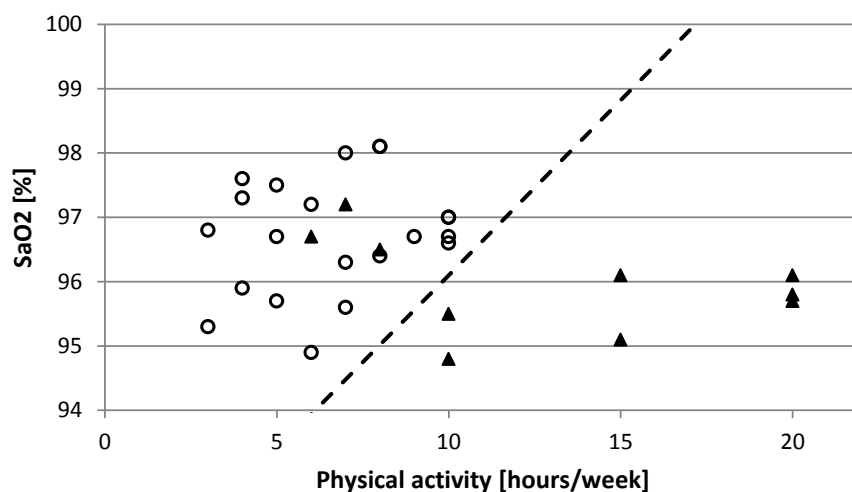


Figure 4. Actual and predicted development of acute mountain sickness (AMS) on the basis of the combination of physical activity and arterial oxygen saturation in normoxia (SaO₂)

▲: AMS+: acute mountain sickness actually developed (n=21), ○: AMS-: acute mountain sickness actually not developed (n=10), broken line: predicted probability for AMS development: 50%

Univariate binary logistic regression analysis showed the following significant predictors: “physical activity” ($p = .017$; $R^2 = 54.0\%$; specificity: 50.0%; sensitivity: 100%; percentage of correctly predicted cases: 83.9%), “arterial oxygen saturation in normoxia” ($p = .036$; $R^2 = 22.8\%$; specificity: 30.0%; sensitivity: 85.7%; percentage of correctly predicted cases: 67.7%), and “rate of perceived exertion on the first day” ($p = .046$; $R^2 = 20.9\%$; specificity: 30.0%; sensitivity: 90.5%; percentage of correctly predicted cases: 71.0%). “Partial pressure of carbon dioxide in normoxia” showed a significant correlation but no significant regression. „Functional vital capacity” showed significant group differences but no significant regression. Figure 2 and Figure 3 show the AMS prediction on the basis of the predictors „physical activity” and “arterial oxygen saturation in normoxia”, respectively.

The power analysis for univariate regression showed 96.1% for the predictor “physical activity”, 56.7% for the predictor “arterial oxygen saturation in normoxia”, and 50.0% for the predictor “rate of perceived exertion on the first day”.

The combination of “physical activity” ($p = .030$) and “arterial oxygen saturation in normoxia” ($p = .205$) showed the best prediction in multivariate binary logistic regression analysis ($R^2 = 58.8\%$, specificity: 70.0%; sensitivity: 100%; percentage of correctly predicted cases: 90.3%).

The regression equation is shown below:

$$P(\text{AMS}) = \frac{1}{1 + e^{-(73.43 - 0.44 \cdot \text{PA} + 0.81 \cdot \text{SaO}_2)}}$$

Equation 1. *Calculation of the probability for acute mountain sickness*

$P(\text{AMS})$: probability for acute mountain sickness, PA : physical activity, SaO_2 : arterial oxygen saturation in normoxia

In Figure 4, actual and predicted AMS development (combination of the predictors “physical activity” and “arterial oxygen saturation in normoxia”) is given.

Discussion with conclusions

Prevalence of acute mountain sickness

The high AMS prevalence at the altitude of 3650m in the present sample (68%) indicates that indeed susceptible individuals have been selected. Studying a selective population on one hand reduces the generalizability of the results; on the other hand it reveals AMS predictors specifically for susceptible individuals. Comparable studies showed similar values of AMS prevalence (75%) in higher altitudes (6000 m) [10] or lower prevalence (34%) at the same altitude [9], respectively. However, these authors assessed AMS prevalence only once, whereas in the present study AMS assessment took place six times.

Univariate prediction of acute mountain sickness

Univariate regression analysis revealed the predictor “physical activity” with the highest percentage of explained variance (54%) and with the highest rate of correctly predicted cases (84%). Participants reporting lower physical activity showed a higher percentage of AMS prevalence compared to subjects reporting higher physical activity. No AMS development has been shown in participants who trained more than 10 hours per week ($n = 5$). The present regression model showed values which are comparable to those of previously reported prediction models. In the past, the best prediction was on the basis of prior severe AMS which requires the experiences of prior (often heterogeneous) exposures to high altitude [15]. In contrast, the assessment of physical activity is easy and possible without any complex measurements and equipment.

Some authors reported preventive effects of endurance training on AMS development [23, 24]. Others showed a negative correlation between physical endurance and hypoxic ventilatory response [25, 26]. Therefore, it could be argued that high physical activity leads to a good physical endurance and hence a higher incidence of AMS. This was not the case in the present study. However, there is also evidence that AMS is independent from endurance training (in terms of maximal oxygen uptake) [7, 27]. The differences between the studies might result from different activity behaviors. Well-trained mountaineers often show ambitious behavior in an uncontrolled situation without specification of the maximal exertion [28]. Therefore, the intense physical activity might be the cause for AMS development [18]. Indeed, in participants who reported higher rates of perceived exertion on the first day, also AMS prevalence was higher compared to the other subjects. The protective effect of a well-trained status could probably be shown because of the low and controlled intensity of physical activity. However, a good threshold value for the level of perceived exertion to effectively avoid AMS is still unknown. In the present study, participants were instructed to choose exercise intensity ≤ 13 (“somewhat hard”) at the Borg’s rate of perceived exertion, but it remains unclear, if lower values would be more effective or higher values would still be possible, respectively. Considering the fact, that in the present study nearly 70% of the participants developed AMS and that heavy exertion showed to be the most meaningful risk factor for the development of AMS [18], the value of 13 might be too high to serve as a good threshold value. Previous studies which did not show this protective effect of a well-trained status often show a cross-sectional design with an uncontrolled intensity of physical activity [3, 27].

More recently, AMS prediction has been tried on the basis of oxygen saturation measured 30 minutes after the beginning of exposure to simulated high altitude [13]. The retrospective regression model showed

a high percentage of correctly predicted cases (86%) with a sample size of $n = 981$. Using the same model prospectively did not show such a high value (62% to 69% of correctly predicted cases) [14]. Moreover, one disadvantage of the prediction of AMS on the basis of oxygen saturation in hypoxia is the necessity to expose individuals to acute hypoxia in real or in simulated high altitude. Therefore, “arterial oxygen saturation in normoxia” was searched for being a predictor in the present study. The regression model showed comparable values of correctly predicted cases (70%) with prospectively collected data [14]. As shown in Table 1 and Figure 3, participants not developing AMS showed significantly lower arterial oxygen saturation in normoxia. This result is in line with the findings of Wu et al. (2012) [29]. The authors reported a lower incidence of AMS in smokers and the smoking participants also showed slightly lower oxygen saturation in normoxia (96.5%) than nonsmoking participants (97.2%). It is known that smoking reduces oxygen saturation in normoxia [30]. Therefore, the same mechanisms might play a role in reducing the incidence for AMS in smokers and in people with general lower oxygen saturation already in normoxia. It can be speculated, that a lower oxygen saturation already in normoxia results in an earlier stabilization of the hypoxia-inducible factor 1. This in turn would have an effect on the up-regulation of genes (e.g. erythropoietin, vascular endothelial growth factor, nitric oxide synthetase) and on the pre-conditioning status of the human body [31]. Consequently, AMS prevalence would be lower in subjects with lower oxygen saturation already in normoxia. However, this explanation remains speculative.

Arterial oxygen saturation in normoxia under resting conditions is easy to determine by capillary blood samples. A simulated altitude exposure is not necessary for this method which therefore facilitates the practical application.

Multivariate prediction of acute mountain sickness

Multivariate analyses were conducted to improve the univariate prediction models. Other authors proposed the tidal volume and the breathing frequency as additional predictors [14]. In the present sample, none of these parameters show a significant prediction (tidal volume: $p = .696$, breathing frequency: $p = .582$).

However, the combination of the predictors “physical activity” and “arterial oxygen saturation in normoxia” correctly predicted 90% of the cases. A higher physical activity and lower arterial oxygen saturation in normoxia decreases the probability to develop AMS. The sensitivity was 100%, which means that every participant who suffered from AMS was correctly predicted. Speaking practically, a high sensitivity of a prediction model is of great importance. On the basis of a prediction model with high sensitivity, the advice of a slow ascent can be

addressed to all individuals predicted as susceptible, with the disadvantage of a slower ascent rate for the incorrectly predicted participants. This disadvantage is acceptable in comparison to predict a susceptible individual as unsusceptible. On the basis of this hypothetical prediction model with low sensitivity, a person could plan a fast ascent and would be at risk for developing AMS.

Limitations

The present study has some limitations. First, the measurement of acute mountain sickness by the Lake Louise Scoring system is depending on the subjective feedback of the participants. However, no objective parameter for the diagnosis of AMS has been shown in literature until now [6]. Therefore, it is not known in which amount the participants’ mood state influenced the results of the Lake Louise Scoring system. Also, the determination of AMS susceptibility depended on the statement of the participants. However, the high AMS prevalence in the present study (68%) actually showed that AMS susceptible individuals were selected. Secondly, the best predictor for AMS development was the self-reported physical activity. It would be desirable to confirm the subjective statements by objective measurements of physical activity in future studies. Thirdly, the participants were advised not to strain themselves above moderate exercise intensity levels. Therefore, AMS induced by intense physical activity could be avoided. In mountain tours, however, the intensity of physical activity often exceeds a moderate level. It is therefore questionable, if the study setting is comparable to a real situation in the mountains. However, the artificial and controlled situation of the present study could have been helpful to detect physical activity as a protector for AMS development.

Conclusions

Summarizing the prediction of AMS prevalence in-susceptible individuals, the predictors “physical activity” and “arterial oxygen saturation in normoxia” showed the best prediction model (uni- and multivariate). Higher physical activity and lower oxygen saturation were negatively related to the probability to develop acute mountain sickness. The two predictors can be measured easily and without simulated altitude exposure. Additionally, a key aspect in the prevention of AMS seems to be a low level of perceived exertion. Future studies should evaluate the influence of physical activity on AMS at different exercise intensities at high altitude.

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PRZEWIDYWALNOŚĆ WYSTĄPIENIA OSTREJ CHOROBY WYSOKOGÓRSKIEJ

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Streszczenie

Wstęp: Ostra choroba wysokogórska (AMS) jest częstym zjawiskiem podczas ekspozycji na duże wysokości. Ponieważ istnieje coraz większa liczba turystów w górach, zapobieganie lub przynajmniej rozwój modeli predykcyjnych dla wystąpienia AMS jest bardzo ważne. Celem tego badania było przewidzenie prawdopodobieństwa wystąpienia AMS.

Materiał i metody: W przeprowadzonym badaniu prospektywnym przetestowano 31 pacjentów (45% mężczyzn, 55% kobiety, wiek: 38 ± 12 lat, BMI: 23 ± 3 kg/m²). W skład badania wchodziły testy w warunkach normoksji, jak i narażenia na działanie dużej wysokości w warunkach naturalnych (3650m, 45 godzin). Głównym badanym parametrem była częstość występowania AMS. Wielowymiarowe logistycznie analizy regresji przeprowadzono w celu wykrycia ewentualnych czynników predykcyjnych dla AMS.

Wyniki: Czynniki prognostyczne „aktywność fizyczna” i „saturacja krwi tętniczej tlenem w warunkach normoksji” pokazały najlepszy model regresji dla występowania AMS (procent poprawnie przewidywanych przypadków: 90%, $R^2 = 59\%$). Wyższa aktywność fizyczna i niższe wysycenie tlenem są czynnikami zmniejszającymi prawdopodobieństwo wystąpienia AMS (negatywnie związane z prawdopodobieństwem rozwinięcia AMS).

Wnioski: Badany model przewidywania występowania objawów AMS pokazał bardzo dobre wyniki i może stanowić rzetelną alternatywę dla istniejących już modeli prognozowania. Dodatkowo, aktywność fizyczna oraz wysycenie tlenem krwi tętniczej są parametrami, które mogą być łatwo oznaczone, bez konieczności symulowania wysokości. Badania pokazały, że „aktywność fizyczna” wymaga dalszych badań pozwalających na dokładne przewidzenie wystąpienia AMS. Przyszłe badania powinny ocenić wpływ aktywności fizycznej o różnej intensywności ćwiczeń na dużych wysokościach na prawdopodobieństwo wystąpienia AMS.

Słowa kluczowe: choroba wysokościowa, saturacja krwi tętniczej tlenem, przewidywanie, aktywność fizyczna

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