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Prediction of Susceptibility to Acute Mountain Sickness by Sa_{O_2} Values during Short-Term Exposure to Hypoxia

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ABSTRACT

Burtscher, Martin, Markus Flatz, and Martin Faulhaber. Prediction of susceptibility to acute mountain sickness by Sa_{O_2} values during short-term exposure to hypoxia. *High Alt. Med. Biol.* 5:335–340, 2004—Prediction of the development of acute mountain sickness (AMS) in individuals going to high altitudes is still a matter of debate. Whereas some studies found that subjects with a blunted hypoxic ventilatory response (HVR) are predisposed to AMS, others did not. However, the HVR has often been determined under very acute (5 to 10 min) isocapnic hypoxia without consideration of the subsequent hypoxic ventilatory decline (HVD), and the assessment of AMS susceptibility was based on a single altitude exposure. Therefore, the aim of the present study was to evaluate the relationship between the individual arterial oxygen saturation (Sa_{O_2}) after a 20- to 30-min exposure to poikilocapnic hypoxia and the AMS susceptibility based on repeated observations. A total of 150 healthy male and female mountaineers (ages: 42 ± 13 yr), 63 of whom had known susceptibility to AMS and 87 of whom never suffered from AMS, were exposed to various degrees of normobaric and hypobaric hypoxia. Sa_{O_2} values were taken by finger pulseoximetry after 20 to 30 min of hypoxic exposure. Sa_{O_2} values after 20 to 30 min of hypoxia were on average 4.9% lower in subjects susceptible to AMS than in those who were not. Logistic regression analysis revealed altitude-dependent Sa_{O_2} values to be predictive for AMS susceptibility. Based on the derived model, AMS susceptibility was correctly predicted in 86% of the selected individuals exposed to short-term hypoxia. In conclusion, Sa_{O_2} values after 20 to 30 min of exposure to normobaric or hypobaric hypoxia represent a useful tool to detect subjects highly susceptible to AMS.

Key Words: mountaineering; high altitude; hypoxic ventilatory response; hypoxic ventilatory decline

INTRODUCTION

Prediction of the development of acute mountain sickness (AMS) in individuals going to high altitude is still a matter of debate. The main determinants of AMS are the altitude reached, rate of ascent, physical activity, and degree of preacclimatization (Bärtsch et al., 1991; Honigman et al., 1993; Roach et al., 1998, 2000; Schneider et al., 2002). However, there is a big variability in individual susceptibility to AMS. Since hypoxia is primarily responsible for the development of AMS, individual ventilatory response to hypoxia and thus differences in tissue oxygenation during acute altitude exposure might partly explain this variability

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(Weil, 1986; Weil and Zwillich, 1976). Some studies reported a relationship between hypoxic ventilatory response (HVR) and altitude illnesses (Hackett and Rennie, 1979; Hackett et al., 1981; King and Robinson, 1972; Moore et al., 1986; Richalet et al., 1988), whereas others failed to find any such association (Bärtsch et al., 2002; Hohenhaus et al., 1995; Milledge et al., 1988, 1991). However, this contrast seems to be due mainly to differences in the study design. In most studies demonstrating a relationship between HVR and susceptibility to AMS, HVR was tested during prolonged exposure to hypoxia, and AMS susceptibility was assessed during the subsequent period of continuing hypoxia, or the studies were based on a retrospective consideration of the AMS history in individuals. Most studies that failed to find any such relationship performed HVR tests during a 5- to 10-min exposure to increasing hypoxia and concentrated on investigating the development of AMS days or weeks later during mountaineering at high altitude. However, ventilation decreases (hypoxic ventilatory decline, HVD) during hypoxemia sustained for 5 to 30 min (Bisgard and Neubauer, 1995; Powell et al., 1998; Reeves et al., 2003) and thus AMS development may be more closely related to HVD, rather than to the initial ventilatory response to hypoxia. Besides, susceptibility to AMS and HVR may change from one exposure to another due to various factors, such as previous exposures to high altitude, state of health, nutrition, sleep, or exercise. To evaluate the role of ventilatory drive during prolonged hypoxia for the pathophysiology of AMS and its importance for AMS prediction, we selected mountaineers who could unequivocally be classified as susceptible or not susceptible to the AMS based on frequent exposures to high altitude.

METHODS

Out of a total of 500 mountaineers, we selected 150 (114 males and 36 females with an average age of 42 ± 13 yr) who could be unequivocally classified as susceptible ($n = 63$) or not susceptible ($n = 87$) to AMS. Within the last 5 yr, all participants had more than 10 exposures (including overnight stays) to altitudes >2500 m. AMS susceptibility (AMS+) was defined as a repeated (≥2 times) experience of headache combined with one additional symptom listed in the Lake Louise AMS scoring system (Roach et al., 1993). However, all of them reported to always suffer from AMS when not preacclimatized. Subjects not susceptible to AMS (AMS−) had never experienced AMS. No differences between groups regarding the frequency of previous altitude exposures could be detected. For inclusion into the study, no exposures to altitudes >2500 m must have occurred for at least 1 month prior to the experiment.

All participants were investigated under conditions of normobaric or hypobaric hypoxia of various degrees. Normobaric hypoxia (simulated altitude) with an inspiratory oxygen concentration between 15% and 10% was offered at sea level by face mask using the HypoxyComplex Hyp_{O_2} (HypoMed, Moscow) or in a hypoxic room (Hypoxic room systems Hypoxico, Germany). Hypobaric hypoxia means real altitudes between 2000 and 4500 m after passive ascent by cable car or helicopter. Immediately after exposure to normobaric hypoxia or arrival at high altitude, subjects were seated in a chair in a relaxed position. After a 20- to 30-min resting period, Sa_{O_2} was measured by finger pulseoximetry (Onyx, Nonin Medical, Inc., USA). Values were taken when they remained constant for at least 1 min. Subjects had performed no exhausting exercises in the 3 days prior to the experiment and had consumed no alcohol during a period of at least 12 h immediately preceding the study. None of the subjects was a regular smoker. Individual coffee-drinking habits were not changed, but no coffee intake was permitted 2 h prior to the experiment.

Normobaric hypoxic conditions are presented as corresponding to simulated altitudes. Data are presented as frequencies or mean values ± standard deviation (SD). Chi-square tests were used to test for significant differences in proportions between subjects susceptible to AMS and those who were not, and unpaired *t*-tests were used for the comparison of continuous variables. Regression analysis was used to evaluate the relationship between alti-

tude and Sa_{O_2} values. Stepwise logistic regression analysis was carried out for prediction of AMS susceptibility (dependent variable) by Sa_{O_2} values, altitude, age, gender, and normobaric or hypobaric exposure (independent variables). A p value <0.05 was considered to indicate statistical significance.

RESULTS

A total of 150 mountaineers, 63 of whom had known susceptibility to AMS, were exposed to various simulated or real altitudes. After a 20- to 30-min exposure, Sa_{O_2} measurements were conducted. Besides light dizziness at altitudes above 3500 m, no side effects were observed. The frequencies regarding gender and type of hypoxia did not differ between subjects susceptible to AMS and those who were not. The mean values of age and altitudes were the same for both groups. Sa_{O_2} values at low altitude (600 m) were not different between AMS+ and AMS− (96.5 ± 0.7% and 96.5 ± 0.7%). However, Sa_{O_2} values reached after 20 to 30 min of hypoxic exposure were on average 4.9% lower in subjects susceptible to AMS (Table 1). The average decline in Sa_{O_2} from 2000 to 6000 m amounts to 5.75%/1000 m. The altitude-dependent Sa_{O_2} values were best described by a nonlinear (quadratic) regression for both groups (Fig. 1). Whereas this relationship is rather linear in AMS+, it is more U-shaped in AMS−. Logistic regression analysis revealed only Sa_{O_2} and altitude to be predictive for AMS susceptibility. Based on the derived model, AMS susceptibility was correctly predicted in 86% of the selected individuals exposed to short-term hypoxia. Age, gender, and the type of hypoxia (normobaric or hypobaric) did not improve success in prediction.

DISCUSSION

We found that Sa_{O_2} values taken after 20 to 30 min of hypoxic exposure are good predictors of AMS susceptibility (Fig. 1). However, selected subjects were studied who could unequivocally be classified as susceptible or not susceptible to AMS. A much more pronounced overlap of Sa_{O_2} values between AMS+ and AMS− will probably be demonstrated when investigating an unselected population, as done by Bärtsch et al. (2002) and Milledge et al. (1988; 1991). Thus, our results mainly confirm the role of hypoventilation in the pathophysiology of AMS.

Low Sa_{O_2} values resulting from a low ventilatory response to hypoxia are in agreement with some previous studies (Hackett and Rennie, 1979; Hackett et al., 1981; King and Robinson, 1972; Moore et al., 1986; Richalet et al., 1988), but in disagreement with others (Bärtsch et al., 2002; Hohenhaus et al., 1995; Milledge et al., 1988, 1991). As mentioned previously, duration of hypoxic exposure when testing and assessment of AMS reproducibility are the most discriminative factors between these studies. A somewhat longer exposure to hypoxia is characteristic in the former compared to the latter studies. The HVD is not given adequate consideration when hypoxic testing is done only for a few minutes. After a marked increase in minute ventilation during the first seconds to minutes of hypoxia, there is a de-

Table 1. Characteristics of Subjects Susceptible and Not Susceptible to AMS and Results of Hypoxic Testing

	AMS−	*AMS+*	p *Value*
Number	87	63	
Age (yr)	40.3 (14)	44.0 (13)	0.1
Males/females (number)	64/23	50/13	0.4
Pretest at low altitude (600 m)			
Arterial oxygen saturation (%)	96.5 (0.7)	96.5 (0.7)	0.9
Test at simulated or real altitude			
Altitude (m)	3525 (920)	3659 (969)	0.4
Normobaria/hypobaria (number)	39/48	33/30	0.4
Arterial oxygen saturation (%)	88.3 (5.6)	83.4 (5.7)	<0.001

Data are frequencies or means ± SD. AMS−, not susceptible to AMS; AMS+, susceptible to AMS.

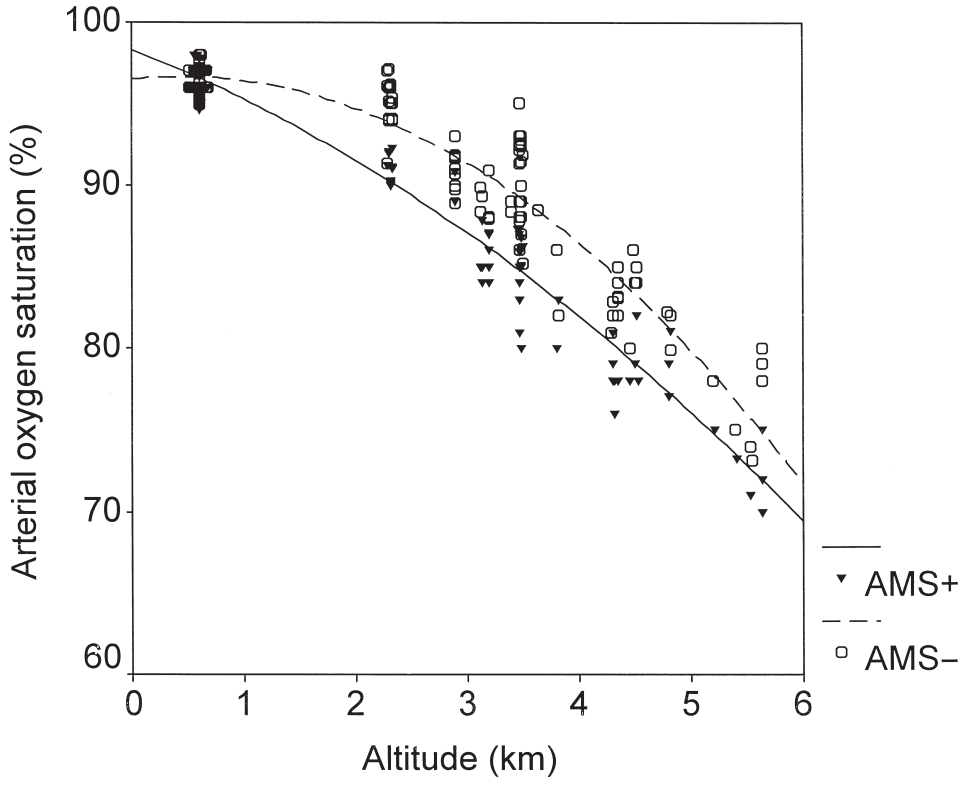

FIG. 1. Altitude-dependent Sa_{O_2} values in AMS-susceptible (AMS+) and nonsusceptible (AMS−) subjects.
Regression equation for AMS+: $Sa_{O_2} = 98.34 - 2.72alt - 0.35alt^2$ ($R^2 = 0.96$)
Regression equation for AMS−: $Sa_{O_2} = 96.51 + 0.68alt - 0.80alt^2$ ($R^2 = 0.92$)
Sa_{O_2}, arterial oxygen saturation (%); alt, altitude (km).

crease in ventilation, especially during poikilocapnic conditions, which is mainly due to the decrease of the central chemoreceptor drive (Bisgard and Neubauer, 1995; Powell et al., 1998; Reeves et al., 2003; Ursino et al., 2001). But the contribution of the central and the peripheral chemoreflexes may vary between subjects (Liang et al., 1997) and thus the ventilatory decline after 20 to 30 min of poikilocapnic hypoxia may differ between individuals and may not be in agreement with acute ventilatory response. On average, AMS+ had lower Sa_{O_2} values than AMS− at all levels of hypoxia, with the most significant differences seen when testing was done at 2300- to 4000-m altitude, or with 12.5% to 15.5% O_2 at sea level. The lower Sa_{O_2} values in AMS+ are presumed to be due to lower ventilation, not to impaired pulmonary gas exchange. Our data do not measure the relative contributions of the two mechanisms responsible for the differences between AMS+ and AMS−, HVD, and ventilatory inhibition by resulting hypocapnia. The AMS+ group might be found to have relatively stronger hypercapnic than hypoxic ventilatory drive, with which hypocapnic inhibition would also be stronger. Conversely, they might show greater HVD in a 20-min isocapnic HVR test.

When Sa_{O_2} values were taken after prolonged exposure to high altitude (hours), a clear relation to subsequent AMS development was demonstrated (Bärtsch et al., 2002; Roach et al., 1998). This, however, might have been due to impaired lung gas exchange (Bärtsch et al., 2002). The question arises as to how much time and altitude are needed to impair gas exchange. Are 20 to 30 min enough? Another important reason for differences between the studies cited might be the different assessment of AMS susceptibility. The conclusion reached in some studies that HVR is not a predictive factor for AMS susceptibility is based on the

observation of AMS development on one occasion days or weeks after hypoxic ventilatory testing (Bärtsch et al., 2002; Hohenhaus et al., 1995; Milledge et al., 1988, 1991). However, AMS susceptibility may change depending on various factors, such as infection, rate of ascent, or fluid intake (Bailey et al., 2003; Schneider et al., 2002). Therefore, AMS susceptibility may also change between HVR testing and altitude exposure. Because we tested subjects with a clearly distinguished susceptibility to AMS ($\geq$2 times or never), we may have excluded persons with a weak AMS susceptibility and thus avoided a marked overlap of altitude-dependent Sa_{O_2} values in AMS+ and AMS− subjects. This is confirmed in the experiment by Moore et al. (1986), who most likely performed a similar selection regarding AMS susceptibility and also demonstrated a clear relation between a low ventilatory response to hypoxia and AMS. Also, Rathat et al. (1992) reported that 80% of AMS-susceptible subjects could be predicted by the ventilatory and cardiac responses to hypoxia during exercise when assessing AMS susceptibility on repeated observations (retrospective). Thus, a more prolonged poikilocapnic hypoxic exposure (20 to 30 min) and testing mountaineers with a clearly distinguishable susceptibility to AMS may be the main reasons for the discrepancies between our results and those studies that did not find HVR testing to have any predictive power.

Our study, however, has several limitations. Most important of them all, the diagnosis of AMS susceptibility has been made retrospectively, and although we tried to avoid biases as carefully as possible, selection and observer biases cannot be entirely excluded. In conclusion, hypoventilation seems to be important in the pathophysiology of AMS and Sa_{O_2} values, determined 20 to 30 min after exposure to hypoxia corresponding to altitudes between 3000 and 4000 m seem to be useful in detecting subjects who are highly susceptible to AMS.

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