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REVIEW

Prediction of the susceptibility to AMS in simulated altitude

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Abstract Acute mountain sickness (AMS) develops when rapidly ascending to high altitudes. However, some mountaineers will suffer from AMS even at 2,000 m and others not until 5,000 m. The awareness of the individual susceptibility for AMS would be helpful for preventive strategies. Thus, the main purpose of this paper is the comparison of existing studies dealing with the prediction of AMS susceptibility and to draw conclusions on presently most valuable tests. Data source: A PubMed search has been performed, and preliminary observations from our laboratory have been included. The cautious conclusion derived from the reviewed 16 studies is that values of arterial oxygen saturation (SaO_2), determined 20–30 min after exposure to simulated hypoxia equivalent to 2,300–4,200 m, seem to be the most useful predictors of AMS susceptibility (>80% correct prediction). Because the sympathetic activation during acute exposure to hypoxia may well contribute to the AMS development, parameters like heart rate variability or blood lactate could even enhance this predictability. The ventilatory response to hypoxia is easily trainable by pre-exposures to hypoxia but considers only part of the complex acclimatization process.

Keywords Acute mountain sickness (AMS) · Intermittent hypoxia · Simulated altitude · Prediction · Mountaineering · Trekking · Hypoxic ventilatory response

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Introduction

Acute mountain sickness (AMS) develops in not acclimatized mountaineers going to high altitudes. The incidence of AMS increases with altitude, and hypoxia is the main causative factor. When mountaineers ascend rapidly to 2,500 m, about 10% of them will suffer AMS, and when ascending to 4,500 m, the AMS incidence will exceed 60% [1, 2]. During slow ascents with multiple overnight stays at altitude, the organism acclimatizes, and AMS can be avoided [3]. Thus, the individual differences in the tolerance to hypoxia and/or the ability to acclimatize may explain the altitude-dependent increase of the AMS incidence. Experiences from prior high-altitude exposures probably represent the most reliable prediction for AMS susceptibility. Nevertheless, for the many mountaineers visiting high altitudes for the first time, it would be helpful to know more about their AMS susceptibility in advance. Although several tests at simulated altitude have been proposed, there is no scientific agreement whether these tests are really useful [4–9]. Thus, the main purpose of this paper is to compare existing studies dealing with the prediction of AMS susceptibility and to draw conclusions on presently most valuable tests.

Materials and methods

Data source Articles were selected from a search of the PubMed database from 1976 to 2007 using the search terms intermittent hypoxia, simulated altitude, acute mountain sickness (AMS), prediction, mountaineering, trekking, hypoxic ventilatory response (HVR), and articles known to the authors and referenced in review articles. Studies evaluating the AMS prediction based on simulated altitude

Table 1 Characteristics of the selected studies dealing with the prediction of AMS susceptibility

Authors	Subjects	Design	Tests for AMS-Prediction	AMS diagnosis	Results
Rathat et al. [8]	*N*=288	Retrospective lab	Ventilatory and cardiac responses to hypoxia (FIO_2=11.5%) at rest and during submaximal exercise	Known susceptibility to AMS	At least 1 abnormal value in cardiac or ventilatory responses to hypoxia in AMS susceptible
Burtscher M et al. [5]	*N*=150 (63 AMS susceptible + 87 controls)	Retrospective lab	SaO_2 during rest after 20-30 min at 2,000–4,500 m (normo- or hypobaric)	Self reported or know susceptibility to AMS	Lower SaO_2 in AMS susceptible (86% identification)
Richalet JP et al. [9]	*N*=128	Prospective lab/field	Ventilatory and cardiac responses to hypoxia (FIO_2=11.2%) at rest and during exercise; cold pressor test (CPT)	Severe AMS during expedition	History of severe AMS or headache at sea-level; low vent. and cardiac responses; rapid pattern of ventilation; blunted response to CPT
Roach RC et al. [14]	*N*=102	Prospective field	SaO_2 during rest at 4,200 m before further ascent	AMS score during further ascent	SaO_2 lower in AMS during further ascent (80–100% identification)
Muza SR et al. [15]	*N*=77 (38 residents at 1,940 m = MAR, 39 residents at 50 m = LAR)	Prospective field (MAR) lab (LAR)	SaO_2 during rest at 1,940, 2,438, 3,048, 4,056 m	AMS symptoms	SaO_2 MAR > SaO_2 LAR (above 2,438 m); 1 AMS in MAR, 9 AMS in LAR
Hayat A et al. [16]	*N*=54	Prospective field	SaO_2 increase after 1 min voluntary hyperventilation (HC) at 2,833 m	AMS sore at 2,833 m	Correlation HC-AMS (r= -0.664)
Austin D et al. [17]	*N*=40	Prospective lab/field	Breath holding time (BHT): s; gag reflex (GR): 0–3 scale; reaction to hyperventilation (RH): 0–3 scale at sea level	AMS score during trek to max. 5,640 m	Relation BHT/GR/RH-AMS
Milledge JS et al. [10]	*N*=32	Prospective lab/field	HVR; HCVR	AMS score at 5,200/4,300 m	No correlation HVR/HCVR-AMS
Hohenhaus E et al. [11]	*N*=30 (10 AMS susceptible + 10 HAPE susceptible + 10 controls)	Retrospective lab	HVR (isocapnic + poikilocapnic); HCVR	Know susceptibility to AMS/HAPE	HVR lower in HAPE susceptible vs controls; HVR not different in AMS susceptible vs controls
Bärtsch P et al. [4]	*N*=24	Prospective lab/field	HVR; HCVR	AMS score at 4,459 m	No relation HVR/HCVR-AMS; HVR lower in AMS subjects at day 1; SaO_2 lower in AMS subjects at days 1, 2, 3
Grant S et al. [18]	*N*=20	Prospective lab/field	SaO_2, $P_{et}CO2$ during rest after 5 min at 3,450, 4,200, 4,850 m (simulated)	AMS score 3,450–4,928 m	Poor correlation SaO_2/$P_{et}CO_2$-AMS
Savourey G et al. [19]	*N*=18	Prospective lab/field	Ventilatory and cardiac responses, blood gases SaO_2 at 4,500 m after 5 and 30 min (normobaric and hypobaric, rest and submaximal exercise)	AMS score (max + mean) during expedition	CaO_2 during submaximal exercise after 30 min in hypoxia is an important predictor of AMS
Milledge JS et al. [6]	*N*=17	Prospective lab	HVR (isocapnic + poikilocapnic); VO_2 max	AMS score at 4,500 m	No correlation HVR/VO_2max-AMS
Moore LG et al. [7]	*N*=12 (8 AMS susceptible + 4 controls)	Retrospective lab	HVR (isocapnic + poikilocapnic)	AMS score at 4,800 m (simulated)	HVR lower in AMS susceptible; SaO_2 lower after 1 h at 4,800 m in AMS subjects

Table 1 (continued)

Authors	Subjects	Design	Tests for AMS-Prediction	AMS diagnosis	Results
Savourey G et al. [12]	*N*=11	Prospective lab/field	VO_2 max, ventilatory and cardiac responses, blood gases at rest and during submaximal exercise at 4,500 m	AMS score during expedition in the Andes	No relation HVR-AMS; close relation AMS-$P_{et}O_2$ (during exercise in normoxia)
Selland MA et al. [13]	*N*=8 (4 HAPE susceptible + 4 controls)	Retrospective lab	HVR, FVC, FEV_1, FEF25-75 at 4,400 m	AMS score/ HAPE after 4 h at 4,400 m (simulated)	No relation HVR-HAPE; larger decrease in FEV1 and FEF25-75 in HAPE susceptible

AMS Acute mountain sickness, CaO_2 peripheral blood oxygen content (hemoglobin concentration × arterial oxygen saturation × 1.34), *FEF25-75* flow rate measured between 25 and 75% of forced vital capacity, FEV_1: forced expiratory volume in the first second, FIO_2 inspiratory fraction of oxygen, *FVC* forced vital capacity, *HAPE* high altitude pulmonary edema, *HCVR* hypercapnic ventilatory response, *HVR* hypoxic ventilatory response, $P_{et}CO_2$ end tidal partial pressure of carbon dioxide, SaO_2 arterial oxygen saturation (pulse oximetry), VO_2max maximal oxygen consumption

exposures have been included. In addition, we present an own study on the AMS predictability by exercise responses at low and high altitude, which has been presented at the hypoxia congress 2007 in Bad Reichenhall (Germany).

Results

The main findings of 16 studies using short-term exposures to simulated altitudes for the prediction of AMS susceptibility are shown in Table 1. Most of the researchers dealing with this issue measured some ventilatory and/or circulatory parameters at rest and/or during exercise in hypoxia and/or normoxia retro- or prospectively for the evaluation of AMS susceptibility.

Studies evaluating iso- or poikilocapnic hypoxic ventilatory response (HVR) or hypercapnic ventilatory response (HCVR) failed to show any relation between test results and AMS [4, 6, 10–12]. Only Moore et al. [7] who used a retrospective design were able to show a lower HVR in persons susceptible to AMS. In subjects developing high altitude pulmonary edema (HAPE), Hohenhaus et al. [11] reported a significant relation between HVR and the susceptibility to HAPE, but Selland et al. [13] were not able to confirm this during a 4-h lasting exposure to simulated altitude. In contrast to the HVR, SaO_2 values during acute hypoxia seem rather to be related to AMS. Burtscher et al. [5] could identify AMS-susceptible persons by SaO_2 values after 20 to 30 min at real or simulated altitude, and also, Roach et al. [14] were able to predict AMS during further ascent by SaO_2 measurements taken at 4,300 m. Muza et al. [15] reported that the higher SaO_2 values above 2,438 m of residents at moderate altitude compared to residents of low altitude were related to the lower incidence of AMS. Furthermore, Hayat et al. [16] investigated the SaO_2 increase after voluntary hyperventilation at altitude and found a significant correlation to the AMS score, and also, the gag reflex has been shown to be related to AMS during a trek to high altitude [17]. Whereas Bärtsch et al. [4] found lower SaO_2 values at the first days at 4,559 m in subjects with AMS, Grant et al. [18] compared SaO_2 values at different simulated altitudes and reported no relation to the AMS score at these altitudes during a subsequent trek. In a recent investigation, Savourey et al. [19] compared normo- and hypobaric exercise tests to determine the susceptibility to AMS. They proposed the arterial oxygen content (CaO_2), based on hemoglobin concentration and SaO_2 by pulse oximetry, during submaximal exercise after 30 min in hypoxia, to be a good predictor for AMS [19]. Because also Rathat et al. [8] and Richalet et al. [9] reported cardiorespiratory responses to hypoxic exercise to be highly predictive for AMS development at high altitude, we performed a similar experiment. The results have been reported at the hypoxia congress 2007 in Bad Reichenhall:

Fifteen subjects (seven males, eight females; age: 44.1; 27–60 years) were tested at low altitude (600 m) and again at about 3,500 m (natural altitude). AMS development was evaluated during the first 10 h at high altitude according to the Lake Louise Scoring System [20]. Beside cardiorespi-

Table 2 Resting and exercising cardiorespiratory responses at low (600 m) and high altitude

Cardiorespiratory responses (differences between low and high altitude)	AMS−	AMS+	*P*-value
SaO_2 rest (%)	8.1 (2.5)	12.0 (1.7)	0.004
SaO_2 exercise (%)	19.4 (5.4)	22.1 (3.5)	0.27
VE exercise (1)	21.5 (11.3)	19.8 (7.1)	0.27
HR exercise (bpm)	13.4 (9.5)	20.3 (4.5)	0.1
Blood Lactate (mmol/l)	0.9 (0.4)	1.4 (.04)	0.02

SaO_2 Arterial oxygen saturation (pulse oximetry), *HR* heart rate, *VE* minute ventilation. Values are means(±SD)

ratory measurements at rest, cardiorespiratory responses to step tests (24 cm, 30 reps/min, 4 min) were determined at low altitude and between 1 and 3 h after arriving at high altitude. We calculated the SaO_2 response, the ventilatory response (hypocapnic), and the cardiac response to exercise as proposed by Rathat et al. [9]:

$$\begin{aligned}
&SaO_2 \text{ response} = SaO_2 \text{ at high altitude} - SaO_2 \text{ at low altitude}\\
&\text{Hypoxic ventilatory response} = (\text{VE at high altitude} - \text{VE at low altitude})/\\
&\qquad (SaO_2 \text{ at high altitude} - SaO_2 \text{ at low altitude})/\text{Body mass}\\
&\text{Hypoxic cardiac response} = (\text{Heart rate at high altitude} - \text{heart rate al low altitude})/\\
&\quad (SaO_2 \text{ at high altitude} - SaO_2 \text{ at low altitude})
\end{aligned}$$

Results are presented in Table 2. Whereas the resting SaO_2 values at high altitude were highly predictive for AMS development (87% correct prediction), the cardiorespiratory responses to exercise, as described above, were not. Logistic regression analysis revealed that the predictability even became improved by including the differences of resting blood lactate values at low and high altitude.

Discussion

Most of researchers dealing with the predictability of AMS by short-term exposures to simulated altitude recorded ventilatory and cardiovascular responses for prediction (see Table 1). Because of the differences regarding conditions and parameters tested, regarding the altitude and mountaineering experience of the study participants, and especially regarding the conditions during real altitude exposure where AMS developed, no clear conclusion can be derived from the reviewed studies. Hypoxia is mainly responsible for AMS development, and the degree of hypoxia when acutely exposed to high altitude varies markedly depending on the individual HVR [21, 22]. Therefore, the individual HVR has been considered to be predictive for the tolerance to acute hypoxia since a long time [7]. This is also reflected in most of the studies which tried to predict AMS susceptibility from short-term exposures to simulated altitude. But isocapnic and poikilocapnic HVR testing did not produce unanimous results. Whereas only a few studies found a relation between the individual HVR and AMS susceptibility [7], the majority did not [4, 6, 10–12]. In contrast, studies including SaO_2 values after prolonged hypoxic exposures found a relatively close relationship between SaO_2 and AMS susceptibility [5, 9, 14]. Thus, the SaO_2 value after a somewhat prolonged exposure to simulated altitude seems to be a better predictor than the HVR. The biphasic pattern of the ventilatory response to hypoxia is not given adequate consideration when hypoxic testing is done only for a few minutes as during HVR determination. After a marked increase in minute ventilation during the first minutes of hypoxia, there is a decrease in ventilation, especially during poikilocapnic conditions,

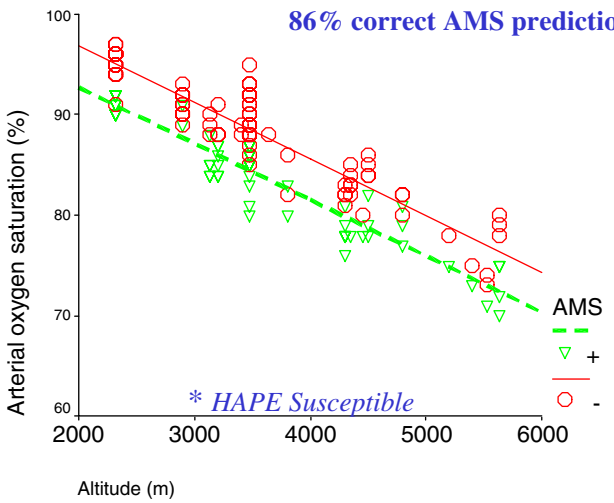

Fig. 1 SaO_2 values after 20–30 min exposure to simulated altitude in mountaineers susceptible (AMS+) or not susceptible (AMS−) to acute mountain sickness. *Asterisk* indicates the SaO_2 value of one subject with known susceptibility [cf. 5]

which is mainly due to the decrease of the central chemoreceptor drive [23]. But the contribution of the central and the peripheral chemoreflexes may vary between subjects [24], and thus, also the ventilatory decline after 20–30 minutes of poikilocapnic hypoxia may differ between individuals and may not be in agreement with acute ventilatory response. When SaO_2 values were taken after prolonged exposure to high altitude (up to hours), a clear relation to subsequent development of headache and/or AMS was demonstrated [4, 5, 14]. During more prolonged altitude exposure, however, impaired lung gas exchange might have occurred [4]. The question arises as to how much time and altitude are needed to impair gas exchange. Is 20–30 min enough? This is unlikely because we demonstrated that the slope of SaO_2 remained unchanged in both AMS susceptible and nonsusceptible subjects at simulated altitudes up to about 5,500 m [5]. Altitudes between 2,300 and 4,200 m may be especially adequate for the determination of AMS susceptibility [5, 14]. Another problem arises when assessing AMS susceptibility. As the AMS incidence increases with increasing altitude, highly susceptible persons will develop AMS already at moderate altitude, e.g., at 2,000–2,500 m. But AMS may also be triggered when normal acclimatization is disturbed by factors such as infection, high rate of ascent, insufficient fluid intake, intense exercise, etc. [3, 14, 25]. Thus, assessment of AMS susceptibility due to repeated altitude exposures may provide a more adequate basis for prediction than occasional observations as done in various studies [6, 10, 12, 18]. Richalet et al. [9] and Rathat et al. [8], for instance, demonstrated that 80%, and we showed that 86%, of AMS susceptible subjects could be predicted when assessing AMS susceptibility on repeated observations [5; Fig. 1]. The French researchers used cardiorespiratory responses during exercise in hypoxia for AMS prediction [8, 9]. We performed a similar experiment (Table 2), and we could not find any enhancement of AMS predictability by inclusion of such exercise responses but confirmed the high predictive value of resting SaO_2 values. However, because the sympathetic activation in acute hypoxia may contribute to AMS development, exercise responses could really be indicative for AMS susceptibility. Possibly, parameters like heart rate variability or blood lactate values should be considered in future studies. In fact, we demonstrated a small improvement in AMS prediction when including the blood lactate response to hypoxia (Table 2).

Taken together for the moment, the cautious conclusion derived from the reviewed studies is that SaO_2 values, determined 20–30 min after exposure to hypoxia equivalent to 2,300–4,200 m, seem to be the most useful predictors of AMS susceptibility. The ventilatory response to hypoxia is easily trainable by pre-exposures to hypoxia, but considers only part of the complex acclimatization process.

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