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Acute mountain sickness is related to nocturnal hypoxemia but not to hypoventilation

P. Erba, S. Anastasi, O. Senn, M. Maggiorini, K.E. Bloch

Acute mountain sickness is related to nocturnal hypoxemia but not to hypoventilation. P. Erba, S. Anastasi, O. Senn, M. Maggiorini, K.E. Bloch. ©ERS Journals Ltd 2004.
ABSTRACT: The purpose of the study was to investigate determinants of acute mountain sickness after rapid ascent to high altitude.

A total of 21 climbers were studied ascending from <1,200 m to Capanna Regina Margherita, a hut in the Alps at 4,559 m, within <24 h. During their overnight stay at 4,559 m, breathing patterns and ventilation were recorded by calibrated respiratory inductive plethysmography along with pulse oximetry. In the following morning, acute mountain sickness was assessed.

Altogether, 11 mountaineers developed pronounced symptoms of acute mountain sickness (Lake Louise score $\geqslant$5) and 10 did not (controls). Compared to controls, subjects with acute mountain sickness had lower nocturnal oxygen saturation (mean±SD 59±13% *versus* 73±6%), higher minute ventilation (7.94±2.35 *versus* 6.06±1.34 L·min^{-1}), and greater mean inspiratory flow, a measure of respiratory centre drive (0.29±0.09 *versus* 0.22±0.05 L·s^{-1}). Periodic respiration was prevalent but not significantly different among the two groups (apnoea/hypopnea index 60.1±34.6 *versus* 47.1±42.6 events per h).

The data suggest that pronounced nocturnal hypoxemia, which was not related to hypoventilation, may have promoted acute mountain sickness. Periodic breathing seems not to play a predominant role in the pathogenesis of acute mountain sickness.
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Pulmonary Division and Intensive Care Unit, Dept of Internal Medicine, University Hospital Zurich, Switzerland.

Correspondence: K.E. Bloch, Pulmonary Division, Dept of Internal Medicine, University Hospital of Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland.
Fax: 41 12554451
E-mail: pneubloc@usz.unizh.ch

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Otherwise healthy subjects ascending rapidly to altitudes >2,500 m often develop acute mountain sickness (AMS), a condition characterised by insomnia, headache, dizziness, loss of appetite, nausea and vomiting [1]. In the Alps, symptoms and signs of AMS sufficiently severe to force a reduction in activity were found in 6–8% of climbers examined at altitudes between 2,850 and 3,650 m, and in 30% of climbers at 4,559 m [2]. AMS is promoted by a rapid ascent rate, depends on the altitude reached, and on acclimatisation [3]. It occurs in both sexes, at all ages, and athletic fitness does not protect against it [1, 4, 5].

Despite its high prevalence, the pathophysiology of AMS is incompletely understood. Hypoxia seems to play an important role [3, 6, 7]. A reduced ventilatory response to hypoxia, and impaired pulmonary gas exchange related to pulmonary fluid accumulation, and water and salt retention have been implicated in development of exaggerated hypoxemia in subjects with AMS [8–10]. As AMS often develops or worsens over the night, when periodic breathing and repetitive oxygen desaturation are also prevalent, a causal relationship or a common pathophysiological pathway have been evaluated [11, 12]. However, the results of these earlier studies were inconclusive due to the small number of subjects with AMS enrolled, and the lack of quantitative estimation of ventilation during sleep.

Therefore, the purpose of the current study was to further explore the potential role of periodic respiration, and other characteristics of breathing patterns, in promoting AMS by employing calibrated respiratory inductive plethysmography to unobtrusively monitor nocturnal ventilation and breathing patterns in relation to AMS. To evaluate the hypothesis that AMS is mainly promoted by hypoxia, the evolution of breathing patterns and oxygenation over two successive nights at 3,560 m and 4,559 m, respectively, in mountaineers ascending from lowlands to 4,559 m within <24 h were studied. Clinical and physiological observations were compared among mountaineers developing AMS (AMS-group) and those remaining well (controls).

Methods

Subjects

A total of 25 healthy volunteers were recruited among mountaineers arriving at the Gnifetti hut (3,610 m), Mt. Rosa, Italy, to spend a night there. All had ascended in the afternoon from Alagna (1,170 m) to Punta Indren (3,220 m) by cable car, and had subsequently walked to 3,610 m within 1–2 h. To be included into the study, subjects had to have no history of previous high altitude pulmonary oedema, and they had to have spent no more than 7 days >2,500 m within the last 30 days. They gave informed consent to participate in the study, which was approved by the Ethics Committee of the University Hospital of Zurich.

Measurements

Clinical evaluation. A medical history and physical examination were performed. Arterial blood gas samples were drawn from the radial artery while the subjects rested

quietly in supine position. The specimen was analysed immediately (Ciba-Corning Diagnostics, Dietlikon, Switzerland). The alveolar-arterial oxygen partial pressure gradient was calculated as:

$$A_{aD,O_2} = P_{A,O_2} - P_{a,O_2} \quad (1)$$

Where P_{a,O_2} is arterial oxygen tension. Alveolar P_{O_2} (P_{A,O_2}) was derived from the simplified alveolar gas equation as:

$$P_{A,O_2} = 0.21 \times (Pb - 47) - P_{a,CO_2} \times (F_{I,O_2} + (1 - F_{I,O_2})/R) \quad (2)$$

Where P_{a,CO_2} is carbon dioxide arterial tension and F_{I,O_2} is inspiratory oxygen fraction. R was assumed to be 0.85 [13]. AMS was assessed according to the Lake Louise protocol (self-report and clinical assessment) (see Appendix) [14]. A score $\geqslant 5$ was considered to indicate AMS [2]. Subjective sleep disturbance was rated on a three-point Likert scale where 0=satisfactory, and refreshing sleep, 1=moderate sleep disturbance, and 2=severe sleep disturbances with difficulties falling asleep, multiple awakenings, and unrefreshing sleep.

Cardiorespiratory sleep studies. Nocturnal breathing patterns were recorded as previously described [15] by computerised devices incorporating a respiratory inductive plethysmograph, a pulse oximeter, an ECG, and a position sensor (Somnostar, SensorMedics, Yorba Linda, CA, USA, or LifeShirt, VivoMetrics, Ventura, CA, USA). Displacement of inductance sensors was avoided as they were built into a snugly fitting shirt (LifeShirt), or were taped to the skin and secured with an elastic net (Somnostar). The Qualitative Diagnostic Calibration method was applied during natural breathing in supine position over 5 min. It provided relative gains of rib cage and abdominal inductive plethysmograph signals [15, 16]. Their sum was subsequently calibrated in absolute units (L) by rebreathing into a bag of known volume (0.8 L) for 5–10 breaths with the nose clipped. Accuracy of calibration was verified in the morning after sleep studies, and regarded as acceptable if inductive plethysmographic tidal volumes were within 20% of the calibration bag volume.

Actigraphy. Rest/activity patterns were recorded by an accelerometer placed at the wrist as an indirect measure of sleep/wakefulness (Actiwatch; Cambridge Neurotechnology, Cambridge, UK) [17–19].

Protocol

After the overnight stay at the Gnifetti hut (3,610 m), subjects hiked to Capanna Regina Margherita (4,559 m) in the following morning, and spent the second night there. They redescended on the third day. Clinical assessment of high altitude illness was performed four times: in the evenings and mornings at 3,610 and 4,559 m. Cardiorespiratory sleep recordings and actimetry were obtained twice: during the nights at 3,610 m and 4,559 m. Arterial blood gas analysis was performed in the evening and morning at 4,559 m. No drugs other than paracetamol, and metoclopramide were allowed.

Data analysis and statistics

Polygraphic recordings were analysed from lights-off in the evening, at around 22:00 h, to lights-on in the morning, at around 05:00 h. This period was termed time in bed (TIB). Inductive plethysmographic tracings were analysed breath by breath and derived variables averaged over the night [15, 20]. The phase shift between rib cage and abdominal excursions was calculated [21]. Apnoeas/hypopnoeas were defined as a reduction of the inductive plethysmographic sum volume signal to <50% over $\geqslant 10$ s in comparison to the preceding 2 min baseline [22, 23]. Transient reductions in breathing amplitude to <50% baseline over 5–10 s were also scored as apnoeas/hypopnoeas if they occurred as part of a periodic breathing pattern with waxing and waning of ventilation with periods of hyperventilation alternating with central apnoeas/hypopnoeas over at least three successive cycles (fig. 1) [24, 25]. Central apnoeas/hypopnoeas were identified by absence of rib cage-abdominal asynchrony [14]. The apnoea/hypopnoea index was defined as the number of apnoeas and hypopnoeas per hour TIB. The duration of apnoea/hypopnoea and the fraction of TIB spent in apnoea/hypopnoea were measured. The cycle times of periodic breathing, *i.e.* the duration of a hyperpnoea and the corresponding apnoea/hypopnoea were measured. The fraction of TIB spent with periodic breathing was determined as the sum of all cycle times of periodic breathing divided by TIB. Counts of oxygen saturation dips $\geqslant 4\%$ and histograms of oxygen saturation averaged over 1 s periods were obtained [26]. Rest and activity periods were derived from actigrams with the aid of dedicated software [17, 18]. The acceleration level below which sleep presumably prevailed was graphically determined. The time from lights-off to the first 10 min with immobile data was defined as estimated sleep latency. The time spent with acceleration below threshold was termed rest time, and estimated sleep efficiency was rest time in per cent of TIB.

Normality of distribution was verified by the Kolmogorov-Smirnov statistics. Results are expressed as mean±SD. Subjects were grouped according to whether AMS had developed, *i.e.* Lake Louise score was $\geqslant 5$, in the morning after the night at 4,559 m. Measurements at different altitudes

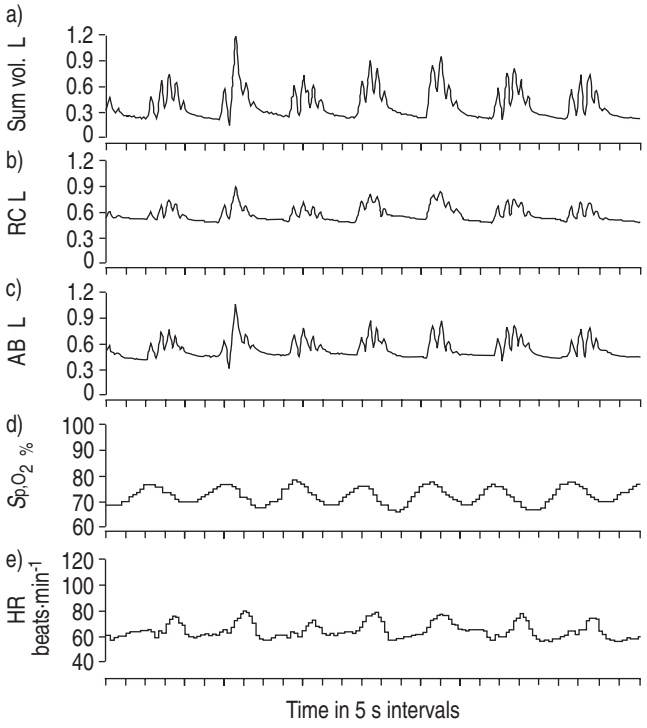

Fig. 1. – Nocturnal polygraphic recording obtained from a mountaineer at 4,559 m. The inductive plethysmographic volume signals of a) the sum volume (Sum vol.) of the ribcage (RC) and abdomen (AB), b) the RC volume, and c) the AB volume, illustrate periodic breathing associated with fluctuations in d) arterial oxygen saturation (S_{p,O_2}) and e) heart rate (HR). The repetitive apnoeas are scored as central, since there is no asynchrony among rib cage and abdomen excursions.

and between groups were compared by analysis of variance followed by Newman-Keuls tests, where appropriate [27]. The effect of potential determinants of AMS was evaluated by logistic regression. A probability of $p<0.05$ was assumed as significant. A power of 80% was assumed to represent appropriate certainty to derive negative conclusions from nonsignificant inter-group differences.

Results

All 25 subjects completed the protocol. In four subjects, the cardiorespiratory sleep studies could not be analysed because of technical failure (three subjects with and one without AMS). These data had to be discarded. Thus, data of the remaining 21 subjects (3 females, 18 males, mean±SD aged 35±12 yrs) are reported.

Clinical and self-assessment

Clinical examination did not show symptoms or signs of high altitude pulmonary oedema, nor ataxia or impaired consciousness (high altitude cerebral oedema) in any subject. Thus, none of the subjects required treatment for severe high altitude related illness, and none of them took metoclopramide. In the morning after having spent one night at 4,559 m, 11 of 21 subjects fulfilled the criteria for AMS (Lake Louise score $\geqslant 5$ [2], range 5–10). This group, termed AMS-group, did not differ in regard to age, sex, or body mass index from the rest of the subjects, termed controls (table 1). The tendency of the AMS-group to be sicker than the control group was already present at lower altitude (evening and morning at 3,610 m), but this difference became significant after subjects had spent a night at 4,559 m only. In controls, the mean change in Lake Louise score from 3,610 m to 4,559 m was not statistically significant (table 1). The AMS-group experienced major subjective sleep disturbances at 4,559 m, whereas sleep disturbance in controls was only mild at 3,610 m and 4,559 m.

Arterial blood gas analysis at 4,559 m in the evening and the following morning revealed a similar degree of hypoxemia, and respiratory alkalosis in the AMS-group as in controls (table 2). The values in the evening were not different from that in the morning in both groups. The study was powered with 80% to detect a difference in the P_{a,O_2} of 1.60 kPa (12 mmHg), in the P_{a,CO_2} of 0.67 kPa (5 mmHg) and in the alveolar-arterial oxygen partial pressure gradient of 9 mmHg. Thus, nonsignificant differences in arterial blood gases might have been related to inadequate sample size.

Table 1. – Clinical evaluation

	Controls	AMS group
Subjects n (females)	10 (1)	11 (2)
Age yrs	32±12	39±12
Height m	1.77±0.08	1.77±0.08
Body mass index $kg \cdot m^{-2}$	23.5±2.1	23.4±2.8
Days spent at >2500 m		
in the last 30 days	3.9±2.6	3.2±1.8
in the last 7 days	2.4±2.3	1.8±1.3
Lake Lousie score		
3610 m day 1 Evening	1.5±1.2	3.5±1.8
3610 m day 2 Morning	1.9±1.7	4.2±1.5
4559 m day 2 Evening	2.8±1.9	5.5±2.2$^{\#}$
4559 m day 3 Morning	3.0±1.2	7.3±1.6$^{\P,\#,+}$
Subjective sleep disturbance§		
3610 m, day 2 Morning	0.9±0.7	1.0±0.6
4559 m, day 3 Evening	0.9±0.6	1.8±0.4$^{\#,+}$

Data are presented as mean±SD. Day 1, 2, 3 refers to the days at $\geqslant$3610 m; morning and evening. Assessments were performed between 05:00–07:00 h, and 20:00–22:00 h, respectively. $^{\#}$: $p<0.05$ *versus* corresponding value at 3,610 m; ¶: $p<0.01$ *versus* previous evening; $^{+}$: $p<0.01$ *versus* controls; §: three point Likert scale from 0: satisfactory, refreshing sleep, to 2: severe sleep disturbance.

Table 2. – Arterial blood gas analysis at 4,559 m

	Controls		AMS group	
	Evening	Morning	Evening	Morning
pH	7.56±0.07	7.54±0.04	7.58±0.06	7.55±0.06
P_{a,CO_2} mmHg	26±5	25±5	24±3	24±2
P_{a,O_2} mmHg	48±10	52±13	47±7	46±7
S_{a,O_2} %	87±7	88±9	88±7	86±8
A_{aD,O_2} mmHg	10±5	9±8	12±5	12±7

Data are presented as mean±SD. No significant difference for comparison of corresponding values among controls and AMS group, and among evening and morning values. P_{a,CO_2}: carbon dioxide arterial tension; P_{a,O_2}: arterial oxygen tension; S_{a,O_2}: arterial oxygen saturation; A_{aD,O_2}: alveolar-arterial oxygen partial pressure gradient. kPa=mmHg×0.133. n=10 (controls), 11(AMS group).

Overnight recordings

Ascending from 3,560 m to 4,559 m was associated with an increase in ventilation, mainly related to an increase in tidal volume, whereas breath rate changed little (table 3). The increase in ventilation was more pronounced in the AMS group than in the controls, and only significant in the former. Accordingly, the AMS group showed a significant increase in mean inspiratory flow, a measure of respiratory centre drive [28], in the night at 4,559 m in comparison to the value at 3,560 m and to the corresponding value in controls at 4,559 m. The rib cage *versus* abdominal phase shift was similarly low in AMS subjects as in controls at both altitudes indicating a nearly perfect synchronisation of chest wall excursions.

Nearly all observed apnoea/hypopnoea were central, whereas obstructive events with asynchronous rib cage-abdominal motion were extremely rare, *i.e.* the obstructive apnoea/hypopnoea index was <5 per night in all subjects in both nights. Therefore, the data on apnoea/hypopnoea are not split into central and obstructive events. Already at 3,560 m, and even more so at 4,559 m, frequent central apnoea/hypopnoea occurred, and a significant time of the night was spent with periodic respiration by the AMS-group and controls (table 3). Although the AMS-group tended to have a greater number of events, and a greater fraction of TIB spent in apnoea/hypopnoea and with periodic respiration, the differences to the controls were not statistically significant. Power calculations indicated that the current study was powered with 80% to detect a difference in the apnoea/hypopnoea index of $45 \cdot h^{-1}$, a difference of 47% in time spent with periodic respiration, and a difference of 18% in time spent in apnoea/hypopnoea. Therefore, the lack of significance ($p>0.05$) for the observed differences in these outcomes may have been due to inadequate sample size.

Mean arterial oxygen saturation was lower in the AMS group than in controls at 4,559 m. Since accuracy of pulse oximetry is not well established at low values the relative time spent with oxygen saturation above and below 70% was also computed. A greater percentage of time was spent at low oxygen saturation (<70%) by AMS-subjects than by controls at 4,559 m confirming the impaired oxygenation in the former

Table 3. – Overnight recordings

	Controls		AMS group	
	3610 m	4559 m	3610 m	4559 m
Recording time min	438±62	447±63	422±92	454±42
Ventilation				
$L \cdot min^{-1}$	4.84±1.19	6.06±1.34	5.42±1.67	$7.94 \pm 2.35^{+,\S}$
$L \cdot min^{-1} \cdot m^2$	1.57±0.45	1.74±0.56	1.96±0.50	$2.54 \pm 0.80^{+}$
Tidal volume L	0.28±0.07	$0.36 \pm 0.10^{+}$	0.28±0.08	$0.42 \pm 0.11^{+}$
Breath rate Breaths·min^{-1}	17.2±1.7	17.6±2.5	19.0±1.6	19.1±2.3
Duty cycle tI/tT	0.41±0.03	0.43±0.03	0.43±0.02	0.43±0.03
Mean inspiratory flow V_T/tI $L \cdot s^{-1}$	0.19±0.05	0.22±0.05	0.19±0.06	$0.29 \pm 0.09^{+,\S}$
Rib cage-abdominal phase shift degrees	11±3	14±4	14±3	16±5
Apnoea/hypopnoea index events·h^{-1}	28.6±28.5	47.1±42.6	20.2±27.3	$60.1 \pm 34.6^{+}$
Apnoea/hypopnoea mean durations	13.3±1.0	$10.3 \pm 2.6^{+}$	13.5±1.2	$10.3 \pm 3.1^{+}$
Time in apnoea/hypopnoea % of TIB	12±11	16±17	10±12	19±14
Cycle time of periodic breathing s	30±6	26±4	29±4	25±4
Time with periodic breathing % of TIB	25±25	34±33	18±26	$43 \pm 27^{+}$
Mean nocturnal S_{p,O_2} %[#]	84±2	$73 \pm 6^{+}$	78±7	$59 \pm 13^{+,\S}$
Time with S_{p,O_2}<70% % of TIB[#]	0±0	30±36	11±19	$74 \pm 39^{+,\S}$
S_{p,O_2} dip rate dips >4%·h^{-1}[#]	3.7±2.9	$70.8 \pm 38.6^{+}$	5.6±5.9	$86.6 \pm 46.2^{+}$
Heart rate $L \cdot min^{-1}$	67±10	$73 \pm 12^{+}$	74±7	$81 \pm 12^{+}$
Rest time min[¶]	368±71	378±54	340±47	302±73
Estimated sleep latency min[¶]	17±9	15±11	14±8	25±46
Estimated sleep efficiency % of TIB[¶]	86±6	85±6	80±8	$68 \pm 17^{+,\S}$

Data are presented as mean±SD. tI: inspiratory time; tT: respiratory cycle time; V_T: tidal volume; TIB: time in bed from lights-off to lights-on; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetery. [#]: S_{p,O_2}: oxygen saturation by pulse oximetry available at 3,650 m in nine controls, and five AMS subjects, at 4,559 m in all 21 subjects; [¶]: actimetry data available at 3,610 m in nine controls, and 10 AMS-subjects, at 4,559 m in 10 controls and 10 AMS subjects; [+]: $p<0.05$ *versus* 3,650 m; [§]: $p<0.05$ *versus* controls. n=10 (controls); 11 (AMS group).

(table 3). The number of oxygen saturation dips $\geqslant 4\%$ in the AMS group exceeded corresponding values in controls but these differences were statistically nonsignificant. Heart rate increased in both groups to a similar extent after ascending to 4,559 m.

In the night at 4,559 m actigraphic recordings revealed that the AMS-group spent a greater percentage of the night moving, *i.e.* had reduced estimated sleep efficiency, than controls (table 3).

To evaluate potential effects of nocturnal hypoxemia, the prevalence of apnoea/hypopnoea, and ventilation on the development of AMS, binary logistic regression analysis was performed on data from overnight recordings at 4,559 m. The percentage of time spent at oxygen saturation <70%, the apnoea/hypopnoea index, and mean nocturnal ventilation adjusted for body surface area (by dividing ventilation by the squared height in m [8]) were the independent variables, and AMS (Lake Louise score $\geqslant 5$ or <5 in the morning at 4,559 m) the binary dependent variable. The analysis revealed that only nocturnal hypoxemia was a significant predictor of the development of AMS (odds ratio for per cent time spent with oxygen saturation <70% 1.034, 95% confidence interval 1.001–1.068, p=0.04). Inclusion of overnight changes in Lake Louise scores into the prediction model did not alter these results, *i.e.* nocturnal hypoxemia (per cent time with arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) <70%) remained the only significant predictor for AMS.

Discussion

The current study assessed nocturnal breathing patterns and oxygenation in mountaineers climbing from lowlands to 4,559 m within <24 h, in relation to symptoms and signs of AMS. It was found that the development of AMS after a night at 4,559 m was preceded by pronounced hypoxemia, a high, and unstable nocturnal ventilation, and restless sleep. The data are consistent with the hypothesis that nocturnal hypoxemia unrelated to hypoventilation but likely due to impaired pulmonary gas exchange is the major determinant of AMS, whereas nocturnal periodic breathing seems not to play a predominant role in promoting AMS.

One of the strengths of the current investigation is the use of noninvasive techniques for continuous monitoring of nocturnal breathing patterns. Thus, the well-known effects of airway instrumentation on ventilation could be avoided [29]. Furthermore, by calibrating the respiratory inductive plethysmograph quantitative estimates of ventilation were obtained in a fairly large number of subjects, information that has not been available from previous studies in a similar setting. By requiring inductance plethysmographic derived tidal volumes to fall within 20% of the reference, *i.e.* the fixed volume bag, at the end of overnight recordings, an acceptable accuracy of the estimates of ventilation was assured.

The more pronounced nocturnal hypoxemia found in subjects developing AMS in comparison with controls matched in regard to anthropometric characteristics and prior acclimatisation is consistent with earlier studies indicating a central role of hypoxemia in causing AMS [6, 7, 11]. In contrast, median nocturnal oxygen saturation by pulse oximetry did not differ among five subjects with AMS and eight controls (*i.e.* it was 63% in both) who underwent a similar ascent protocol to Capanna Regina Margherita, as that in the current study [12]. This discrepancy may relate to the fact that EICHENBERGER *et al.* [12] had assessed AMS by a clinical score different from the Lake Louise protocol that was employed in the current study, and to differences in the prevalence of subclinical pulmonary oedema between the cited and the current study. Since calibration of pulse oximetry is less well established at low oxygen saturation (<70%), a technical dissimilarity in pulse oximeters between studies is an additional potential explanation for the discrepancy [30].

In the AMS-group, a trend for decreased mean nocturnal oxygen saturation, augmented ventilation, and symptoms of

AMS already evolved in the first night at 3,650 m. These differences to the controls became statistically significant over the course of the night at 4,559 m (table 3). Since mean nocturnal ventilation in the AMS-group exceeded that of controls by >30% (table 3), and since mean inspiratory flow ($\dot{V}T/tI$), a measure of central respiratory drive [28], was also increased by a similar amount in the AMS-group, the data from the current study do not suggest a reduced central respiratory drive as the cause of more pronounced hypoxemia in AMS-subjects. Instead, an impaired pulmonary gas exchange, possibly related to interstitial fluid accumulation, seems to be a more likely explanation. Although arterial blood gas analysis in the morning at 4,559 m revealed a lower P_{a,O_2}, a lower P_{a,CO_2}, and a greater alveolar-P_{a,O_2} arterial oxygen tension gradient (A_{aD,O_2}) in the AMS-group than in controls (table 2), these differences were not statistically significant. Therefore, the results from the current study do not substantiate (nor exclude) an impaired gas exchange due to subclinical pulmonary oedema in the AMS-group. Potential explanations for this negative finding are an inadequate sample size or inaccuracies in estimation of the A_{aD,O_2}, which was based on an assumed respiratory exchange ratio of 0.85. Since the P_{a,CO_2} values measured in the current study (table 3) are lower than values observed previously under similar circumstances [31, 32] it is conceiveable that the subjects were hyperventilating to some degree, which might have increased their respiratory exchange ratio. Nevertheless, an association of a widened A_{aD,O_2} with AMS has been observed in several previous investigations [8, 31, 33].

In a study by BARTSCH *et al.* [8], subjects with AMS revealed a transient decrease in isocapnic hypoxic ventilatory response (but neither in poikilocapnic hypoxic nor hypercapnic ventilatory response) within 4 h after arrival at 4,559 m, whereas this was not observed in controls. No differences in isocapnic and poikilocapnic hypoxic, and in hypercapnic ventilatory responses were present among AMS and control subjects at low altitude, and after they had spent a night at 4,559 m. A low ventilatory response to hypoxia has also been observed in subjects experiencing symptoms of AMS during short-term exposure to 4,800 m in a hypobaric chamber over up to 7 h [10]. Thus, subjects prone to AMS may have an initial relative hypoventilation within hours after rapid ascent to high altitude. Nevertheless, the lack of differences between subjects with AMS and controls in measures of ventilatory response and resting ventilation after >12 h at 4559 m does not support a persistent role of impaired ventilatory response in propagating AMS during prolonged altitude sojourn [8]. Consistent with this hypothesis are the higher nocturnal ventilation and mean inspiratory flow recorded in the current study in subjects developing AMS as compared with controls during a nocturnal recording that started >10 h after arrival at 4,559 m (table 3). However, direct measurements of respiratory drive would have been required to corroborate this point. A potentially confounding influence on nocturnal ventilation derives from the sleep/wakefulness-state dependence of ventilatory drive [24]. Since actigraphic recordings indicate reduced sleep efficiency in AMS subjects, their higher ventilation might in part be related to a shorter nocturnal sleep period (table 3). Other unpleasant symptoms of AMS might also have stimulated ventilation.

Although the apnoea/hypopnoea index, the time spent with periodic breathing, and oxygen saturation dip rate were higher during the night at 4,559 m in the AMS-group than in controls, the differences were not statistically significant (table 3). Furthermore, only nocturnal hypoxemia, *i.e.* the percentage of time spent with low arterial oxygen saturation <70%, was a significant predictor of AMS in a multiple logistic regression analysis. The odds ratio of 1.034 indicates that for each % TIB spent with S_{p,O_2}<70%, the risk of developing AMS is increased by a factor of 1.034. Thus, a subject spending 74% of time with S_{p,O_2}<70% (*i.e.* the mean value of the AMS-group, table 3) has a nearly 12-fold increased risk (*i.e.* odds-ratio of 1.034^{74}) of developing AMS compared with another subject spending the entire night with S_{p,O_2}>70%. In contrast, mean nocturnal ventilation, and the apnoea/hypopnoea index did not significantly contribute to the prediction model. Therefore, periodic breathing seems not to be a critical determinant of AMS, and in this regard the results from the current study are consistent with earlier investigations that failed to demonstrate a significant association of periodic breathing with development of AMS [11, 12]. Nevertheless, neither the current nor the earlier studies had sufficient statistical power to definitively rule out some association of periodic breathing with AMS.

A limitation of the current and of previous studies on AMS relates to the lack of objective measures to assess this condition. This may have hampered a more precise evaluation of the pathophysiological determinants of AMS.

Conclusions

In unacclimatised mountaineers spending a night in a mountain hut at 4,559 m, an association among the development of acute mountain sickness and preceding pronounced nocturnal hypoxemia has been confirmed by the current study. This investigation extends previous studies [11, 12] by providing quantitative data on nocturnal ventilation and breathing patterns measured by nonobtrusive means. These observations are consistent with the hypothesis that the hypoxemia in subjects with subsequent acute mountain sickness is not related to nocturnal hypoventilation or reduced respiratory centre drive, nor to periodic breathing, although confirmation in a larger number of subjects is required.

Appendix 1: Assessment of acute mountain sickness

Lake Louise score questions and rating [2, 14]
Self-report by mountaineer:

1. Headache	0 None 1 Mild 2 Moderate 3 Severe, incapacitating
2. Gastrointestinal symptoms	0 None 1 Poor appetite or nausea 2 Moderate nausea or vomiting 3 Severe nausea or vomiting, incapacitating
3. Fatigue and/or weakness	0 None 1 Mild 2 Moderate 3 Severe, incapacitating
4. Dizziness/lightheadedness	None Mild Moderate Severe, incapacitating
5. Difficulty sleeping	0 Slept as usual 1 Did not sleep as well as usual 2 Woke up many times, poor night sleep 3 Could not sleep at all

Clinical assessment by investigator:	
6. Change in mental status	0 None
	1 Lethargy/lassitude
	2 Disoriented/confused
	3 Stupor/semiconsciousness
	4 Coma
7. Ataxia (heel-to-toe walking)	0 None
	1 Manoeuvres to maintain balance
	2 Steps off line
	3 Falls down
	4 Can't stand
8. Peripheral oedema	0 None
	1 Peripheral oedema at one location
	2 Peripheral oedema at two or more locations

The sum of the scores of self-rating and clinical assessment is the Lake Louise Score. A sum score of $\geqslant 5$ was considered as indicating acute mountain sickness (AMS).

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