Exercise intensity typical of mountain climbing does not exacerbate acute mountain sickness in normobaric hypoxia

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Submitted 14 March 2012; accepted in final form 1 August 2012

Schommer K, Hammer M, Hotz L, Menold E, Bärtsch P, Berger MM. Exercise intensity typical of mountain climbing does not exacerbate acute mountain sickness in normobaric hypoxia. J Appl Physiol 113: 1068–1074, 2012. First published August 2, 2012; doi:10.1152/japplphysiol.00329.2012.—Physical exertion is thought to exacerbate acute mountain sickness (AMS). In this prospective, randomized, crossover trial, we investigated whether moderate exercise worsens AMS in normobaric hypoxia (12% oxygen, equivalent to 4,500 m). Sixteen subjects were exposed to altitude twice: once with exercise (3 × 45 min within the first 4 h on a bicycle ergometer at 50% of their altitude-specific maximal workload (maximal oxygen uptake)), and once without. AMS was evaluated by the Lake Louise score and the AMS-C score of the Environmental Symptom Questionnaire. There was no significant difference in AMS between the exposures with and without exercise, neither after 5, 8, nor 18 h (incidence: 64 and 43%; LLS: 6.5 ± 0.7 and 5.1 ± 0.8; AMS-C score: 1.2 ± 0.3 and 1.1 ± 0.3 for exercise vs. rest at 18 h; all P > 0.05). Exercise decreased capillary PO2 (from 36 ± 1 Torr at rest to 31 ± 1 Torr), capillary arterial oxygen saturation (from 72% at rest to 67 ± 2%), and cerebral oxygen saturation (from 49 ± 2% at rest to 42 ± 1%, as assessed by near-infrared spectroscopy; P < 0.05), and increased ventilation (capillary Pco2 27 ± 1 Torr; P < 0.05). After exercise, the increase in ventilation persisted for several hours and was associated with similar levels of capillary and cerebral oxygenation at the exercise and rest day. We conclude that moderate exercise at ~50% maximal oxygen uptake does not increase AMS in normobaric hypoxia. These data do not exclude that considerably higher exercise intensities exacerbate AMS.

High altitude; AMS; oxygen saturation; near-infrared spectroscopy; hypoxemia

ACUTE MOUNTAIN SICKNESS (AMS) is the most frequent high-altitude-associated illness. The pathophysiology of AMS is incompletely understood (3). However, several reports suggest that the degree of altitude-induced hypoxemia is an important pathophysiological determinant (5, 19, 26). In line with these reports, a recent study showed that subjects with higher AMS scores have more severe hypoxemia than subjects with lower AMS scores (23).

Under hypoxic conditions, exercise at higher intensities decreases arterial oxygen saturation (SaO2) in most healthy subjects (14, 28, 36). Thus it is conceivable that exercise increases the incidence and severity of AMS compared with resting conditions. Indeed, a previous study on seven subjects indicates that moderate exercise, i.e., four 30-min exercise bouts at 50% of the individual maximal oxygen uptake (V02 max) in the first 6 h, exacerbates symptoms of AMS after 10 h at 429 Torr (equivalent to 4,800 m; Ref. 28). However, the short observation time in that study (28) does not exclude the possibility that exercise only triggered an early onset of AMS, and that, after an overnight stay, i.e., when AMS symptoms usually are most prominent, no difference in AMS between rest and exercise would have been detectable. In addition, it is possible that some exercise-induced nonspecific symptoms, like headache (35), nausea (12), and fatigue (34), which cannot necessarily be attributed to AMS, affected the 10-h AMS score.

We, therefore, investigated, in a prospective, randomized and crossover controlled trial, whether moderate exercise (three 45-min exercise bouts at 50% V02 max in the first 4 h) affects the incidence and severity of AMS during an 18-h exposure in normobaric hypoxia (FiO2 0.12, equivalent to 4,500 m). The study day included an overnight stay. Our hypothesis was that exercise causes more severe hypoxemia and exacerbates AMS in simulated altitude.

MATERIAL AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and its current amendments and was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg. Before the study, all participants provided written, informed consent.

Study Cohort

Sixteen healthy, nonsmoking lowlanders (12 men, 4 women; age: 29 ± 2 yr; body weight: 70.3 ± 2.9 kg; height: 176 ± 2 cm) participated in the study. None of the subjects had an altitude exposure >2,000 m within 30 days before the study and during the study period. The mean V02 max of the study group assessed in hypoxia on a bicycle ergometer in a ramp test was 46.6 ± 1.8 ml·min⁻¹·kg⁻¹, and the maximum workload in this test was 3.12 ± 0.1 W/kg. None of the participants took any regular medications, and none had a history of chronic daily headache. All subjects were encouraged to match their diet on the days of the study, but no monitoring of intake was performed. During the study days, the subjects received standardized food and beverages ad libitum.

Assessment of V02 max in Hypoxia

Several days before the first study day, subjects performed a ramp test on a bicycle ergometer (type 906900, Lode BU Medical Technology, Groningen, The Netherlands) in normobaric hypoxia [inspired O2 fraction (FiO2) = 0.12] to determine V02 max (ZAN 300 USB, nSpire Health). The test was done in hypoxia to adjust the relative workload of 50% V02 max to the decline of V02 max, with increasing altitude (10, 16). The ramp test protocol started at 20 W, and workload increased by 40 W over 3 min. All subjects exercised in seating position until exhaustion, as verified by a capillary lactate concentration >8 mmol/l, a respiratory exchange ratio >1.10, or a visual plateau in the O2 uptake plotted against the minute ventilation at the end of the test. The power corresponding to 50% V02 max was determined using linear regression.
Study Days

On 2 different days, subjects were studied for 18 h in a hypoxia room that provided a constant level of normobaric hypoxia (FiO2 = 0.12, equivalent 4,500 m) by admixture of nitrogen (System Linde Gas, Unterschleissheim). Figure 1 summarizes the study protocol. On 1 study day, subjects performed three exercise sessions on a bicycle ergometer over 45 min each at 50% of their VO2 max. The exercise bouts began after the subjects had been in hypoxia for 1 h, and every exercise session was followed by 15 min of rest. Heart rate was continuously monitored (Polar S810i, Buttellborn), and blood pressure was measured using a sphygmomanometer. The SaO2 was measured by pulse oximetry (BCI 3043 Oxilink, Smiths Medical), and cerebral oxygen saturation (SO2) was assessed by near-infrared spectroscopy (Invo System, Somanetics), as described previously (17, 21, 22). At the end of each exercise cycle, a capillary blood sample was taken from the ear lobe treated with vasodilator cream (Finalgon) for the measurement of blood gases and pH (Siemens Rapidpoint 400/405, Bayer Diagnostics, Sudbury, UK). As shown previously, this technique generally results in good repeatability for lactate and PCO2 measurements and closely correlates with blood samples drawn from the radial artery (9, 11, 15, 31). After completing the last bout of exercise, the participants stayed at rest in hypoxia until the next morning. At 5, 8, and 18 h, SaO2 and cerebral SO2, blood gases, blood pressure, heart rate, and AMS scores were assessed (Fig. 1A).

On the other study day, subjects were sedentary and exposed to the same degree of normobaric hypoxia (FiO2 = 0.12) for 18 h as on the exercise day. All measurements performed at the exercise day were repeated at exactly the same time points (Fig. 1B). The order of the exercise day and rest day was randomized for each subject, and the trials were 4–6 wk apart to minimize acclimatization effects.

Diagnosis of AMS

The severity of AMS was evaluated by clinical examination and was quantified by using the Lake Louise scoring protocol (25) and the AMS-C score of the Environmental Symptom Questionnaire (29). For the Lake Louise scoring protocol, each participant answered questions about the severity of headache, gastrointestinal symptoms, fatigue, lightheadedness or dizziness, and insomnia. A score of 0 to 3 points (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) was assigned for each item. In the clinical examination, a score of 0 (normal) to 4 points was given for mental status (for which 4 points indicated coma) and ataxia (for which 4 points indicated inability to stand on the heel-to-toe walking test). The sum of all points yielded the Lake Louise score.

The AMS-C score of the Environmental Symptom Questionnaire is composed of 11 items, which are graded from 0 (not present) to 5 (extremely severe). The factorial weight of each item is given in parentheses: light-headed (0.489), headache (0.465), dizziness (0.446), feeling faint (0.346), dim vision (0.501), off-coordination (0.519), feeling weak (0.387), sick to stomach (0.347), loss of appetite (0.413), feeling sick (0.692), and feeling hung-over (0.584). To obtain the AMS-C score, the sum of all item scores multiplied by the respective factorial weight was multiplied by 5 and divided by 25.95, as described previously (29).

Subjects were classified as AMS positive if they had a Lake Louise score ≥5 and an AMS-C score ≥0.70 points (25, 29). The scores were obtained at the beginning of each study day in normoxia and at 5, 8, and 18 h of hypoxia (Fig. 1). If only one of both scores was positive, the subject was classified as non-AMS. With respect to the study endpoint, i.e., AMS after 18 h, this was the case in two subjects at both the rest and the exercise day.

Statistical Analysis

Sample size analysis. Before the study, we performed a sample size analysis that was based on the observations that the incidence of AMS is ~50% (4, 6, 18, 24) and 90% (28) at rest and moderate exercise, respectively. To detect this difference with a Fisher and Yates test and with a power of 80% at P = 0.05, we required 16 subjects (nQuery Advisor, version 7.0).

Main analysis. Normal distribution of the data was tested using the Kolmogorov-Smirnov test. Differences in the incidence of AMS were analyzed by using the Fisher and Yates test, and differences in AMS severity were analyzed by two-way repeated-measures ANOVA. Data obtained periodically throughout the experiment, such as hemodynamic variables, were analyzed by one-way repeated-measures ANOVA, if they were normally distributed, or by Friedman repeated-measures ANOVA on ranks if the data were not normally distributed. Pairwise multiple-comparison procedures were made using Student-

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**Fig. 1. Study protocol for the study day during exercise (A) and at rest (B) in normobaric hypoxia [inspired O2 fraction (FiO2) = 0.12; equivalent to 4,500 m].** Acute mountain sickness (AMS) scores were assessed with the Lake Louise score and the AMS-C score of the Environmental Symptom Questionnaire. Cerebral oxygen saturation (SO2) was assessed with near-infrared spectroscopy. The individual maximal oxygen uptake (VO2 max) was assessed with an exercise test several days before the first study day.
Newman-Keuls test, if the overall test was significant. The relationship between pairs of variables was expressed with the Pearson correlation coefficient. Data are expressed as mean values ± SE. A P value of ≤0.05 was considered significant. Statistics were performed using the SigmaStat software package (SPSS, Chicago, IL).

RESULTS

Compliance and Study Drop Outs

Two subjects were excluded from the data analysis because of incomplete data sets. One of these subjects left the hypoxia room after 8 h on both study days with an AMS-C score of 2.5 and a Lake Louise score of 9 at the rest day, and an AMS-C score of 3.1 and a Lake Louise score of 10 at the exercise day. The other subject dropped out on the exercise day after 8 h with an AMS-C score of 4.3 and a Lake Louise score of 16. Thus the presented data refer to the 14 subjects who completed both study days. However, excluding these two subjects does not significantly affect the differences in AMS between rest and exercise, as shown in Table 1.

Incidence and Severity of AMS During Rest and Exercise

As given in Table 1, at none of the time points, i.e., 5, 8, and 18 h, was there a significant difference in the incidence of AMS between the study day at rest and with exercise (all P > 0.05). There was also no significant difference with respect to the severity of AMS as evaluated by the Lake Louise score and the AMS-C score (Fig. 2). Indeed, there was a positive correlation between both AMS scores with a correlation coefficient of 0.78 and 0.87 at the rest and exercise day, respectively (both P < 0.001).

Oxygenation, Ventilation, and Hemodynamics During Exercise

All three exercise bouts caused a significant decrease in capillary PO2 (Fig. 3A). Concomitantly, there was a decrease in capillary SaO2 of 6 ± 3% (P = 0.03) during the first bout, and of 7 ± 3% (P = 0.02) during the second bout of exercise. During the third bout of exercise, capillary SaO2 decreased by 4 ± 3% (nonsignificant). These changes were accompanied by an exercise-induced decrease in cerebral SO2 (Fig. 3B). During all three exercise bouts, there was a positive correlation between capillary SaO2 and cerebral SO2 (1st exercise bout: R = 0.75, P < 0.01; 2nd exercise bout: R = 0.69, P < 0.05; 3rd exercise bout: R = 0.90, P < 0.001).

Ventilation at rest yielded a capillary carbon dioxide pressure (PCO2) of 33.5 ± 0.5 Torr and a capillary pH value of 7.48 ± 0.01. All three exercise bouts induced a significant decrease in capillary PCO2 (Fig. 3C) and an increase in capillary pH to 7.51 ± 0.01 (P < 0.05 vs. rest) at the end of the third exercise bout. Upon exercise, heart rate significantly increased (at rest: 76 ± 4 beats/min, last minute of 1st exercise bout: 141 ± 3 beats/min, last minute of 2nd exercise bout: 144 ± 4 beats/min, last minute of 3rd exercise bout: 148 ± 4 beats/min; all P < 0.001 for exercise vs. rest). This increase in heart rate was accompanied by a significant increase in systolic blood pressure, while diastolic blood pressure decreased (at rest: 120 ± 4/76 ± 3 mmHg, last minute of 1st exercise bout: 151 ± 7/55 ± 2 mmHg, last minute of 2nd exercise bout: 139 ± 5/45 ± 4 mmHg, last

### Table 1. Incidence of AMS at the various time points during both study days

<table>
<thead>
<tr>
<th>Study Condition</th>
<th>5 h</th>
<th>8 h</th>
<th>18 h</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>n = 14</td>
<td>21 (n = 3)</td>
<td>43 (n = 6)</td>
<td>43 (n = 6)</td>
</tr>
<tr>
<td></td>
<td>n = 16</td>
<td>25 (n = 4)</td>
<td>44 (n = 7)</td>
<td>n/a</td>
</tr>
<tr>
<td>Exercise</td>
<td>n = 14</td>
<td>36 (n = 5)</td>
<td>57 (n = 8)</td>
<td>64 (n = 9)</td>
</tr>
<tr>
<td></td>
<td>n = 16</td>
<td>38 (n = 6)</td>
<td>62 (n = 10)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n, No. of subjects. The raws for 14 subjects refer to the data obtained from all subjects who completed both study days. The raws for 16 subjects include data of the 2 subjects who did not complete both study days (for details, see Compliance and Study Drop Outs). The overall incidence reflects all subjects who were classified as acute mountain sickness (AMS) positive to at least one of the three time points. AMS was diagnosed by a combined Lake Louise score of ≥5 points and an AMS-C score of ≥0.7 points. If only one of both scores was positive, the subject was classified as AMS negative. n/a, Not applicable. All P > 0.05.
minute of 3rd exercise bout: 140 ± 7/44 ± 6 mmHg; all P < 0.01 for exercise vs. rest).

Oxygenation, Ventilation, and Hemodynamics After Exercise

There was no significant difference in capillary PO2, capillary SaO2, and cerebral SO2 between subjects at rest and at 5, 8, and 18 h after exercise (Table 2). Capillary PCO2 was significantly lower after 18 h compared with values after 5 and 8 h on the day without exercise, indicating an increased ventilation during the exposure (Table 2). In contrast, at the day with exercise, capillary PCO2 remained stable after the exercise bouts, with significantly lower values at 5 and 8 h than at the rest day (Table 2), indicating that the exercise-induced hyperventilation persisted for several hours. After 18 h, capillary PCO2 was comparable between both study days. There was a negative correlation between capillary PCO2 and SO2 on both study days (exercise day: R = −0.443; P < 0.01; rest day: R = −0.365; P < 0.05).

Oxygenation and Ventilation in Subjects With and Without AMS

Neither during rest nor during exercise was there a significant difference in capillary PO2, capillary SaO2, and cerebral SO2 between subjects with and without AMS. There was also no difference in ventilation, as indicated by the comparable capillary PCO2 values (data not shown).

DISCUSSION

The main finding of the present study is that, against our hypothesis, moderate exercise did not exacerbate the incidence and severity of AMS in normobaric hypoxia (FIO2 = 0.12; equivalent to 4,500 m). There was no significant difference in AMS scores between the exposures with and without exercise neither after 5, 8, nor 18 h.

Effect of Exercise on Oxygenation

Several reports suggest that the degree of altitude-induced hypoxemia is important in the pathophysiology of AMS (5, 19, 23, 26). Under hypoxic conditions, exercise at higher intensities decreases SaO2 in most healthy subjects (14, 28, 36). Therefore, it was conceivable to expect that exercise increases the incidence and severity of AMS compared with rest.

In our study, subjects exercised 3 × 45 min at 50% V\textsubscript{O2 max} measured in hypoxia. This exercise intensity was comparable with the intensity of an ascent to the Capanna Regina Margherita [4,559 m; (8)], as occurred in many field studies (6, 7, 13, 30). It was also similar to the exercise intensity of a previous study by Roach et al. (28), who found that four 30-min exercise bouts at 50% V\textsubscript{O2 max} exacerbate symptoms of AMS after 10 h at a simulated altitude of 4,800 m. In our study, capillary arterial PO2 and SaO2 values decreased during exercise. The degree of desaturation was similar to the exercise-induced desaturation observed by Roach et al., where the decrease of capillary SaO2 was ~8% (28). Thus the exercise intensity and the degree of exercise-induced hypoxemia are comparable between both studies and do not explain why we could not confirm the finding of Roach et al. of moderate exercise worsening AMS. However, we cannot exclude that considerably higher exercise intensities with a V\textsubscript{O2 max} >50% enhance AMS. But this was not investigated in the present study.

AMS symptoms are primarily of neurogenic origin (1). Therefore, we also measured cerebral SO2 by near-infrared spectroscopy, an optical imaging technique that is well established for the continuous monitoring of regional cerebral SO2 (17, 21, 22). We found that exercise decreased cerebral SO2 by about the same magnitude as capillary SaO2, and that the degree of systemic and cerebral deoxygenation closely correlated. Thus, if a decrease in systemic or cerebral oxygenation upon
exercise would later worsen AMS, we should have observed an increased incidence and/or severity of AMS after exercise. However, this was not the case.

Postexercise Oxygenation and Ventilation

With cessation of exercise, oxygenation returned to the higher resting levels. Thus 75 min after the last exercise bout, i.e., at 5 h, we could not observe a difference in peripheral and cerebral oxygenation between rest and exercise, as demonstrated by equivalent values in arterial \( \text{PO}_2 \), \( \text{SaO}_2 \), and cerebral \( \text{SO}_2 \). There was also no difference in these values at 18 h, the time of the primary study endpoint. Roach and coworkers (28) also found that oxygenation quickly returned to the resting levels and documented equivalent \( \text{SaO}_2 \) values between rest and exercise at 3 and 6 h, respectively. These findings indicate that exercise-induced hypoxemia is transient, and resting oxygenation levels are quickly restored.

One explanation for the restoration of oxygenation after exercise might be a sustained exercise-related hyperventilation. We observed that, after exercise, \( \text{PCO}_2 \) values remained at the level measured during exercise and were thus lower compared with the exposure without exercise. However, after 18 h, \( \text{PCO}_2 \) was comparable between both study days (Table 2). This finding suggests that exercise leads to a persistent increase of ventilation to a level that is reached through ventilatory acclimatization at rest after about 18 h.

Incidence and Severity of AMS

The incidence of AMS after 18 h was 54% when the data of both exposures were combined. This incidence is consistent with previous findings in field studies (4, 6, 18, 24) and other studies at simulated altitude (2, 20, 33). The group-specific analysis showed that the incidence of AMS after 18 h was 43% at the rest day and 64% at the exercise day, respectively. This difference was not significant and indicates that exercise at 50% \( \text{VO}_2 \text{max} \) did not increase the incidence of AMS. This conclusion is further supported by the observation that the severity of AMS, assessed by the two most widely used scoring systems (3), was not significantly different between rest and exercise at any time point in our study.

There was a trend for higher AMS scores at the exercise day compared with rest. Therefore, it appears plausible that, in a larger study population, the difference would be statistically significant. However, we tested the effect of moderate exercise on AMS in the largest group of people to date, and the clinical significance of the detected differences is probably very minor. This is supported by the sample size analysis that was performed before the study, suggesting that 16 subjects were enough to detect an increase in AMS of 40% with a power of 80% at \( \alpha \leq 5 \). Therefore, our data suggest that moderate exercise does not relevantly influence the incidence and severity of AMS in non-acclimatized subjects after an overnight stay in normobaric hypoxia.

The cutoff values we used were \( \geq 5 \) points for the Lake Louise score and \( \geq 0.70 \) points for the AMS-C score and are considered to have a sensitivity and specificity of \( \approx 80–90\% \) at an altitude of 4,550 m for identifying those who feel sick or those who have to reduce activity, respectively (3). This criterion is more rigorous than that in the study by Roach et al. (28), where only the Lake Louise score was used and subjects were classified as AMS positive if they had a score \( \geq 5 \) points. Applying this cutoff value to our study also did not lead to a significant difference between rest and exercise, with incidences of AMS of 86 and 79% at 8 h, and of 86 and 93% at 18 h, respectively.

What are possible explanations for the discrepancies between the present findings and those of Roach et al. (28), who reported that exercise increased the incidence and severity of AMS after 10 h at a simulated altitude of 4,800 m? First, our subjects were exposed to normobaric hypoxia, whereas Roach et al. exposed their subjects to hypobaric hypoxia. Several reports suggest that hypobaric hypoxia leads to more severe hypoxemia and induces AMS to a greater extent than does normobaric hypoxia (27, 32). However, the degree of exercise-induced desaturation in our study was comparable to that in the Roach study so that we consider this factor to be of minor importance. Moreover, the incidence and severity of AMS in our study was equivalent to that of many field studies (6, 7, 13, 30), suggesting that our model sufficiently induced AMS.

A second difference is the time of observation. Roach et al. (28) exposed their subjects for 10 h. This short time of exposure does not exclude the possibility that exercise only triggered an early onset of AMS or that the higher AMS score upon exercise was due to symptoms caused by exercise itself. Because AMS symptoms are usually most prominent after the first night, we exposed our subjects for 18 h and included an overnight stay. This also allowed us to minimize the confounding effect of exercise-induced nonspecific symptoms. Thus the evaluation of our subjects after 18 h should more accurately reflect the effects of exposure to hypoxia on the occurrence of AMS in both groups. However, we found no significant difference in AMS between rest and exercise, neither at 5, 8, or 18 h, nor if we applied the Lake Louise score with a cutoff value of \( \geq 3 \) points, as outlined above.

The third difference is the statistical power of the two studies. Roach and coworkers (28) investigated seven subjects,
while we included more than twice as much, as suggested by the sample size analysis we performed before the study. Thus, while in our study the risk for a type 2 error based on these calculations was small, the results of Roach et al. could be explained by a statistical type 1 error. Indeed, only one of the subjects (14%) in the study of Roach et al. developed AMS during the exposure at rest, which is an unusually low incidence considering the altitude of 4,800 m and the low Lake Louise cutoff score of ≥3 points. Thus we suggest that the unusually low incidence of AMS during the control trial explains the apparent effect of exercise in the study of Roach et al.

In summary, we found that repeated bouts of moderate exercise in normobaric hypoxia induced a significant decrease in cerebral and peripheral oxygenation. However, the exercise-induced increase in ventilation persisted for several hours after exercise and was associated with similar levels of oxygenation at both the exercise and the rest day. Probably this increase in ventilation might explain the main finding of the study, namely that moderate exercise did not increase the incidence and severity of AMS in normobaric hypoxia at 5, 8, and 18 h, respectively. These data do not exclude that considerably higher exercise intensities exacerbate AMS.

ACKNOWLEDGMENT

We gratefully acknowledge all of the subjects who took part in the study, Martina Haselmayr for excellent technical assistance, and Tilmann Deutler for statistical advice.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


