Exercise exacerbatess acute mountain sickness at simulated high altitude

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1Division of Physiology, Department of Life Sciences, New Mexico Highlands University, Las Vegas 87701-9000; 2Lovacase Respiratory Research Institutes, Albuquerque 87108-5127; 3Department of Health Promotion, Physical Activity, and Exercise, University of New Mexico, Albuquerque 87131-5686; 4VA Hospital and Department of Cardiology, University of New Mexico School of Medicine, Albuquerque, New Mexico 87131-5686; and 5Department of Physiology, School of Medicine, University of Graz, A-8010 Graz, Austria

Roach, R. C., D. Maes, D. Sandoval, R. A. Robergs, M. Icenogle, H. Hinghofer-Szalkay, D. Lium, and J. A. Loepky. Exercise exacerbates acute mountain sickness at simulated high altitude. J. Appl. Physiol. 88: 581–585, 2000.—We hypothesized that exercise would cause greater severity and incidence of acute mountain sickness (AMS) in the early hours of exposure to altitude. After passive ascent to simulated high altitude in a decompression chamber [barometric pressure = 429 Torr, ~4,800 m (J. B. West, J. Appl. Physiol. 81: 1850–1854, 1996)], seven men exercised (Ex) at 50% of their altitude-specific maximal workload four times for 30 min in the first 6 h of a 10-h exposure. On another day they completed the same protocol but were sedentary (Sed). Measurements included an AMS symptom score, resting minute ventilation (Ve), pulmonary function, arterial oxygen saturation (SaO2), fluid input, and urine volume. Symptoms of AMS were worse in Ex than Sed, with peak AMS scores of 4.4 ± 1.0 and 1.3 ± 0.4 in Ex and Sed, respectively (P < 0.01); but resting Ve and SaO2 were not different between trials. However, SaO2 during the exercise bouts in Ex was at 76.3 ± 1.7%, lower than during either Sed or at rest in Ex (81.4 ± 1.8 and 82.2 ± 2.6%, respectively, P < 0.01). Fluid intake-urine volume shifted to slightly positive values in Ex at 3–6 h (P = 0.06). The mechanism(s) responsible for the rise in severity and incidence of AMS in Ex may be sought in the observed exercise-induced exaggeration of arterial hypoxemia, in the minor fluid shift, or in a combination of these factors.

fluid balance; edema; oxygen saturation; pathophysiology

ACUTE MOUNTAIN SICKNESS (AMS) is a syndrome encountered by travelers to high altitude who ascend too high too fast (7, 19). Symptoms include headache, nausea, malaise, dizziness, and difficulty sleeping. AMS has been well described for several hundred years, but the pathophysiology is unresolved. Surprisingly, the role of exercise in the pathogenesis of AMS has not been systematically studied. Our personal observations, anecdotal reports by others (5, 13, 16), and one preliminary study (4) suggest that overexertion, independent of prior physical condition (11), may be related to the development of AMS. This notion is supported by the finding that the incidence of AMS is lower when subjects passively ascend to high altitude (as in an altitude chamber or by helicopter ascent on mountains) or actively ascend, but slowly (7), compared with active and rapid ascent (14). However, because passive transport to high altitude can occur within minutes, and climbing to the same altitude can take hours or days, the importance of exertion and rate of ascent remains unclear.

In the present study, volunteers were exposed to altitude twice; once they were sedentary, and once they performed intermittent exercise. Our goal was to determine whether such intermittent exercise in the early hours of exposure to high altitude caused an increase in the incidence and severity of AMS.

METHODS

Subjects. Seven young (aged 20–40 yr), healthy, and recreationally active men participated in this study. All were nonsmokers and familiar with bicycle exercise. Their physical characteristics were the following: height 181 ± 2.0 (SE) cm (range 178–188 cm); weight 79 ± 3 kg (range 69–92 kg); and body surface area 2.0 ± 0.04 m² (range 1.9–2.2 m²). Three of the seven subjects had previously experienced altitude illness. All were naive as to the expected outcome of the study. None took any self-prescribed drugs during the study. All lived at altitudes between 1,600 and 1,800 m. All gave informed consent as approved by the University of New Mexico Human Research Review Committee.

Study protocol. Several days before the study, each subject completed a progressive exercise test to his voluntary maximal workload on a cycle ergometer (Ergo, Amsterdam, The Netherlands) at 429 Torr in a hypobaric chamber. Subsequently, they were exposed twice to the same simulated altitude for 10 h. On 1 day they performed repeated bouts of submaximal exercise (Ex), and on the other they were sedentary (Sed). Trials were at least 1 wk apart, with Ex occurring after Sed in five of the seven subjects. Subjects were instructed to match their prestudy diet and fluid intake for the day before the two trials, but there was no verification of compliance. During Ex, within the first 6 h, subjects completed four 30-min exercise bouts at 50% of their maximal altitude-specific workload. After the fourth round of exercise, they sat in the chamber for an additional 4 h. To compensate

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for body water losses secondary to increased ventilation and sweating during Ex, subjects were weighed before and after each exercise bout (model UC300, Seca). A decrease in body weight was compensated for with the intake of 100 ml water/100 g weight loss. No change was noted in body weight in Sed from measurements made at the same intervals as in Ex. Chamber barometric pressure (PB), temperature (25 ± 0.3°C), and humidity (28 ± 1%) were similar for each trial. Measurements were made on arrival at 429 Torr and at 3, 6, and 9 h.

Measurements. Each subject’s overnight (12-h) urine volume was recorded on the morning before each trial. To reach equivalent levels of presstudy hydration between Ex and Sed, subjects drank a volume of water equal to the difference between 1,000 ml and the urine volume if the overnight urine volume was <1,000 ml. Subjects (and investigators who used supplementary oxygen) were then decompressed to 429 Torr in ~15 min. We measured AMS symptoms, resting minute ventilation (Ve), pulmonary function, arterial oxygen saturation (SaO2), fluid input, and urine volume every 3 h beginning when 429 Torr was reached.

Presence and severity of the AMS symptoms of headache, gastrointestinal upset (nausea and vomiting), unusual fatigue, and dizziness were evaluated by investigator interview (17). Each symptom was graded on a scale ranging from zero (absent) to three (most severe). Thus 12 points represent the maximum possible AMS score in this study. The Lake Louise AMS score guidelines state that the criteria for AMS are the presence of a headache, and any other symptom(s) (17). A score of three or more points on this scale represents AMS of moderate severity; a score of six or more points represents debilitating AMS. Subjects also marked a 10-cm-long visual analog scale that queried their general state of well-being. At one end of the visual analog scale were the words “I feel great,” and at the other end the words “I feel terrible.” Their visual analog score was the distance (in cm) of their mark from the “I feel terrible” end of the scale.

Resting Ve was measured after the subject breathed for at least 5 min through a mouthpiece with a noseclip in place. A digital flowmeter (VMM, Interface Associates, Sunnyvale, CA) was used for measuring Ve, and end-tidal gases were monitored by a fuel cell oxygen analyzer [end-tidal Po2 (PETO2); Applied Electrochemistry, Cleveland, OH] and infrared carbon dioxide analyzer [end-tidal PCO2 (PETCO2); Sensormedics, Rancho Viejo, CA]. The SaO2 was monitored by pulse oximetry (Criticare 503). Pulmonary function [forced vital capacity (FVC), forced expired volume in 1 s, and peak expiratory flow] was measured by using an automated electronic spirometer (Vitograph).

Normoxic control experiments. An additional six subjects completed, in a normal laboratory room at sea level, an exercise protocol with identical exercise intensity, duration, and timing as in the chamber study. Their physical characteristics were the following: age 29 ± 5 yr, height 179 ± 7 cm, and weight 71 ± 7 kg. AMS symptom scores were measured as above, i.e., before and at 3, 6, and 9 h elapsed time.

Statistical analyses. AMS symptom score differences were analyzed by using Wilcoxon signed-ranks test, SaO2, during exercise was analyzed by using a paired t-test, and all other variables measured over time at altitude were analyzed with a two-way ANOVA for repeated measures, using Tukey’s post hoc tests. Data are expressed as means ± SE.

RESULTS

Symptoms of AMS were more pronounced in Ex compared with Sed (Fig. 1A, P < 0.01). Incidence of AMS was also higher in Ex; six of seven subjects (86%) had AMS scores of 3 or more compared with only one of seven in Sed (14%) with a score of 3 (P < 0.02). Moreover, in Ex AMS scores were uniformly higher than in Sed for the six subjects with symptoms. Of note is that one subject was immune to AMS in both trials. In contrast, in Ex one subject was removed from the chamber after 6 h due to severe headache, nausea, and dizziness (AMS score = 7). That Ex exacerbated AMS is further supported by the low visual analog scores (0 = “I feel terrible”) in Ex (3.6 ± 1.2 and 6.3 ± 0.9 cm in Ex and Sed, respectively, P < 0.01). In the normoxic control experiments, no significant symptoms were reported before or after exercise up to 9 h (mean Lake Louise score = 0.2). The order of testing did not alter AMS symptom response or any other measured variables.

Ad libitum fluid intake was similar between Ex and Sed (P > 0.1; see Table 3). Urine volume showed a tendency to decline in Ex at 3–6 h (Table 1), reflected in a positive fluid intake-to-urine output balance at 3–6 h (P = 0.06). Fluid intake and urine volume averaged over 0–9 h were not different between Ex and Sed.

Ve was similar between Ex and Sed and did not change over time at altitude (Table 2), despite the presumed increased metabolic demand from 120 min of submaximal exercise early during Ex. SaO2, PETO2, and PETCO2 values were also similar between Ex and

Fig. 1. A: acute mountain sickness (AMS) symptom scores rose in 6 of 7 subjects who exercised at 50% of their altitude-specific maximal workload 4 times for 30 min in the first 6 h of a 10-h exposure to high altitude (Ex; symbols represent individual subjects) (*P < 0.01). B: arterial oxygen saturation (SaO2) fell during exercise bouts in Ex compared with rest in Ex group or in those subjects who performed the same protocol as in Ex but were sedentary (Sed) at similar times of exposure (*P < 0.01).
EXERCISE AND AMS

The novel finding of this study was that exercise during the early hours at simulated high altitude resulted in a higher incidence and greater severity of AMS compared with a similar sedentary trial. This is the first study to report findings in the same subjects on repeat exposures to altitude when an intervention (exercise) was used to exaggerate the symptoms of AMS. During Ex, subjects in the present study became worse during the exercise trial ($P < 0.01$, Fig. 1A). Pulmonary function was similar in Ex and Sed at the beginning of altitude exposure. After 9 h, FVC and peak expiratory flow were lower in Ex compared with Sed ($P < 0.05$, Table 3). The ratio of forced expired volume in 1 s to FVC was not different between Ex and Sed and did not change over time at altitude (average 0.9 ± 0.05).

**DISCUSSION**

The novel finding of this study was that exercise during the early hours at simulated high altitude resulted in a higher incidence and greater severity of AMS compared with a similar sedentary trial. This is the first study to report findings in the same subjects on repeat exposures to altitude when an intervention (exercise) was used to exaggerate the symptoms of AMS. During Ex, subjects in the present study became worse, but that was not the case during Sed, when they were less ill or not ill at all. The increase in severity of AMS during Ex was related to lower SaO2 during exercise (Fig. 1B); a small, positive fluid intake-urine volume value in Ex at 3–6 h; and a lower FVC and peak expiratory flow (Table 3). In contrast, Ve, resting SaO2, and fluid intake were similar between trials and not related to AMS.

AMS. In six of the seven subjects (86%), AMS was worse during the exercise trial ($P < 0.01$, Fig. 1A). This finding is consistent with historical and anecdotal observations that AMS is more common in people who exercise to get to altitude than in those who are sedentary during the ascent (13, 16). In the late 1800s Kronecker (13) was convinced that exercise would exacerbate AMS. To prove his point he had seven volunteers carried on muleback and in litters to above 3,000 m in the Alps; the subjects did not become ill, but the litter bearers did (13). No other studies have examined AMS pathophysiology and exercise after passive ascent to simulated altitude. Field studies exist in which volunteers were airlifted to high altitude (>4,000 m) in a few minutes; but even the fastest recreational climbers take 12 h or more to climb to such heights. Thus, when field studies are compared, the influence of the rate of ascent cannot be separated from the effects of passive vs. active ascent. In the present study, ascent was passive and exercise began (in Ex) after baseline measurements on reaching simulated high altitude. The repeated exercise bouts were used as a tool to exacerbate AMS instead of as a means of locomotion. Hence, comparison of the present investigation to field studies of helicopter ascent, or to several days of climbing to gain altitude, may not be meaningful.

Our data indicate that exercise worsens AMS, yet several factors could conceivably confound such a conclusion. For example, the power of the crossover design

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**Table 1. Fluid intake and urine volume for Sed and Ex**

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Fluid Intake, ml/h</th>
<th>Urine Volume, ml/h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sed</td>
<td>Ex</td>
</tr>
<tr>
<td>0–3</td>
<td>191 ± 18</td>
<td>265 ± 69</td>
</tr>
<tr>
<td>3–6</td>
<td>142 ± 36</td>
<td>107 ± 22</td>
</tr>
<tr>
<td>6–9</td>
<td>193 ± 23</td>
<td>114 ± 19</td>
</tr>
<tr>
<td>Average (0–9)</td>
<td>173 ± 18</td>
<td>160 ± 25</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects. Sed, trial in which subjects were exposed to simulated high altitude and then remained sedentary; Ex, trial in which subjects were exposed to simulated high altitude and then engaged in repeated bouts of submaximal exercise. Fluid intake and urine volume were measured in 3-h aliquots and were not significantly different between groups, or with time at simulated altitude.

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**Table 2. Resting Ve, end-tidal gases, and SaO2 measurements for Sed and Ex trials after 0, 3, 6, and 9 h at Pa = 429 Torr**

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Ve, l/min, BTPS</th>
<th>PetO2, Torr</th>
<th>PetCO2, Torr</th>
<th>SaO2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sed</td>
<td>Ex</td>
<td>Sed</td>
<td>Ex</td>
</tr>
<tr>
<td>0</td>
<td>11.1 ± 0.5</td>
<td>12.8 ± 1.4</td>
<td>45.8 ± 1.7</td>
<td>52.6 ± 2.7</td>
</tr>
<tr>
<td>3</td>
<td>12.2 ± 0.8</td>
<td>14.2 ± 0.6</td>
<td>48.3 ± 1.4</td>
<td>47.6 ± 2.0</td>
</tr>
<tr>
<td>6</td>
<td>12.7 ± 0.5</td>
<td>13.6 ± 1.0</td>
<td>47.1 ± 1.0</td>
<td>47.3 ± 1.6</td>
</tr>
<tr>
<td>9</td>
<td>13.1 ± 0.9†</td>
<td>13.1 ± 0.6*</td>
<td>46.8 ± 1.5</td>
<td>48.5 ± 2.4*</td>
</tr>
<tr>
<td>Average (0–9)</td>
<td>12.3 ± 0.4</td>
<td>13.4 ± 0.5</td>
<td>47.0 ± 0.7</td>
<td>49.0 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects except where noted. Ve, resting minute ventilation; SaO2, arterial O2 saturation; Pa, barometric pressure; PetO2 and PetCO2, end-tidal Po2 and Pco2, respectively. *n = 6 Due to subject removal from chamber due to illness. †n = 6 Due to equipment malfunction.

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**Table 3. FVC and FEV1 after 9 h at simulated altitude**

<table>
<thead>
<tr>
<th>Time, h</th>
<th>FVC, liters</th>
<th>FEV1, liters</th>
<th>PEF, l/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sed</td>
<td>Ex</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5.5 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>742.8 ± 52.9</td>
</tr>
<tr>
<td>9</td>
<td>4.9 ± 0.4</td>
<td>4.4 ± 0.3</td>
<td>626.4 ± 58.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 subjects. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow. FVC and FEV1 after 9 h at simulated altitude were lower in Ex compared with Sed. The slight drop in PEF during Ex compared with Sed did not reach statistical significance. *P < 0.05 compared with Sed.
used in the present study depends on the reproducibility of AMS incidence and severity. In support of our findings, AMS is highly reproducible in a given individual on repeat exposure to the same altitude. Nine of 11 (82%) subjects reported nearly identical symptom response when they were exposed on two occasions to 4,267 m for 36 h (18). Another possible confounding factor could be that greater symptom severity in Ex was due to exercise per se. The sea-level control data do not support this contention. No significant symptoms were reported in six subjects who completed at sea level a similar exercise protocol as in the present study. Further study is needed to determine whether AMS in Ex would be of similar severity to Sed if both groups stayed at altitude for 24 h. In other words, did Ex trigger an early onset of AMS? In the present study, men who exercise early in an altitude exposure experience more severe AMS than if they were sedentary. Among the mechanisms that may explain such exacerbation of AMS by exercise is an alteration of ventilation or fluid balance.

Ventilation and oxygenation. A higher VE and SaO2, and lower PaCO2, are important for successful adjustment to high altitude and, therefore, have been repeatedly investigated to determine their role in the pathogenesis of AMS (2, 6, 15). In the present study, VE, SaO2, and PETCO2 values at rest were stable across time at simulated altitude and not related to AMS. This is in contrast to the results of Moore et al. (15), who studied 12 subjects during 7 h at simulated altitude (PaO2 430 Torr). Eight subjects had a prior history of AMS on ascent to altitude, and they developed significant symptomatic. In addition, VE and SaO2 values in the eight susceptible subjects were lower at simulated altitude compared with the four subjects who remained free of AMS. One explanation for this discrepancy is that only three of the subjects in the present study had a history of severe AMS, compared with eight in the study by Moore et al. Perhaps control of ventilation in persons susceptible to severe AMS differs from that seen in less susceptible or nonsusceptible persons, as is the case in persons susceptible to high-altitude pulmonary edema (8).

While exercising in Ex, the subjects spent a total of 120 min with a SaO2 ~8% lower than during the same period in Sed (Fig. 1B), reflecting a slight drop in estimated PaO2 (4–6 Torr). The effect was transient, and oxygenation quickly returned to the higher resting levels with cessation of exercise. A similar degree of desaturation was noted by Bärtsch and co-workers (1) in subjects exercising at a PaO2 similar to that used in the present study. It seems unlikely that the small and transient drop in PaO2 would be by itself sufficient to cause the observed increase in AMS severity during Ex. However, further study, where the drop in SaO2 is prevented during exercise by breathing supplemental oxygen, is necessary to resolve whether arterial desaturation during exercise is linked to the onset of AMS in this exercise-AMS model.

Fluid intake and urine volume. Alterations of fluid balance have been implicated in the pathophysiology of AMS (1, 6, 19). In the present study, during Ex the fluid intake-urine volume balance shifted toward positive at 3–6 h (P = 0.06) but was similar at 9 h. Also, the average over 0–9 h for fluid intake, urine flow, and the balance between them was not different. One explanation is that the fluid shifts represented by the small increment in fluid input-output balance seen in Ex at 3–6 h represent an event early in the pathophysiology of AMS. How a small fluid shift might cause a rise in AMS symptom severity is not known. Hansen and Evans (10) hypothesized that a change in intracranial dynamics secondary to a small increase in intracranial fluid could cause distortion or compression of pain-sensitive regions in the brain (3). Compression of the corpus collosum recently has been documented in the brains of patients with high-altitude cerebral edema (9), a syndrome considered by most to be a rare, late-stage form of AMS. Whether such changes occur in AMS, and if they are accelerated by exercise, is not presently known. Further scrutiny of the role of fluid shifts in AMS comes from a recent preliminary report that suggests that fluid retention is not a mandatory feature in established AMS (12). In the present study, the suggestion of fluid redistribution based on the fluid intake-urine flow balance is inconclusive because fluid and electrolyte balance was not obtained before the study. Confirmation of these findings in a larger number of subjects with carefully controlled dietary and fluid intake and direct measurement of body fluid compartments before exposure to simulated altitude is necessary to resolve the role of fluid shifts in the pathogenesis of AMS.

Conclusion. From the present study it is clear that exercise in the early hours of altitude exposure results in a marked increase in the severity and incidence of AMS. The pronounced worsening of AMS with exercise was associated with greater hypoxemia during the exercise and an indication of a small fluid shift favoring retention. The greater hypoxemia during exercise may have accelerated AMS; whether Ex and Sed would have comparable symptom severity after 24 h at simulated altitude is not known. Further study with control of oxygenation during exercise, and controlled diet and fluid intake, is necessary to determine the role of hypoxemia during exercise and of the observed minor fluid shifts in the exacerbation of AMS by exercise.
REFERENCES