The effect of hypoxemia and exercise on acute mountain sickness symptoms

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Submitted 22 June 2012; accepted in final form 12 November 2012

Rupp T, Jubeau M, Millet GY, Perrey S, Estève F, Wuyam B, Levy P, Verges S. The effect of hypoxemia and exercise on acute mountain sickness symptoms. J Appl Physiol 114: 180–185, 2013. First published November 15, 2012; doi:10.1152/japplphysiol.00769.2012.—Performing exercise during the first hours of hypoxic exposure is thought to exacerbate acute mountain sickness (AMS), but whether this is due to increased hypoxemia or other mechanisms associated with exercise remains unclear. In 12 healthy men, AMS symptoms were assessed during three 11-h experimental sessions: 1) in Hypoxia-exercise, inspiratory O2 fraction (FiO2) was 0.12, and subjects performed 4-h cycling at 45% FiO2-specific maximal power output from the 4th to the 8th hour; 2) in Hypoxia-rest, FiO2 was continuously adjusted to match the same arterial oxygen saturation as in Hypoxia-exercise, and subjects remained at rest; and 3) in Normoxia-exercise, FiO2 was 0.21, and subjects cycled as in Hypoxia-exercise at 45% FiO2-specific maximal power output. AMS scores did not differ significantly between Hypoxia-exercise and Hypoxia-rest, while they significantly lower in Normoxia-exercise (Lake Louise score: 5.5 ± 2.1, 4.4 ± 2.4, and 2.3 ± 1.5, and cerebral Environmental Symptom Questionnaire: 1.2 ± 0.7, 1.0 ± 1.0, and 0.3 ± 0.4, in Hypoxia-exercise, Hypoxia-rest, and Normoxia-exercise, respectively; P < 0.01). Headache scored by visual analog scale was higher in Hypoxia-exercise and Hypoxia-rest compared with Normoxia-exercise (36 ± 22, 35 ± 25, and 5 ± 6, P < 0.001), while the perception of fatigue was higher in Hypoxia-exercise compared with Hypoxia-rest (60 ± 24, 32 ± 22, and 46 ± 23, in Hypoxia-exercise, Hypoxia-rest, and Normoxia-exercise, respectively; P < 0.01). Despite significant physiological stress during hypoxic exercise and some AMS symptoms induced by normoxic cycling at similar relative workload, exercise does not significantly worsen AMS severity during the first hours of hypoxic exposure at a given arterial oxygen desaturation. Hypoxemia per se appears, therefore, to be the main mechanism underlying AMS, whether or not exercise is performed.

altitude illness; hypoxemia; physical effort; fatigue; headache

ACUTE MOUNTAIN SICKNESS (AMS) is a syndrome of nonspecific symptoms (headache, nausea, dizziness, fatigue, etc.) encountered after several hours of hypoxic exposure. Its incidence is >40% at altitudes above 3,000 m, depending on the rate of ascent, the altitude reached, and individual physiology (7, 13). Some reports suggest that performing physical activity during the first hours of hypoxic exposure may accentuate symptoms of AMS (1, 9, 16). Roach et al. (16) demonstrated, for instance, that performing physical exertion during 10-h hypobaric hypoxia exacerbates AMS compared with similar hypoxic exposure at rest.

One potential mechanism leading to more severe AMS in hypoxia when performing physical effort is the accentuation of arterial deoxygenation due to increased muscle oxygen extraction during exercise (16). Measurements of tissue oxygenation with near-infrared spectroscopy confirmed that both muscle and cerebral oxygenation are impaired during exercise in hypoxia (8, 11, 17, 20). In addition to greater arterial deoxygenation, other mechanisms may also be involved, such as increased ventilation, increased blood pressure, and altered fluid balance (16). Whether the effect of exercise on AMS symptoms in hypoxia is the consequence of larger arterial oxygen desaturation remains to be determined. Furthermore, because of the nonspecificity of symptoms characterizing AMS, exercise per se (even when performed in normoxia) could lead to some symptoms enhancing the AMS score. Hence, the effect of exercise on AMS severity in hypoxia needs to be controlled for the effect of normoxic exercise at similar relative work output (i.e., taking into account the reduction in maximal work output in hypoxia compared with normoxia) on symptoms characterizing AMS.

The present study aimed to compare the effect on AMS symptoms of several hours of normobaric hypoxic exposure, including prolonged exercise at moderate intensity (mimicking altitude exposure and climbing) to 1) normobaric hypoxic exposure at identical arterial oxygen saturation (SpO2) levels under resting conditions; and 2) normoxic exposure with prolonged exercise at the same relative power output. We hypothesized that hypoxic exposure coupled with physical exercise would lead to more severe AMS scores compared with resting conditions at similar arterial oxygenation levels and compared with physical exercise at identical relative intensity in normoxia, indicating a synergic effect of exercise-induced arterial deoxygenation and other exercise-induced physiological responses on AMS development.

MATERIALS AND METHODS

Subjects. Twelve healthy endurance-trained men were studied. Their physical characteristics were as follows (means ± SD): age 35 ± 8 yr, weight 71 ± 9 kg, and height 177 ± 7 cm. Six subjects had previous experiences of high-altitude exposure, and none had developed severe AMS. All subjects were unacclimatized to high altitude (no sojourn above 2,000 m of altitude over the past 3 mo), and none had history of chronic migraine, cardiorespiratory, or metabolic diseases. Subjects did not take any medication and refrained from intense physical activity on the 2 days before testing and from drinking caffeinated beverages on test days due to the potential effects of

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caffeine on exercise responses and AMS (6). Subjects were informed about the risks and signed an informed consent form, but were kept naïve regarding the expected outcomes of the study. The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki.

**Preliminary tests.** Each subject completed two progressive cycling exercise tests to exhaustion, at least 2 days apart: one in normoxia (FiO₂ (inspiratory oxygen fraction) = 0.21) and one in hypoxia (FiO₂ = 0.12). The tests were performed on a computer-controlled electrically braked cycle ergometer (Corival, Lode, Groningen, the Netherlands) and started at 90 W (normoxia) or 60 W (hypoxia), followed by 15-W increments every minute until volitional exhaustion. Subjects inhaled a gas mixture delivered by an Altitrainer 200 (SMTEC, Nyon, Switzerland) via a face mask and were blinded to the gas composition and their maximal performances. Maximal workload, oxygen uptake (Medisoft, Dinant, Belgium), and blood lactate concentration at exhaustion (Lactate Plus, Nova Biomedical, Waltham, MA) were determined during each test.

In addition, since the hypoxic ventilatory response has been proposed as a key factor regarding the development of AMS (3, 12, 14), the hypoxic ventilatory response during exercise was calculated as follows (14):

\[
\text{SpO}_2 \text{ difference} = \left( \frac{V_{\text{E hypoxia}} - V_{\text{E normoxia}}}{(\text{SpO}_2_{\text{normoxia}} - \text{SpO}_2_{\text{hypoxia}})} \right) \times \text{subject’s body weight} \times 100
\]

where Ve (minute ventilation) and SpO₂ are measured during maximal test in hypoxia (FiO₂ = 0.12) and in normoxia (FiO₂ = 0.21) at the power corresponding to 45% of the maximal workload reached in normoxia (i.e., 60 ± 4% of the maximal workload in hypoxia).

**Experimental sessions.** At least 1 wk after preliminary tests, three experimental sessions were performed in a semirandomized order. In the first session (Hypoxia-exercise), subjects inhaled an hypoxic gas mixture (FiO₂ = 0.12) for 11 h and performed three 80-min cycling bouts at 45% of maximum hypoxic workload, separated by 30 min of recovery from the 4th to 8th hour. In the second session (Hypoxia-rest), subjects inhaled a hypoxic gas mixture (FiO₂ = 0.08–0.12, continuously adjusted by the experimenters to match the individual SpO₂ measured during Hypoxia-exercise) for 11 h at rest, while sitting in a comfortable clinical chair. In the third session (Normoxia-exercise), subjects inhaled a normoxic gas mixture (FiO₂ = 0.21) for 11 h and performed three 80-min cycling bouts at 45% of maximum normoxic workload, separated by 30 min of recovery from 4 to 8 h. Subjects breathed through a face mask throughout all test sessions and were blinded to gas mixture composition. SpO₂, end-tidal carbon dioxide partial pressure (PETCO₂), heart rate (HR), and mean arterial blood pressure (MAP) were measured continuously (DATEX Ohmeda, Madison, WI). To check the accuracy of pulse oximetry to determine SpO₂, both at rest and during exercise in hypoxia, we compared, in seven volunteers, SpO₂ determined simultaneously by pulse oximetry (Ohmeda) and arterialized ear lobe blood sample analysis (Rapidlab 1265, Bayer Healthcare, Leverkusen, Germany), at rest with FiO₂ = 0.12 (oxyhemoglobin: 80 ± 8%; deoxyhemoglobin: 81 ± 5%; HbO₂: 71 ± 9%; deoxyHb: 74 ± 5%; all P > 0.05 between oximetry and blood sample). Correlation (r² = 0.78, P < 0.05) and Bland-Altman analysis (Fig. 1) demonstrated good agreement between both methods. The SpO₂ difference between both methods was similar in all three conditions (P = 0.59), indicating that pulse oximetry provided comparable estimation of SpO₂ during resting and exercise conditions in hypoxia.

At the end of each session, subjects completed the Lake Louise Questionnaire (LLS) (15), the Environmental Symptom Questionnaire (18), and two 10-cm visual analog scales (VAS) to score perceived headache and general fatigue. Headache and fatigue scores were also assessed at the end of the third 80-min exercise (in Hypoxia-exercise and Normoxia-exercise)/rest (in Hypoxia-rest) period. For the LLS questionnaire, each participant graded between 0 and 3 the severity of headache, gastrointestinal symptoms, fatigue, and light headedness or dizziness. No item regarding sleep was used, since there was no hypoxic overnight in the present study. For the Environmental Symptom Questionnaire (69 items in total, graded between 0 and 5), 11 items with different factorial weight (in parentheses) were used to calculate the cerebral subscore (ESQc): 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 ESQc 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 (18). AMS was defined as a LLS score ≥ 3 with headache ≥ 1 (15, 16) or an ESQc score ≥ 0.70 (18).

Commercially available high-energy drinks and cookies (GO2, Rennes, France) were provided ad libitum (subjects drank through a straw with the face mask in place and were allowed to lift the mask for 1–2 s twice per cookie while holding their breath). Capillary blood glucose (ACCU-CHEK Performa, Roche Diagnostics, Mannheim, Germany) and lactate (Lactate Plus, Nova Biomedical) concentrations were measured before gas exposure at the start of each experimental session, at the end of each exercise/rest period, and at the end of the session.

**Data analysis.** Normality of distribution and homogeneity of variances of the main variables were confirmed using a Skewness-Kurtosis normality test and the Levene’s test, respectively. Preliminary testing data (maximal workload and oxygen uptake, lactate, SpO₂, and HR) were compared between normoxic and hypoxic protocols with paired t-tests. For experimental sessions, physiological variables (SpO₂, PETCO₂, HR, MAP, glucose and lactate concentrations) and FiO₂ were analyzed I) at rest [at the start of the session before gas exposure (baseline)], after 2 h, 4 h, 5 h 50 min, 7 h 40 min, and 11 h of gas exposure; and 2) during exercise/rest periods (after 40 and 80 min for each of the three periods) by two-way (session × time) ANOVA with repeated measures. Fisher’s least significant difference tests were used for post hoc analysis when the ANOVA revealed a significant main effect or interaction effect. Symptom scores were compared between sessions by one-way ANOVA for repeated measures and Fisher’s least significant difference tests for post hoc analyses. Relationships
The mean hypoxic ventilatory response during exercise was 1.29 ± 0.53 l·min⁻¹·kg⁻¹ (range: 0.56–2.22). Target power outputs during the Hypoxia-exercise and Normoxia-exercise sessions were 113 ± 14 W and 152 ± 22 W, respectively.

**Symptoms.** LLS, ESQc, and VAS scores are shown in Fig. 2. LLS and ESQc scores were higher in Hypoxia-exercise and Hypoxia-rest compared with Normoxia-exercise (all P < 0.01), but no significant difference was observed between Hypoxia-exercise and Hypoxia-rest (LLS: P = 0.11; ESQc: P = 0.25). AMS in the Hypoxia-exercise and Hypoxia-rest sessions occurred in 11 (92%) and 9 (75%) subjects (out of 12), respectively, according to the LLS score (P = 0.16), and in 9 (75%) and 5 (42%) subjects, respectively, according to the ESQc score (P = 0.054). In the Normoxia-exercise session, LLS score ≥ 3 was observed in 5 (out of 12) subjects, and ESQc score ≥ 0.70 in 2 subjects. Headache VAS scores both at the end of exercise/rest period and at the end of the session were higher in Hypoxia-exercise and Hypoxia-rest compared with Normoxia-exercise (P < 0.001), while it was higher in Hypoxia-rest compared with Hypoxia-exercise at the end of exercise/rest period only (P = 0.049). Fatigue VAS score at the end of exercise was higher in Hypoxia-exercise and Normoxia-exercise compared with Hypoxia-rest (P < 0.01), with no significant difference between Hypoxia-exercise and Normoxia-exercise (P = 0.26). Fatigue VAS score at the end of Hypoxia-exercise was higher compared with Hypoxia-rest (P < 0.01), but similar to Normoxia-exercise (P = 0.15). Scores obtained at the end of Hypoxia-exercise and Hypoxia-rest correlated significantly for the ESQc (r² = 0.70, P < 0.001) and headache VAS (r² = 0.76, P < 0.001), but not for LLS (r² = 0.25, P = 0.10) or fatigue VAS (r² = 0.13, P = 0.24). LLS and ESQc scores were correlated at the end of Hypoxia-exercise (r² = 0.44, P < 0.05) and Hypoxia-rest (r² = 0.82, P < 0.001).

**FIO₂ and physiological parameters.** FIO₂ during the 80-min exercise/rest periods was significantly reduced in Hypoxia-rest compared with Hypoxia-exercise (Fig. 3). SpO₂ was lower in Hypoxia-exercise and Hypoxia-rest compared with Normoxia-exercise.

### RESULTS

**Maximal exercise capacity in normoxia and hypoxia.** Subjects had lower maximal power output, maximal oxygen uptake, and maximal HR, but higher blood lactate concentration, at exhaustion in hypoxia compared with normoxia (Table 1). The mean hypoxic ventilatory response during exercise was 1.29 ± 0.53 l·min⁻¹·kg⁻¹ (range: 0.56–2.22). Target power outputs during the Hypoxia-exercise and Normoxia-exercise sessions were 113 ± 14 W and 152 ± 22 W, respectively.

### Table 1. Incremental maximal exercise tests in normoxia and hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Normoxia (FIO₂ = 0.21)</th>
<th>Hypoxia (FIO₂ = 0.12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental test duration, min</td>
<td>19.6 ± 3.3</td>
<td>15.7 ± 2.1*</td>
</tr>
<tr>
<td>Maximal power output, W</td>
<td>339 ± 49</td>
<td>250 ± 32*</td>
</tr>
<tr>
<td>Maximal oxygen uptake, ml·min⁻¹·kg⁻¹</td>
<td>61.1 ± 10.8</td>
<td>40.6 ± 6.5*</td>
</tr>
<tr>
<td>As percentage of normoxic value</td>
<td>74 ± 5</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Peak blood lactate concentration, mmol/l</td>
<td>11.5 ± 2.5</td>
<td>13.4 ± 2.8*</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>98.3 ± 1.0</td>
<td>83.5 ± 4.9*</td>
</tr>
<tr>
<td>At the beginning of the test, %</td>
<td>94.9 ± 1.8</td>
<td>73.7 ± 5.7*</td>
</tr>
<tr>
<td>Maximal heart rate, beats/min</td>
<td>189 ± 9</td>
<td>177 ± 9*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 12. FIO₂, inspiratory oxygen fraction. *Significantly different compared with normoxia (P < 0.05).

between physiological parameters and symptoms were also evaluated by Pearson product correlation. McNemar’s tests were applied to evaluate difference of AMS incidence between Hypoxia-exercise and Hypoxia-rest sessions according to the LLS and ESQc scores. For all statistical analyses, a two-tailed α-level of 0.05 was used as the cut-off for significance. All descriptive statistics presented are mean values ± SD.
exercise ($P < 0.001$), with no significant difference between Hypoxia-exercise and Hypoxia-rest ($P > 0.05$, Fig. 3).

Table 2 shows $\text{PETCO}_2$, HR, MAP, and blood lactate and glucose concentrations during the three experimental sessions. $\text{PETCO}_2$ at rest was not significantly different between the three sessions ($P > 0.05$), while during exercise/rest periods it was higher in Normoxia-exercise compared with Hypoxia-exercise and in Hypoxia-exercise compared with Hypoxia-rest (all $P < 0.01$). HR was higher in Hypoxia-exercise and Normoxia-exercise compared with Hypoxia-rest ($P < 0.001$), with significantly higher values in Hypoxia-exercise compared with Normoxia-exercise at rest ($P < 0.001$), but not during exercise/rest periods. MAP was similar at rest between all three sessions, but was higher in Hypoxia-exercise and Normoxia-exercise compared with Hypoxia-rest during exercise/rest periods ($P < 0.01$). Lactatemia at rest was similar among all three sessions, while it was higher in Hypoxia-exercise compared with Hypoxia-rest and in Hypoxia-rest compared with Normoxia-exercise ($P < 0.05$) during exercise/rest periods. Glycemia did not differ at rest between the sessions, but was significantly lower in Normoxia-exercise compared with Hypoxia-rest during exercise/rest periods ($P < 0.01$).

Correlations between symptoms and physiological parameters. LLS and ESQc scores did not correlate with $\text{SpO}_2$ (either at rest or during exercise/rest periods) during Hypoxia-exercise and Hypoxia-rest (all $r^2 < 0.15$ and $P > 0.20$). Similarly, symptoms did not correlate with any physiological parameters measured during the experimental sessions, nor with the hypoxic ventilatory response assessed from the maximal incremental cycling tests (results not shown, all $P > 0.05$).

DISCUSSION

This study shows that the severity of AMS induced by 11-h normobaric hypoxic exposure at identical $\text{SpO}_2$ did not differ significantly whether the subjects were at rest or performed 4 h of moderate-intensity exercise. Hence, despite significant cardiorespiratory and metabolic stress and enhanced perception of fatigue associated with exercise, exercise does not appear to worsen AMS severity during the first hours of hypoxic exposure at a given $\text{SpO}_2$ level.

Exercise-induced hypoxemia and AMS symptoms. Roach et al. (16) showed that 10 h of hypobaric hypoxia led to more severe AMS symptoms when cycling for 2 h at moderate intensity (i.e., 50% altitude-specific maximal workload) was performed. The larger hypoxemia observed during the 2-h
exercise period (SpO2 being ~8% lower in exercise compared with the rest session) was thought to be the main reason for greater AMS symptoms. In a similar study design, Schommer et al. (19) recently reported contrasting results with similar AMS severity and occurrence during 18-h normobaric hypoxia exposure (FiO2 = 0.12), with or without 2 h 15 min of cycling at the same intensity as in Roach’s study. In both studies, SpO2 quickly returned to levels similar to the resting session as soon as exercise was stopped, leading to similar average SpO2 values over both sessions. Therefore, based on these studies, whether larger hypoxemia during exercise in hypoxia or other mechanisms associated with exercise may exacerbate AMS remains unclear. The present study evaluates the effect of exercise on AMS symptoms development for exercise duration twice longer than in Roach and Schommer studies (4 h vs. ~2 h, the former being more comparable to typical physical effort performed at altitude) and independently of exercise-induced hypoxemia by matching SpO2 in both hypoxic sessions. This SpO2 matching was successfully performed by continuously adjusting FiO2 during the Hypoxia-rest session (Fig. 3), simulating altitudes ranging from ~4,000 to 7,000 m. The absence of significant difference in LLS and ESQc scores at the end of the two hypoxic sessions suggests that SpO2 is the determinant factor underlying the development of AMS symptoms in hypoxia, whether or not exercise is performed. The correlations of scores obtained in Hypoxia-exercise and Hypoxia-rest for ESQc and headache VAS further emphasize that both conditions induced similar symptoms. Interestingly, this correlation did not reach significance for LLS score. When comparing single LLS items, fatigue only was significantly different between Hypoxia-exercise and Hypoxia-rest (results not shown), and the LLS scores calculated without this item correlated between both hypoxic sessions (r2 = 0.49, P = 0.01). Hence, exercise-induced fatigue appears to have some effect on AMS scoring, although it did not translate into significantly more severe AMS.

There was, however, a trend for higher AMS severity and occurrence during Hypoxia-exercise than Hypoxia-rest, and one can wonder whether this difference may not become significant in larger study population. To assess whether the present study had adequate statistical power, we performed a post hoc power calculation. It reveals that, to obtain significantly larger LLS and ESQc scores in Hypoxia-exercise vs. Hypoxia-rest with a statistical threshold of 0.05 and a power of 80%, 88 and 320 subjects, respectively, should be tested. Similarly, to obtain a significantly larger AMS occurrence according to LLS and ESQc scores, 87 and 41 subjects, respectively, should be tested. These calculations indicate that the propensity to develop more severe AMS when performing exercise during a 11-h hypoxic exposure at identical SpO2 is relatively weak. Therefore, the enhanced severity of AMS when exercise is performed during hypoxic exposure, as suggested by several authors (1, 9, 16), is probably the consequence of a greater hypoxemia, even though hypoxemia is exacerbated only during the exercise periods.

The critical importance of hypoxemia regarding AMS symptoms seems also to be supported by previous observations of larger exercise-induced hypoxemia in subjects with more severe AMS (10, 14). In the present study, individual AMS scores and symptoms did not correlate with SpO2 in hypoxia, either at rest or during exercise. Thus, while the similar AMS scores and symptoms in Hypoxia-exercise and Hypoxia-rest suggest that, for a given subject, SpO2 is the determinant factor of AMS, our results do not confirm that interindividual differences in AMS symptoms are associated with differences in arterial oxygenation. Among the individual physiological characteristics able to explain differences in AMS susceptibility, the hypoxic ventilatory response at exercise has recently been proposed (14). In the present study, however, it did not correlate with symptoms, and, therefore, no conclusion can be drawn regarding mechanisms underlying interindividual differences in AMS development.

Others mechanisms associated with exercise and hypoxia. Because AMS is assessed from nonspecific symptoms, such as headache, gastrointestinal disturbances, fatigue, or dizziness, prolonged and fatiguing exercise may promote some symptoms corresponding to LLS and ESQc items and, therefore, artificially increase AMS severity. To evaluate the effect of exercise per se (independent of hypoxemia), subjects inhaled a normoxic gas mixture for the same duration and performed 4-h cycling at the same relative intensity as during the Hypoxia-exercise session. Interestingly, LLS and ESQc scores increased slightly at the end of the Normoxia-exercise session, with five subjects even reaching LLS and/or ESQc scores corresponding to the definition of moderate AMS. The perception of fatigue was relatively large following exercise in both normoxia and hypoxia, and this may explain the slightly higher AMS scores obtained in hypoxia when exercise was performed.

Exercise in hypoxia led to a significant increase in HR, MAP, and blood lactate concentration compared with hypoxia at rest. The present results show, however, that this substantial cardiometabolic stress for a prolonged duration (4 h) did not accentuate AMS symptoms following 11-h hypoxic exposure. Physiological perturbations associated with exercise, similar to the fatigue perception discussed above, probably recovered during the subsequent hours (as shown by similar MAP, blood lactate, and glucose concentrations at the end of the sessions), finally leaving hypoxemia as the main mechanism underlying AMS symptoms at the end of both Hypoxia-exercise and Hypoxia-rest sessions.

Study limitations. As discussed above, the present study provides a relatively low statistical power. In addition, the results remain to be confirmed in hypobaric hypoxic conditions, since recent debates suggest that some differences may exist between physiological and pathophysiological responses to hypobaric vs. normobaric hypoxia (5) and may explain the contradictory results from Roach et al. (16) and Schommer et al. (19). Hence, further studies are needed under hypobaric hypoxic conditions with large sample size to confirm the effect of exercise on AMS. Also, more intense exercise may induce pathophysiological responses, such as pulmonary microcirculation stress (4), that could exacerbate AMS to a greater extent than moderate-intensity exercise, as performed in the present study. Such high-intensity exercise is, however, less frequent during typical climbing at high altitude that is thought to correspond to ~50% of the altitude-specific maximal oxygen consumption (2, 19). Repetitive arterial blood samplings could not be performed in the present study, but in preliminary experiments we confirmed the validity of oximetry to match SpO2 in Hypoxia-exercise and Hypoxia-rest sessions (see MATERIALS AND METHODS). Finally, to confirm similar physiological adaptations to hypoxia when exercise is performed or absent...
during the first hours of exposure, additional objective measurements of hypoxic responses are necessary, such as pulmonary arterial pressure, pulmonary and cerebral subedema, as assessed with Doppler, or magnetic resonance imaging.

In conclusion, the present study assessed the effect of exercise on AMS symptoms independent of the exercise-induced hypoxemia exacerbation by continuously adjusting $\text{FiO}_2$ to match Hypoxia-exercise $\text{SpO}_2$ during the Hypoxia-rest session. AMS scores did not differ significantly after 11-h hypoxic exposure, with or without exercise, indicating that the exacerbation of AMS previously reported when exercise was performed in hypoxia likely results from greater hypoxic exposure, with or without exercise, indicating that factors other than hypoxemia may also underpin interindividual differences regarding AMS symptoms.

ACKNOWLEDGMENTS

We thank the subjects for the time and effort they dedicated to this study, and John Temesi for English editing.

GRANTS

Financial support was provided by the French National Research Agency (Grant NT09_653348).

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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