Does exercise really exacerbate acute mountain sickness symptoms?

Hypoxia, exercise and acute mountain sickness

RUPP Thomas[1, 2 *], JUBEAU Marc[6,7 *], MILLET Guillaume Y[1, 6], PERREY Stéphane[5], ESTEVE François[4], WUYAM Bernard[1, 2, 3], LEVY Patrick[1, 2, 3], VERGES Samuel[1, 2, 3]

[1] INSERM U1042, Grenoble, F-38000, France

[2] HP2 laboratory, Joseph Fourier University, Grenoble, F-38000, France

[3] Physiology, Sleep and Exercise Unit, Grenoble University Hospital, F-38000, Grenoble, France

[4] INSERM U836/team 6, Grenoble Institute of Neurosciences, F-38000, Grenoble, France

[5] Movement To Health (M2H), Montpellier-1 University, Euromov, F-34090, Montpellier, France

[6] Université de Lyon, F-42023, Saint-Etienne, France

[7] Laboratoire "Motricité, Interactions, Performance", University of Nantes, F-44000, Nantes, France.

* Both authors contributed equally to this work

Corresponding author:

Dr. Verges Samuel

Laboratoire HP2 (U1042 INSERM), UF Recherche sur l'Exercice

Hôpital Sud, Avenue Kimberley, 38 434 Echirolles - France

Tel: +33 4 76 76 68 60 - Fax: +33 4 76 76 89 21 - E-mail: sverges@chu-grenoble.fr

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27 **Author contributions:**

28 RT, JM, MG, SP and SV designed the study and performed the measurements. RT, JM and
29 SV analyzed the data. RT, JM, MG, SP, EF, WB, LP and SV discussed the data and approved
30 the final version of the manuscript.

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ABSTRACT

Performing exercise during the first hours of hypoxic exposure is known 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 males, AMS symptoms were assessed following three 11-h experimental sessions: i) in HEX, inspiratory O_2 fraction (FiO_2) was 0.12 and subjects performed 4 h cycling at 45% FiO_2-specific maximal power output from 4 h to 8 h; ii) in HRE, FiO_2 was continuously adjusted to match the same arterial oxygen saturation as in HEX and subjects remained at rest; iii) in NEX, FiO_2 was 0.21 and subjects cycled as in HEX at 45% FiO_2-specific maximal power output. AMS scores did not differ significantly between HEX and HRE, while they were significantly lower in NEX (Lake Louise score: 5.5±2.1, 4.4±2.4, 2.3±1.5 and cerebral Environmental Symptom Questionnaire: 1.2±0.7, 1.0±1.0, 0.3±0.4, in HEX, HRE and NEX, respectively; $P<0.05$). Headache scored by visual analogue scale was higher in HEX and HRE compared to NEX (36±22, 35±25, 5±6) while the perception of fatigue was higher in HEX compared to HRE (60±24, 32±22, 46±23 in HEX, HRE and NEX, respectively; $P<0.05$). 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.

Keywords: altitude illness, hypoxemia, physical effort, fatigue, headache

INTRODUCTION

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 3000 m depending on the rate of ascent, the altitude reached and individual physiology (6, 12). Some reports suggest that performing physical activity during the first hours of hypoxic exposure may accentuate symptoms of AMS (1, 9, 15). Roach et al. (15) provided the only study that specifically evaluates this issue. They assessed the effect of 10-h hypobaric hypoxic exposure with or without physical exertion (four times 30 min cycling at moderate intensity) on AMS symptoms and showed that exercise significantly accentuated the severity and incidence of AMS.

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 (15). Measurements of tissue oxygenation with near-infrared spectroscopy confirmed that both muscle and cerebral oxygenation are impaired during exercise in hypoxia (7, 11, 16, 18). In addition to greater arterial deoxygenation, other mechanisms may also be involved such as increased ventilation, increased blood pressure and altered fluid balance (15). 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 non-specificity of symptoms characterising 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 to normoxia) on symptoms characterising AMS.

The present study aimed to compare the effect on AMS symptoms of several hours normobaric hypoxic exposure including prolonged exercise at moderate intensity (mimicking altitude exposure and climbing) to i) normobaric hypoxic exposure at identical arterial oxygen saturation (SpO_2) levels under resting conditions and ii) 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 to resting conditions at similar arterial oxygenation levels and compared to 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, having given their written informed consent. Their physical characteristics were as follows (mean ± SD): age 35 ± 8 years, weight 71 ± 9 kg, height 177 ± 7 cm. Six subjects had previous experiences of high altitude exposure and none had developed severe AMS. Subjects did not take any medication, refrained from intense physical activity on the two days prior testing and from drinking caffeinated beverages on test days. Subjects were naïve regarding the expected outcomes of the present 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 (FiO_2 (inspiratory oxygen fraction) = 0.21) and one in hypoxia (FiO_2 = 0.12). The tests were performed on a computer-controlled

106 electrically-braked cycle ergometer (Corival, Lode, Groningen, Netherlands) and started at 90
107 W (normoxia) or 60 W (hypoxia) followed by 15 W increments every minute until volitional
108 exhaustion. Subjects inhaled the gas mixture delivered by an Altitrainer 200® (SMTEC,
109 Nyon, Switzerland) via a face mask and were blinded to the gas composition and their
110 maximal performances. Maximal workload, oxygen uptake (Medisoft, Dinant, Belgium) and
111 blood lactate concentration at exhaustion (Lactate Plus, Nova biomedical Corporation,
112 Waltham, MA) were determined during each test. In addition, the hypoxic ventilatory
113 response during exercise was calculated as follows (13):
114 $(VE_{hyp}-VE_{nor}) / (SpO_{2,nor}-SpO_{2,hyp})$ / subject's body weight * 100
115 where VE and SpO_2 represent minute ventilation and arterial oxygen saturation measured at
116 45% of the maximal workload in normoxia, *hyp* represents hypoxia and *nor* represents
117 normoxia.
118
119 ***Experimental sessions.*** At least one week after preliminary tests, three experimental sessions
120 were performed in a semi-randomized order. In the first session (HEX), subjects inhaled an
121 hypoxic gas mixture (FiO_2 = 0.12) for 11 h and performed three 80-min cycling bouts at 45%
122 of maximum hypoxic workload separated by 30 min of recovery from 4 h to 8 h. In the
123 second session (HRE), subjects inhaled a hypoxic gas mixture (FiO_2 = 0.08-0.12,
124 continuously adjusted by the experimenters to match the individual SpO_2 measured during
125 HEX) for 11 h at rest while sitting in a comfortable clinical chair. In the third session, subjects
126 inhaled a normoxic gas mixture (FiO_2 = 0.21) for 11 h and performed three 80-min cycling
127 bouts at 45% of maximum normoxic workload separated by 30 min of recovery from 4 h to 8
128 h. Subjects were blinded to gas mixture composition. SpO_2, end-tidal carbon dioxide partial
129 pressure ($PetCO_2$), heart rate (HR) and mean arterial blood pressure (MAP) were measured
130 continuously (DATEX Ohmeda, Madison, WI). At the end of each session, subjects

completed the Lake Louise Questionnaire (LLS, 5 items) (14), the Environmental Symptom Questionnaire, including two sub-scores on cerebral (ESQc, 11 items) and respiratory (ESQr, 12 items) symptoms (17) and two 10-cm visual analogue 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 HEX and NEX) / rest (in HRE) period. AMS was defined as a LLS score $\geq$ 3 (14), an ESQc sub-score $\geq$ 0.70 or an ESQr sub-score $\geq$ 0.60 (17). Commercially available high-energy drinks and cakes (GO2, Rennes, France) were provided *ad libitum* and fluid and food intakes were recorded during all experimental sessions. Subjects were weighed before and after each session and total urine volume was measured during each session. Weight loss was calculated as the difference between measurements before and after each session and corrected weight loss was calculated as follows: (weight before the session + fluid and food intake) – (weight after the session + urine volume). Capillary blood glucose (ACCU-CHEK Performa, Roche Diagnostics, Mannheim, Germany) and lactate (Lactate Plus, Nova Biomedical Corporation) 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, SpO_2 and HR) were compared between normoxic and hypoxic protocols with paired t-tests. For experimental sessions, physiological variables (SpO_2, $PetCO_2$, HR, MAP, glucose and lactate concentrations) and FiO_2 were analysed at the following time-points for each experimental session: 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; ii) during exercise/rest periods, after 40 and 80

min for each of the three periods. Physiological variables were analysed i) at rest and ii) during exercise/rest periods by two-way (session × time) ANOVA with repeated measures. Fisher's LSD tests were used for post hoc analysis when the ANOVA revealed a significant main effect or interaction effect. Other variables (symptom scores, fluid and food intake, body weight and urine volume) were compared between sessions by one-way ANOVA for repeated measures and Fischer's LSD-tests for post hoc analyses. Relationships between physiological parameters and symptoms were also evaluated by Pearson product correlation. McNemar's tests were applied to evaluate difference of AMS incidence between HEX and HRE sessions according to the LLS and ESQ scores. For all statistical analyses, an alpha level of 0.05 was used as the cut-off for significance. All descriptive statistics presented are mean values ± SD.

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 to normoxia (Table 1). The mean hypoxic ventilatory response during exercise was 1.29 ± 0.53 $l.min^{-1}\cdot\%^{-1}\cdot kg^{-1}$ (range: 0.56-2.22). Target power outputs during the HEX and NEX sessions were 113 ± 14 W and 152 ± 22 W, respectively.

Symptoms. LLS, ESQ and VAS scores are shown in Figure 1. LLS scores and ESQ sub-scores were higher in HEX and HRE (except ESQr) compared to NEX but no significant difference was observed between HEX and HRE (LLS: $F_{(2,22)} = 13.3$, $P < 0.001$; ESQc: $F_{(2,22)} = 10.8$, $P < 0.001$; ESQr: $F_{(2,22)} = 4.1$, $P < 0.05$). AMS in the HEX and HRE sessions occurred in 11 and 9 (out of 12) subjects, respectively, according to the LLS score ($P = 0.16$), in 9 and

5 subjects, respectively, according to the ESQc sub-score ($P = 0.05$) and in 2 and 3 subjects, respectively, according to the ESQr sub-score ($P = 0.32$). In the NEX session, LLS score ≥ 3 was observed in 5 (out of 12) subjects, ESQc sub-score ≥ 0.70 in 2 subjects and ESQr sub-score ≥ 0.60 in 2 subjects. Headache VAS scores both at the end of exercise/rest period and at the end of the session were higher in HEX and HRE compared to NEX while it was higher in HRE compared to HEX at the end of exercise/rest period only ($F_{(2,22)} = 12.2$, $P < 0.001$). Fatigue VAS score at the end of exercise was higher in HEX and NEX compared to HRE with no significant difference between HEX and NEX ($F_{(2,22)} = 8.3$, $P < 0.01$). Fatigue VAS score at the end of the session was higher in HEX compared to HRE only ($F_{(2,22)} = 4.4$, $P < 0.05$). Scores obtained at the end of HEX and HRE correlated significantly for the ESQ (ESQc $r^2 = 0.70$, $P < 0.001$; ESQr $r^2 = 0.52$, $P < 0.01$) and headache VAS ($r^2 = 0.76$, $P < 0.001$) but not for LLS ($r^2 = 0.25$, $P = 0.10$) or fatigue VAS ($r^2 = 0.13$, $P = 0.24$).

FiO_2 and physiological parameters. Figure 2 shows FiO_2, SpO_2 and $PetCO_2$ time course during the three experimental sessions. FiO_2 was lower in HEX and HRE compared to NEX (main session effect: $F_{(2,22)} = 1015.5$, $P < 0.001$) and it was lower during the 80-min exercise/rest periods in HRE compared to HEX (session main effect: $F_{(2,22)} = 1559.8$, $P < 0.001$). SpO_2 was lower in HEX and HRE compared to NEX, with no significant difference between HEX and HRE (session main effect at rest: $F_{(2,22)} = 101.9$, $P < 0.001$; session main effect during exercise/rest periods: $F_{(2,22)} = 173.6$, $P < 0.001$). $PetCO_2$ at rest was not significantly different between the three sessions while during exercise/rest periods it was higher in NEX compared to HEX and in HEX compared to HRE (session main effect: $F_{(2,22)} = 44.5$, $P < 0.001$).

Figure 3 shows HR, MAP and blood lactate and glucose concentrations during the three experimental sessions. HR was higher in HEX and NEX compared to HRE, with

206 significantly higher values in HEX compared to NEX at rest (session main effect: $F_{(2,22)}$ =
207 17.7, $P < 0.001$) but not during exercise/rest periods (session main effect: $F_{(2,22)} = 216.9$, $P <$
208 0.001). MAP was similar at rest between all three sessions but was higher in HEX and NEX
209 compared to HRE during exercise/rest periods (session main effect: $F_{(2,16)} = 7.74$, $P < 0.01$).
210 Lactatemia at rest was similar among all three sessions while it was higher in HEX compared
211 to HRE and in HRE compared to NEX during exercise/rest periods (session main effect: $F_{(2,22)}$
212 = 14.1, $P < 0.001$). Glycaemia did not differ at rest between the sessions but was significantly
213 lower in NEX compared to HRE during exercise/rest periods (session main effect: $F_{(2,22)}$ =
214 4.1, $P < 0.05$).
215 Table 2 shows body weight loss, fluid and food intake and urine volume during the three
216 experimental sessions. Weight loss and fluid and daily energy intake were greater in HEX and
217 NEX compared to HRE (session main effects: $F_{(2,22)} = 9.3$, $P < 0.001$; $F_{(2,22)} = 48.8$, $P < 0.001$;
218 $F_{(2,22)} = 85.6$, $P < 0.05$, respectively). Food intake was greater (session main effect: $F_{(2,22)}$ =
219 6.4, $P < 0.01$) and corrected weight loss was lower (session main effect: $F_{(2,22)} = 85.6$, $P <$
220 0.001) in HEX compared to NEX. Urine volume was not significantly different between
221 sessions.
222
223 ***Correlations between symptoms and physiological parameters.*** LLS and ESQ scores did not
224 correlate with SpO_2 (either at rest or during exercise/rest periods) during HEX and HRE (all r^2
225 < 0.15 and $P > 0.20$). Similarly, symptoms did not correlate with any physiological
226 parameters measured during the experimental sessions nor with the hypoxic ventilatory
227 response assessed from the maximal incremental cycling tests (results not shown, all $P >$
228 0.05).
229
230

DISCUSSION

This study was the first to evaluate the effect of hypoxemia and exercise, in association or independently, on symptoms of AMS by taking into account the exercise-induced worsening of hypoxemia in hypoxia and the difference in maximal exercise capacity between normoxic and hypoxic conditions. The severity of AMS induced by 11-h normobaric hypoxic exposure at identical arterial oxygen desaturation did not differ significantly whether the subjects were at rest or performed 4 h of moderate-intensity exercise. The VAS level of fatigue after 11 h of hypoxia was however larger when exercise was performed. Hence, despite significant cardio-respiratory and metabolic stress during hypoxic exercise and some AMS symptoms induced by normoxic exercise at similar relative workload, exercise does not appear to worsen AMS severity during the first hours of hypoxic exposure at a given arterial oxygen desaturation level.

Exercise-induced hypoxemia and AMS symptoms. Factors influencing the development of AMS are still a matter of debate although the altitude level, the rate of ascent, previous experience of AMS and individual physiological differences are important predictors (6, 12). From the study of Roach et al. (15) and other observations (1, 8-10), exercise performed during the first hours of hypoxic exposure is thought to exacerbate symptoms of AMS (12). Roach et al. (15) showed that 10 h of hypobaric hypoxic exposure led to more severe AMS symptoms when 2 h exercise was performed [average LLS = 1.9 *versus* 4.5 and general state of well being (assessed on VAS with 0 = "I feel terrible") = 6.3 *versus* 3.6, in rest and exercise sessions, respectively]. The larger hypoxemia observed during the 2-h exercise period (SpO_2 being ~8% lower in exercise compared to the rest session) was thought to be the main reason for greater AMS symptoms. This reasoning leads to the notion that performing

exercise at a given altitude is equivalent to being at rest at higher altitude (in Roach's study, ~8% SpO_2 worsening would approximately correspond to an increase of 2000 m in altitude (12)). In Roach's study (15), SpO_2 quickly returned to levels similar to the resting session as soon as exercise was stopped, leading to similar average SpO_2 values over the 10 h in both sessions (81% *versus* 82% in rest and exercise sessions, respectively). The authors thus stated "it seems unlikely that the small and transient drop in arterial oxygenation would be by itself sufficient to cause the observed increase in AMS severity" and concluded that "further study with control of oxygenation" was needed to clarify the role of enhanced hypoxemia and other mechanisms in the exercise-induced exacerbation of AMS. In the present study, the effect of exercise on AMS symptoms development was assessed for slightly longer and less severe hypoxic conditions (11 h of normobaric hypoxia equivalent to ~4200 m *versus* 10 h of hypobaric hypoxia equivalent to ~4800 m) and for twice the exercise duration (4 h *versus* 2 h, the former being more comparable to typical physical effort performed at altitude) than in Roach et al. (15). A critical aspect of the present protocol design is that SpO_2 was maintained at similar levels throughout the 11-h hypoxic experimental sessions with or without exercise in order to distinguish the effect of exercise-induced hypoxemia (as in Roach et al. (15)) from other potential effects of exercise able to exacerbate AMS. This SpO_2 matching was successfully performed by continuously adjusting FiO_2 during the HRE session (Figure 2*A* and *B*) simulating altitudes ranging from ~4000 to 7000 m. The absence of significant difference in LLS and ESQ scores at the end of the two hypoxic sessions as well as the correlations between symptoms measured in HEX and HRE (although not reaching significance for LLS score, probably due to the influence of fatigue perception - significantly different between HEX and HRE - on this score) suggest that SpO_2 is the determinant factor underlying the development of AMS symptoms in hypoxia, whether or not exercise is performed. Therefore, the enhanced severity of AMS when exercise is performed during the

first hours of hypoxic exposure (15) is mostly the consequence of greater hypoxemia, even though hypoxemia is exacerbated only during the exercise periods.

The critical importance of hypoxemia regarding AMS symptoms seems also supported by previous observations of larger exercise-induced hypoxemia in subjects with more severe AMS (10, 13). In the present study, individual AMS scores and symptoms did not correlate with SpO_2 in hypoxia, either at rest or during exercise. Thus, while the similar AMS scores and symptoms in HEX and HRE suggest that for a given subject SpO_2 is the determinant factor of AMS, our results do not confirm that inter-individual 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 (13). In the present study however, it did not correlate with symptoms and therefore no conclusion can be drawn regarding mechanisms underlying inter-individual differences in AMS development.

Normoxic exercise and AMS symptoms. Because AMS is assessed from nonspecific symptoms such as headache, gastro-intestinal disturbances, fatigue or dizziness, prolonged and fatiguing exercise may promote some symptoms corresponding to LLS and ESQ 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 HEX session, *i.e.* 45% of their normoxic maximal power output. Interestingly, LLS and ESQ scores increased slightly at the end of the NEX session, 5 subjects even reaching LLS and/or ESQ scores corresponding to the definition of moderate AMS. Moreover, at the end of the 4-h exercise period, general fatigue scored on the VAS was higher in the NEX session compared to the HRE session, indicating at this time point even larger effects of exercise *per se* compared to

306 hypoxia at rest. Therefore, based on this hypoxemia-independent effect of exercise on AMS
307 scores, one would expect larger AMS scores when hypoxia and exercise are combined
308 compared to hypoxia at rest. General fatigue scored on the VAS was greater in HEX
309 compared to HRE, probably reflecting fatigue perception specific to muscular work.
310 Nevertheless, despite the effect of normoxic exercise on LLS and ESQ scores and even with
311 the larger fatigue perception in hypoxia when exercise was performed, AMS scores in
312 hypoxia were not significantly accentuated when exercise was performed. Hence, it appears
313 that the effect of exercise is somehow transient, as shown by the fatigue VAS recovery from
314 immediately after exercise to the end of the NEX session. This is in contrast to the sustained
315 high fatigue perceived from the end of exercise to the end of the HEX session (Figure 1*D*).
316 Moreover, the clear effect of hypoxia (both in resting and exercising sessions) on headache
317 level compared to the normoxic session probably had a major effect on the global AMS score
318 explaining that despite larger fatigue perception in HEX compared to HRE, similar AMS
319 scores were observed. Nevertheless, the tendency toward larger incidence of AMS (based on
320 LLS and ESQ scores) in HEX compared to HRE still indicates that in some subjects,
321 performing exercise in hypoxia may slightly worsen AMS symptoms.
322
323 ***Others mechanisms associated with exercise and hypoxia***. Because alterations in fluid
324 balance have been implicated in the pathophysiology of AMS (2, 5, 6), one may suggest that
325 exercise could worsen AMS by impairing fluid balance. Roach et al. (15) observed that the
326 fluid intake-urine volume balance shifted slightly toward more positive values between the 3rd
327 and the 6th hour of hypoxic exposure when exercise was performed compared to the resting
328 session, suggesting that a slight fluid retention may underlie AMS (5). In the present study,
329 weight losses were observed in both hypoxic sessions and were larger when exercise was
330 performed despite similar urine volume and greater fluid intake, probably due to sweating.

These data do not support the involvement of fluid retention in AMS development although direct measurements of body fluid balance would be necessary to accurately address this question. Also, corrected weight loss was smaller in HEX compared to NEX, probably due to larger absolute power output in the NEX session leading to greater energy consumption and sweating.

Exercise in hypoxia led to significant increase in HR, MAP and blood lactate concentration compared to hypoxia at rest. The present results show however that this substantial cardio-metabolic 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 HEX and HRE sessions.

Study limitations. The results of the present study remain to be confirmed in hypobaric hypoxic conditions since recent debates suggest that some differences may exist between physiological and pathophysiological responses to hypobaric *versus* normobaric hypoxia (4). Also, more intense exercise may induce pathophysiological responses such as pulmonary microcirculation stress (3) 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. 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, hormonal changes (*e.g.* aldosterone and antidiuretic hormone)

and pulmonary and cerebral sub-oedema as assessed with Doppler or magnetic resonance imaging.

In conclusion, the present study successfully assessed the effect of exercise on AMS symptoms independent of the exercise-induced hypoxemia exacerbation by continuously adjusting FiO_2 to match HEX SpO_2 during the HRE 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 mostly results from greater hypoxemia. These results support the notion that exercise inducing important hypoxemia should be avoided during the first hours of altitude exposure, although factors other than hypoxemia may also underpin inter-individual differences regarding AMS symptoms.

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FIGURE LEGENDS

Figure 1. Lake Louise (panel A) and Environmental Symptom (ESQ, panel B) questionnaire scores and headache (panel C) and general fatigue (panel D) scored on a visual analogue scale (VAS) at the end of the three experimental sessions. Headache and general fatigue scores measured at the end of the last 80-min exercise/rest period are also provided. * significant difference between two experimental sessions, $P < 0.05$.

Figure 2. Inspiratory oxygen fraction (FiO_2, panel A), arterial oxygen saturation (panel B) and end-tidal carbon dioxide partial pressure ($PetCO_2$, panel C) during the three experimental sessions. Grey zone indicate the three 80-min exercise periods in HEX and NEX. Session main effects are reported over exercise/rest periods (grey zones) and over the rest of the sessions (BL, +2h, +4h, +5h50, +7h40 and +11h; with a braces on the right); $^{£}$ significant difference between HEX and HRE, $^{\$}$ between HEX and NEX, $^{\#}$ between HRE and NEX ($P < 0.05$).

Figure 3. Heart rate (panel A), mean arterial blood pressure (MAP, panel B)), blood lactate (panel C) and glucose (panel D) concentrations during the three experimental sessions. Grey zone indicate the three 80-min exercise periods in HEX and NEX. Session main effect are reported over exercise/rest periods (grey zones) and over the rest of the sessions (BL, +2h, +4h, +5h50, +7h40 and +11h; with a braces on the right); $^{£}$ significant difference between HEX and HRE, $^{\$}$ between HEX and NEX, $^{\#}$ between HRE and NEX ($P < 0.05$).

457 **Table 1.** Incremental maximal exercise tests in normoxia and hypoxia.

458

459

	Normoxia (FiO_2 = 0.21)	Hypoxia (FiO_2 = 0.12)
Incremental test duration, min	19.6 ± 3.3	15.7 ± 2.1 *
Maximal power output, W	339 ± 49	250 ± 32 *
as percent of normoxic value	/	74 ± 5
Maximal oxygen uptake, $mL \cdot min^{-1} \cdot kg^{-1}$	61.1 ± 10.8	40.6 ± 6.5 *
as percent of normoxic value	/	67 ± 8
Peak blood lactate concentration, $mmol \cdot L^{-1}$	11.5 ± 2.5	13.4 ± 2.8 *
Arterial oxygen saturation		
at the beginning of the test, %	98.3 ± 1.0	83.5 ± 4.9 *
at exhaustion, %	94.9 ± 1.8	73.7 ± 5.7 *
Maximal heart rate, bpm	189 ± 9	177 ± 9 *

460 Mean ± SD, n = 12. FiO_2, inspiratory oxygen fraction.* significantly different compared
461 with Normoxia ($P < 0.05$)
462
463
464

465 **Table 2.** Change in body weight, fluid and food intake and urine volume during the three
466 experimental sessions.

467

468

	HEX	HRE	NEX
Weight change, g	-1417 ± 760 [£]	-842 ± 864	-1796 ± 759 [£]
Fluid intake, g	2209 ± 659 [£]	738 ± 685	2331 ± 497 [£]
Food intake, g	339 ± 174 [£$]	199 ± 187	256 ± 102
Urine Volume, g	1134 ± 688	1148 ± 535	915 ± 368
Corrected weight change, g	-2831 ± 893 [£$]	-630 ± 152	-3468 ± 805 [£]
Energetic intake, kcal	1461 ± 718 [£]	752 ± 756	1178 ± 536 [£]

469 Mean ± SD, n = 12. $P < 0.05$, [£] significantly different compared with HRE, [$] significantly
470 different compared with NEX.
471

Fig 1.

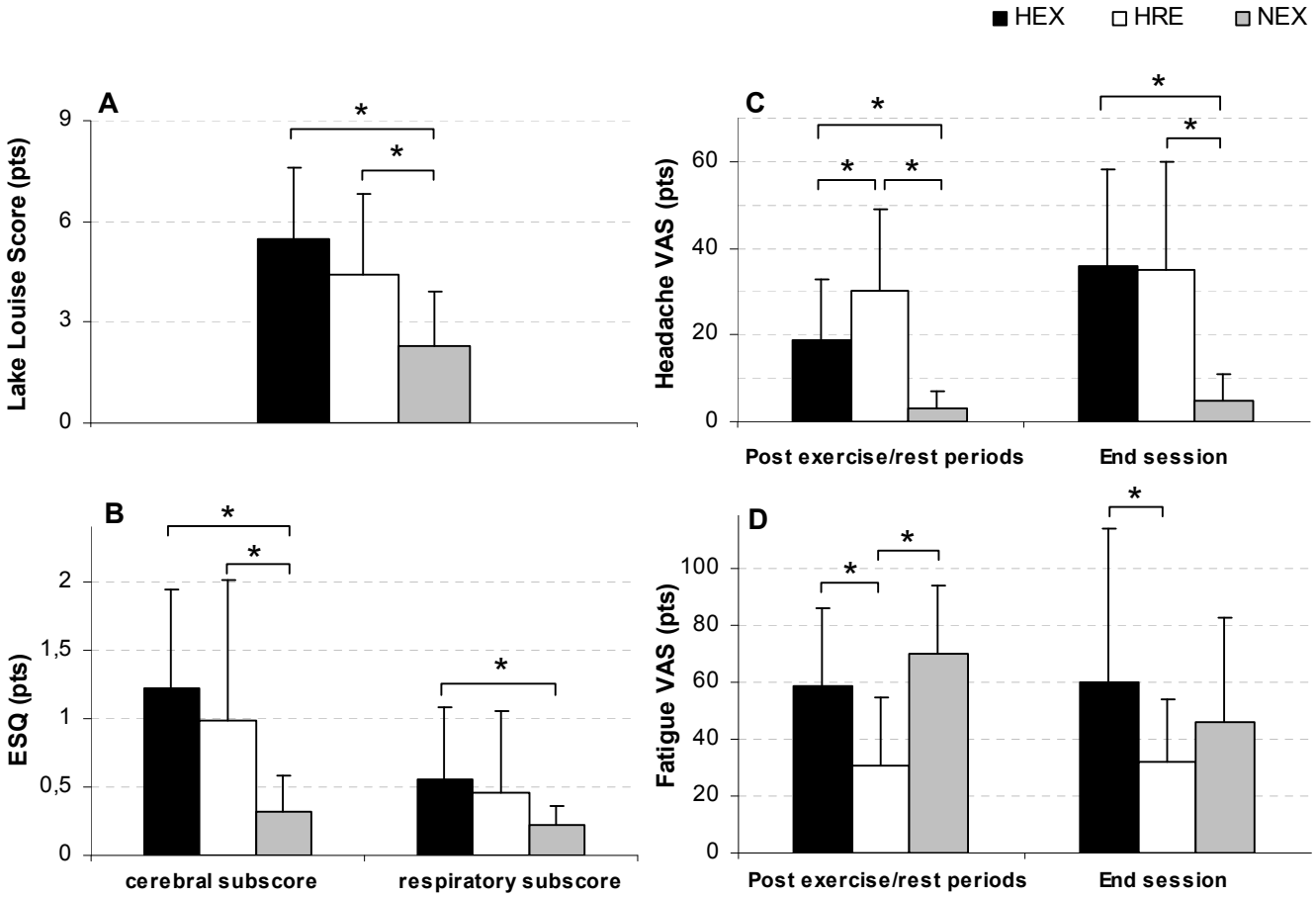

HEX
HRE
NEX
A
Lake Louise Score (pts)
9
6
3
0
*
*
B
ESQ (pts)
2
1,5
1
0,5
0
*
*
*
cerebral subscore
respiratory subscore
C
Headache VAS (pts)
60
40
20
0
*
*
*
*
*
Post exercise/rest periods
End session
D
Fatigue VAS (pts)
100
80
60
40
20
0
*
*
*
Post exercise/rest periods
End session

Fig 2.

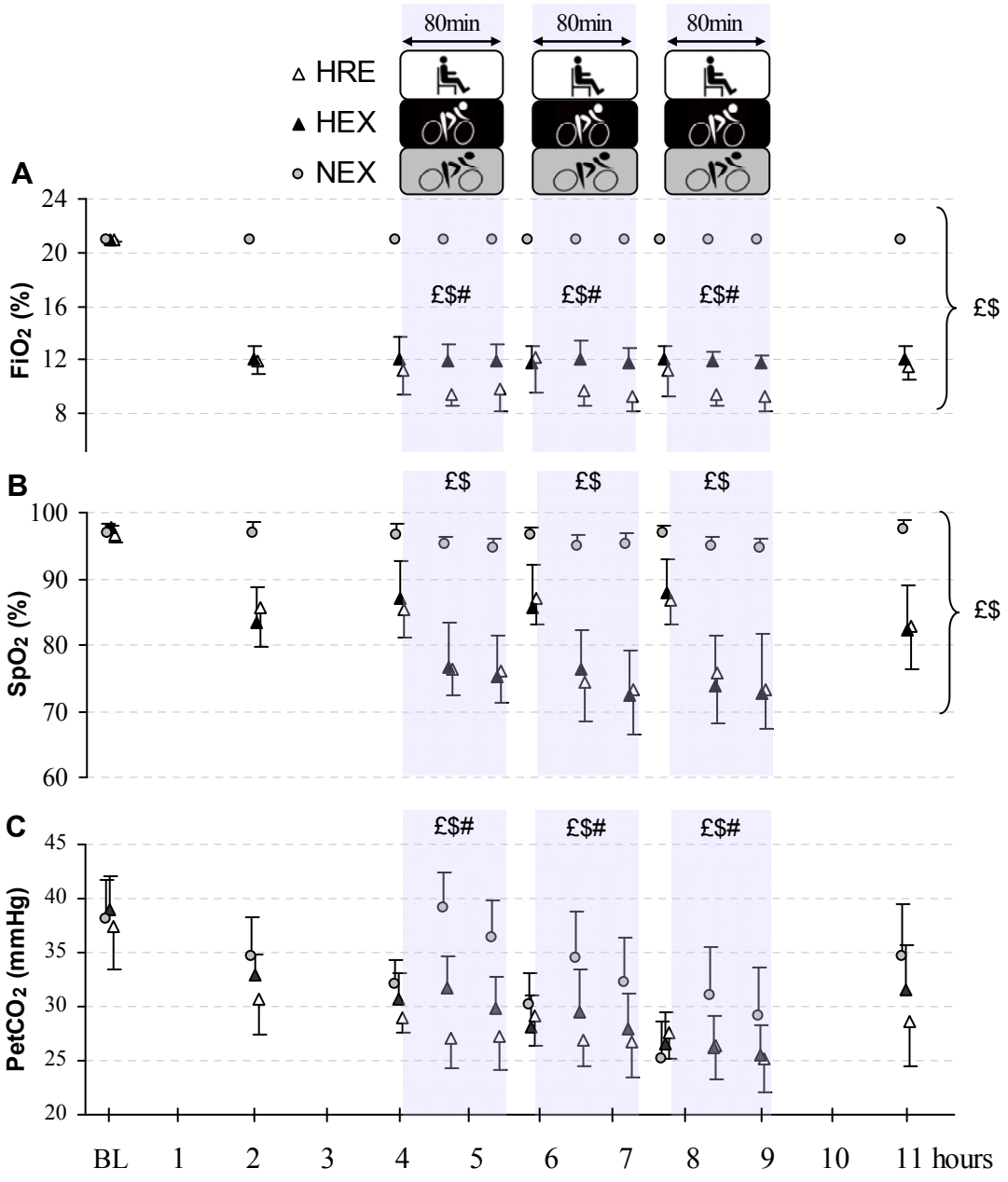
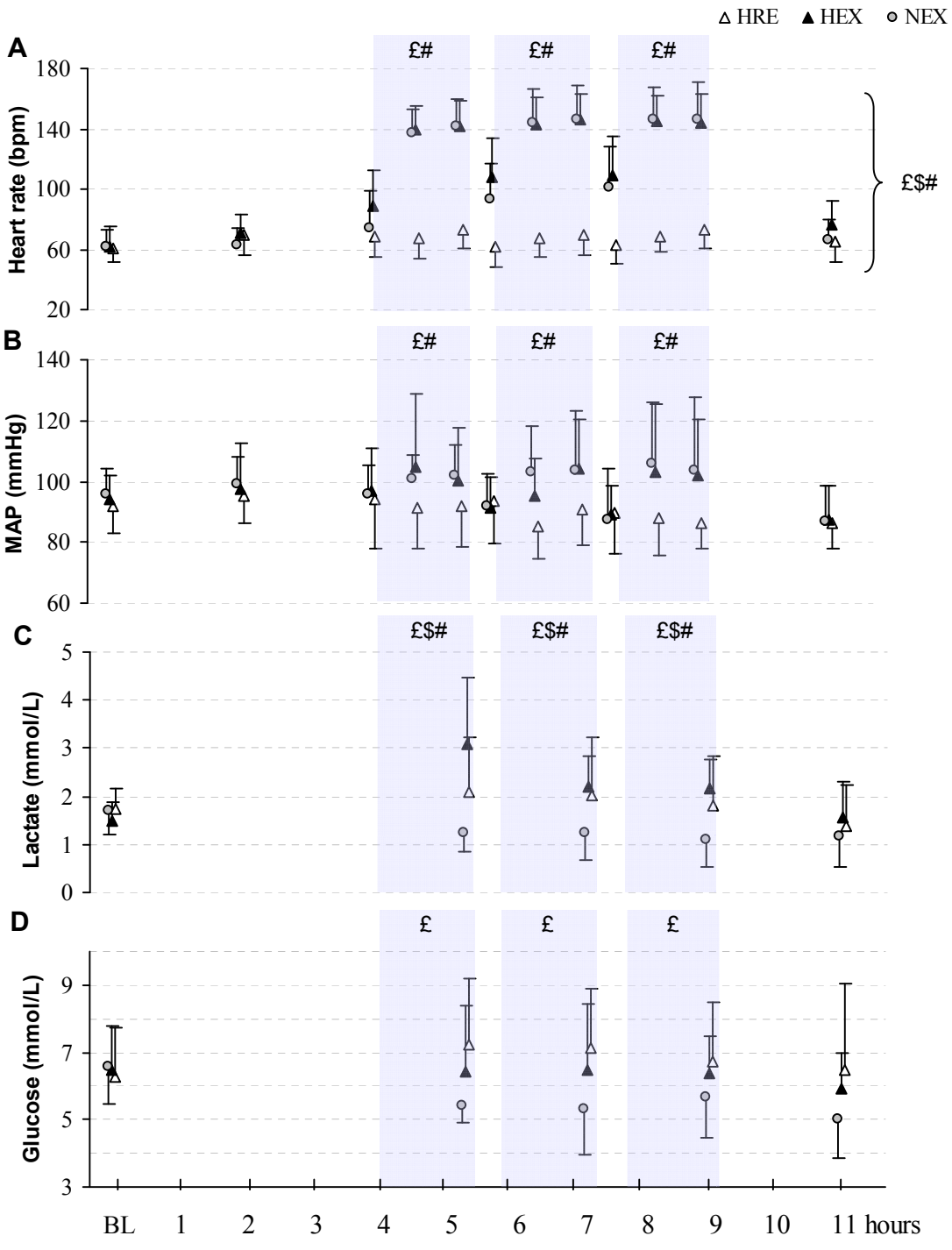

80min
80min
80min
HRE
HEX
NEX
A
B
C
FiO2 (%)
SpO2 (%)
PetCO2 (mmHg)
£$#
£$
£$
£$
£$
£$#
£$#
£$#
BL
1
2
3
4
5
6
7
8
9
10
11 hours

Fig 3.


△ HRE ▲ HEX ○ NEX
A
Heart rate (bpm)
180
140
100
60
20
£#
£#
£#
£$#
B
MAP (mmHg)
140
120
100
80
60
£#
£#
£#
C
Lactate (mmol/L)
5
4
3
2
1
0
£$#
£$#
£$#
D
Glucose (mmol/L)
9
7
5
3
£
£
£
BL
1
2
3
4
5
6
7
8
9
10
11 hours