Exercise-induced cardiovascular responses during combined normobaric vs. hypobaric and normoxic vs. hypoxic acute exposures in military air pilot trainee

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Running title: Submaximal exercise in hypoxia and hypobaria

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Abstract

Introduction: This study aimed to evaluate the putative effects of hypobaria on ventilatory, cardiovascular and muscle oxygenation during exercise in normoxia and hypoxia.

Methods: Eighteen healthy air pilot trainees (26±3 years, 177±10 cm, 70±11 kg) performed a 6-min moderate-intensity cycling exercise (1 W/kg) in four randomized conditions: normobaric normoxia (NN), hypobaric normoxia (HN), normobaric hypoxia (NH) and hypobaric hypoxia (HH) in a hypobaric chamber. Inspired oxygen pressure was matched between normoxic (NN vs. HN, 141.2±0.8 vs. 141.5±1.5 mmHg) and hypoxic (NH vs. HH, 75.7±0.4 vs. 74.3±1.0 mmHg) conditions. Gas exchanges, pulse oxygen saturation (SpO_2), heart rate (HR), middle cerebral artery blood flow velocity (MCAv), cerebral and muscular oxygenation (NIRS), and cerebral O_2 delivery (cDO_2) were recorded.

Results: SpO_2, brain and muscle oxygenation were significantly lower and ventilation higher in HH than in NN and HN, and NH, during both rest and exercise (exercise SpO_2 99.0±1.5, 80.8±4.2, 97.6±1.9, 69.2±5.7 % and ventilation 12.5±2.3, 13.3±3.1, 12.4±2.6, 14.6±2.4, l/min in NN, NH, HN and HH respectively). cDO_2 was decreased to the same extent in HH and NH, compared with NN and HN (exercise 865.5±147.6, 731.8±152.2, 857.8±157.8, 755.8±163.3 $cm.ml O_2/s.dl_{bl}$). Specific effects of hypobaria in normoxia was lesser than in hypoxia, since only blood O_2 and CO_2 partial pressures were lower in HN than NN.

Discussion: Respiratory, cardiovascular responses and brain/muscle oxygenation were more altered in HH than in NH, which confirms the additive effects of hypobaria on exercise in severe hypoxia. However, the effects of hypobaria are likely of negligible clinical relevance in normoxia.

New and Noteworthy:

- A hypobaric normoxia (HN) condition was used to disentangle the effects of hypoxia and hypobaria
- There was an additive effect of hypobaria and hypoxia
- Cerebral and muscular tissue oxygenation were lower in hypobaric normoxia than normobaric hypoxia during rest and exercise
- The effects of hypobaria were negligible in normoxia

Introduction

The effects of altitude on human physiology were first studied about a century ago using data from the historical expeditions in Himalaya and in the Andes (1–4). This exposition to hypobaric hypoxia (HH) has progressively been complemented by laboratory studies using normobaric hypoxia (NH) for various reasons including ease of use, safety, and the ability to use cutting edge medical devices and methods which can be difficult to transpose from laboratory studies to field expeditions. However, some high-altitude field studies are still organized nowadays.

In this process, it was long speculated that HH and NH could be used interchangeably and were equivalent. Indeed, ventilatory and cardiac responses recorded in NH were shown predictive of acute mountain sickness during HH exposure (5); pre-acclimatization using NH was shown protective of acute mountain sickness in HH (6, 7) even if less effective than pre-acclimatization in HH (8); training in HH or NH was shown to elicit comparable performance improvement (9) and baroreflex sensitivity was similarly affected in HH and NH (10). Yet, recent studies demonstrated that HH is a stronger stimulus than NH for an equivalent altitude (i.e., inspired pressure in oxygen, P_IO_2) notably reporting increased ventilation (11–13), and decreased blood oxygen saturation (14) or exercise performance (15). Several opposing views have been published on this topic (16–19). Moreover, a recent study in an hypobaric chamber confirmed that HH and NH were not strictly equivalent, but reported higher maximal oxygen consumption and higher minute ventilation counteracting desaturation at maximal exercise in HH ,when compared to NH (20).

To our knowledge the previous studies which aimed to isolate the effects of hypobaria in normoxia by using a hypobaric normoxic condition (HN) did so mostly at rest (21–24) but rarely during exercise (25). HN is an artificial condition, which consists in decreasing the barometric pressure whilst adding oxygen in the inspired gas mixture so that P_IO_2 would be comparable to the sea-level (normobaric normoxic, NN) condition. This additional and somewhat unusual HN condition would allow the disentanglement of the effects of hypoxia and hypobaria and would also clarify whether hypoxia and hypobaria have an additive effect, i.e., the hypoxic and hypobaric stimuli have a stronger effect when combined (HH) than the hypoxic effect isolated (NH). In a previous study, the authors reported increases in ventilation at maximal exercise and in time to exhaustion with no differences in arterial oxygen saturation or oxygen consumption in HN condition compared with NN (25).

The primary goal of the present study was to investigate the putative additive effects of hypobaria on the physiological responses at rest and during a light-intensity exercise, both in normoxic and hypoxic conditions, encompassing ventilatory, cardiovascular and tissue oxygenation data but also self-perceived lack of concentration to assess whether modifications in cerebral oxygen delivery might be of clinical significance. The present hypotheses were (i) exercising in HH would induce greater increase in ventilation and greater decrease in blood oxygen saturation than in NH; (ii) hypobaria would induce an additive detrimental effect in hypoxia regarding cerebral and muscular oxygenation during exercise than hypoxia alone; and (iii) conversely, the effects of hypobaria would be negligible in normoxic conditions given the light exercise intensity.

Methods

Ethics

This study was performed according to the Declaration of Helsinki and was approved by the Swiss Ethic Committee of Zürich (Swissethics, BASEC ID: 2018–00006). This clinical trial can be found on ClinicalTrials.gov (ID: NCT03439202). All participants were informed about all procedures of this study and gave their written informed consent before participation.

Participant recruitment and screening

Eighteen healthy pilot trainees (four women, age 26 ± 3 years; height 177 ± 9 cm; weight 70 ± 11 kg) participated voluntarily in this study. A physician screened the participants during the familiarization visit to ensure they were healthy and did not report any medical or altitude-related issues. During this visit, the participants were familiarized with the hypobaric chamber, the ergocycle and the facial mask to be used. None of the participants was on medication during this study. They attested not being exposed to altitude above 1000 m in the two months preceding the experimental visit nor to hypoxia before enrolment in the present study (including potential flights in under-pressured cabin). Twenty-four hours before the experimental visit, the participants were asked to avoid physical exercise and consuming a heavy meal, alcohol, and caffeine. For the women included, there was no record of their menstrual cycle phase or control at the time of measurements, and any sex specificity in the effects of the intervention was not investigated.

Study design

This study was conducted in the hypobaric chamber located at the Aeromedical Center of the Swiss Air Force (Dübendorf, Switzerland, altitude of 440 m above sea level) where ambient temperature and relative humidity were controlled and kept constant throughout the experiments. Participants came for one familiarization and one experimental visit. During the latest, they were exposed to four environmental conditions in a randomized order, namely: normobaric normoxia (NN), hypobaric normoxia (HN), normobaric hypoxia (NH) and hypobaric hypoxia (HH). Each condition was interspersed with a 30-min rest period in NN. This experiment was conducted as a single blind study, the participants were not informed of the order of the conditions they were exposed to.

During each condition, recordings were performed at rest and during exercise. Participants remained seated on a cycle ergometer (eBike II basic, GE medical systems, Germany) for five minutes before cycling for six minutes (1W/kg at 80 rpm). They gave their rating of perceived exertion (RPE) using the BORG scale at the end of exercise (26). In line with the aims of the present study, the same absolute workload for all conditions was used to allow direct comparison of the measurements across conditions. No maximal exercise was recorded essentially because in the current design the four conditions were performed successively in a randomised order which avoids the day-to-day variability but clearly prevents repeating maximal exercise four times in a row within the same day.

Condition comparison

To efficiently isolate the effects of hypobaria, the two normoxic conditions (NN and HN) must be performed at identical inspired oxygen pressures (P_IO_2) reflecting an altitude close to sea-level whilst the two hypoxic conditions (NH and HH) must also be performed at an identical P_IO_2 but reflecting an altitude above sea level. This was achieved by adjusting the barometric pressure (P_B) in the hypobaric chamber on the one hand and by adjusting the inspired fraction of oxygen (F_IO_2) on the other hand.

Table 1 (result section) indicates the values of P_B, P_IO_2, and F_IO_2 across the four conditions. As expected, the P_IO_2 values were close between NN and HN on the one hand and between NH and HH on the other hand. In the present study, the chosen altitude was equivalent to 5000 m above sea level.

The matching of P_IO_2 was achieved using the following equation:

$$P_IO_2 = (P_B - 47) \times F_IO_2$$

where the water vapour pressure at 37°C is 47 mmHg (27).

Blood draw

A capillary blood sample was taken at the earlobe at rest in seating position on the ergocycle and immediately analysed using a blood gas analyser (ABL 900 FLEX, Radiometer, France) for Hb, pH, PaO_2 and $PaCO_2$.

Ventilation

Ventilatory data were measured using a gas analyser (K5, Cosmed, Roma, Italy), calibrated outside of the hypobaric chamber before the experimental visit, according to the manufacturer instructions. Flow and volume were calibrated using a 3-L syringe. Zero CO_2 calibration was performed with a scrubber. Gas concentration calibration was performed using a certified gas bottle (16% O_2 and 5% CO_2, Cosmed, Italy). Ventilatory data were recorded breath-by-breath and then exported with dedicated software for later analysis (OMNIA, Cosmed, Roma, Italy). Means were calculated over the last minute of seated rest and the last minute of exercise.

Heart rate and pulse oxygen saturation

Heart rate (HR, bpm) was monitored during the entire experimental procedure using a heart rate monitor (Polar RS800CX, FI-90440 Kempele, Finland). Pulse oxygen saturation (SpO_2, %) was monitored at the left earlobe using an oximeter (3100 pulse oximeter, Nonin, Plymouth, MN) and acquired at 0.5 Hz. Mean HR and SpO_2 were calculated over the last minute of rest and exercise.

Cerebral blood flow velocity and oxygen delivery

Middle cerebral artery velocity (MCAv, cm/s) was acquired from the left middle cerebral artery at depths ranging from 43 to 54 mm using a transcranial Doppler device (2 MHz; Spencer Technologies, Seattle, WA, USA). Mean MCAv was calculated over the last minute of rest and exercise.

Cerebral oxygen delivery (cDO_2) was estimated as described previously (21) based on the measurements of MCAv, SpO_2 as described earlier, and blood haemoglobin concentration (Hb, g/dl) from the capillary blood draw.

cDO_2 was computed as follow: $cDO_2 = MCAv \times Hb \times 1.36 \times SpO_2$

where 1.36 is the carrying capacity of haemoglobin for O_2, expressed in in ml of oxygen per gram of haemoglobin ($ml O_2/g_{Hb}$). cDO_2 was expressed in $(cm \,.\, ml O_2)/(s \,.\, dl_{bl})$; with dl_{bl} representing decilitre of blood.

Near-infrared spectroscopy

Changes in total haemoglobin concentration (tHb, the sum of deoxy- and oxy-haemoglobin relative concentrations) and tissue oxygenation index (TOI) were monitored using a near-infrared spectroscopy (NIRS) device (NIRO-200NX, Hamamatsu Photonics, Hamamatsu City, Japan). A first probe was placed on the participants' forehead horizontally. A second probe was placed on the left *vastus lateralis* (VL) at one third of the distance from the patella to the greater trochanter of the femur. Data were collected at the sampling frequency of 1 Hz during the entire experimental visit. Based on manufacturer recommendations, pathlengths of 17.8 mm and 14 mm were chosen for brain and muscle, respectively. Mean ± SD values are reported over the last minute of rest and the last minute of exercise.

Questionnaire

During rest and immediately after exercise the participants were asked to fill the Karolinska Sleep Scale (KSS) which is an assessment of self-perceived sleepiness (28) This questionnaire was performed to determine whether the expected altered cDO_2 in hypoxic condition may contribute to alter self-perceived sleepiness.

Statistical Analysis

A priori computations using a repeated measure ANOVA with an expected effect size of 0.4 and a significance level at 0.05 resulted a sample size of sixteen participants. Eighteen participants were included in this study to anticipate potential dropouts. Data are expressed as mean ± standard-deviation. Repeated measures ANOVA was used for condition comparison and the Tuckey *post-hoc* test was performed when appropriate, using the Bonferroni correction. Pearson's coefficient of

correlation was determined between cDO_2 and KSS scores. Statistical analysis was performed using MATLAB (R2023b, The MathWork Inc., Natick, Ma, USA). Significant difference was set at $p<0.05$.

Results

Condition comparison

Cf. Table 1.

Ventilation

At rest, $\dot{V}E$ was not significantly different between the four conditions. During exercise, $\dot{V}E$ was higher in hypobaric hypoxia than in normobaric normoxia ($p < 0.05$), hypobaric normoxia ($p < 0.05$), and normobaric hypoxia ($p < 0.05$) as shown in **Figure 1**. There were no significant differences in VT or Rf either during rest or exercise (**Figure 1**).

Cardiovascular data

At rest, heart rate was higher in HH than in NN ($p < 0.01$). During exercise, HR was higher in HN and HH than in NN (both $p < 0.01$), and it was also higher in HH than in HN ($p < 0.05$) as shown on **Figure 2**. As expected, SpO_2 was higher in the two normoxic conditions than in the two hypoxic conditions (all $p < 0.001$). Moreover, SpO_2 was lower in HH than in NH at rest ($p < 0.001$) and during exercise ($p < 0.001$) as shown on **Figure 2**. At rest, MCAv was similar between the four conditions, whereas during exercise it was significantly greater in HH compared with the two normoxic conditions (both $p < 0.05$). Furthermore, no significant differences in MCAv were found between NH and HH nor between NH and the two normoxic conditions. Estimated cDO_2 was lower in NH and HH than in NN, during both rest (both $p < 0.01$) and exercise ($p < 0.01$ and $p < 0.05$, respectively). Finally, RPE was greater in NH (11.3 ± 2.2, both $p < 0.05$) and HH (11.8 ± 2.3, both $p < 0.05$) than in NN (8.1 ± 1.3) and HN (9.1 ± 1.3).

Cerebral and muscular oxygenation

Values of tHb and TOI at rest and during exercise are reported in **Figure 3**. Neither cerebral nor muscle TOI were significantly different between the two normoxic conditions at rest or during exercise. Nevertheless, cerebral TOI was lower during rest and exercise in the two hypoxic conditions than in the two normoxic conditions (all $p < 0.05$), and was significantly lower in HH than in NH, during both rest ($p < 0.05$) and exercise ($p < 0.01$) (**Figure 3**).

Blood gas analysis

Figure 4 shows blood pH, PO_2 and PCO_2 drawn from the earlobe at rest. Blood pH was higher in HN ($p < 0.001$) and HH ($p < 0.001$) than in NN and NH. It was also higher in HH ($p < 0.001$) than in HN. Blood PO_2 was decreased in HN ($p < 0.001$) compared with NN, even further decreased in NH ($p < 0.001$), and again even further decreased in HH ($p < 0.001$). Blood PCO_2 was significantly lower in HN ($p < 0.001$) and HH ($p < 0.001$) than in NN and NH.

In addition, blood haemoglobin concentrations were not significantly different between any of the four conditions (NN: 15.6±0.8, NH:15.6±1.0, HN:15.5±0.7, HH:16.2±0.8 g/dl, main effect $p = 0.101$).

KSS score

The KSS score was higher in HH (4.6 ± 0.7, $p < 0.05$) and NH (5.7 ± 0.8, $p < 0.05$) than NN (3.6 ± 0.7) and HN (2.7 ± 0.6) at rest and immediately after exercise (5.1 ± 0.7, $p < 0.05$; 6.2 ± 0.8, $p < 0.05$; 2.8 ± 0.6; 3.7 ± 0.7). Interestingly, there was a moderate correlation between cDO_2 and KSS score across all four conditions ($p < 0.001$). The relationship was a little stronger at rest than during exercise as shown on **Figure 5**.

Discussion

The present study investigated the respiratory and cardiovascular responses as well as the cerebral and muscular tissue oxygenation at rest and during a moderate-intensity exercise in conditions of acute exposure to combined normobaria vs. hypobaria and normoxia vs. hypoxia. The present findings confirm the most common statement of an additive effect of hypobaria in hypoxic condition with a significantly increased minute ventilation during exercise and a significantly decreased blood oxygen saturation at rest and during exercise in hypobaric hypoxia compared with normobaric hypoxia. Yet, the novel findings lie in the additive effects of hypobaria resulting in significant decreases in cerebral and muscular tissue oxygenation in HH, compared with NH, during both rest and exercise. Overall, the present study further helps to disentangle the effects of hypobaria and hypoxia.

Additive effect of hypobaria on minute ventilation and blood oxygen saturation

Previous reports about the additive effects of hypobaria *per se* on minute ventilation were contradictory, reporting no additive effects at 3200 or 3800 m (29, 30) or reporting an increased minute ventilation in HH compared with NH at 4000 m (20), 4500 m (13, 31, 32) and presently at 5000 m. On the one hand the altitude at which the experiments were conducted likely influenced the outcome, on the other hand some explanations have been put forward regarding the mechanisms potentially underlying these observations.

Hypobaria *per se* may affect pulmonary resistance through changes in pressure gradient from ambient air, to pulmonary alveoli and subsequently to pulmonary capillary bed (33). Lower air density leading to respiratory muscle unloading may also contribute to the higher ventilation in HH than in NH (20). Interestingly, the present study reports a HN condition which illustrates the pressure changes occurring in hypobaria when isolated from hypoxia. In HN, P_IO_2 was not significantly different from NN but the barometric pressure was (**Table 1**), which resulted in a significant decrease in blood PO_2 in HN compared with NN, but this decrease was smaller than in the two hypoxic conditions, as observed in NH or HH (**Figure 4**). However, the decrease in blood PCO_2 in HN was of the same magnitude as that of HH, whereas in NH blood PCO_2 was comparable to that of NN. In other words, in the HN condition the participants were exposed to limited hypoxia regarding O_2 but were as if in altitude regarding CO_2. Therefore, the decrease in barometric pressure *per se* likely decreased blood CO_2 content, which may in turn affect the pulmonary resistance and/or the ventilatory drive (34). Minute ventilation was increased only during exercise in HH (**Figure 1**), when blood O_2 and CO_2 content were likely at their lowest, indicating that both O_2 and CO_2 are key in driving the hypoxic ventilatory response (35) and that the changes in blood CO_2 content in HN were likely of little clinical relevance, as confirmed by the similar SpO_2 values as in NN. In HH, the reported lower SpO_2 values during both rest and exercise (**Figure 2**) could logically be associated with the reduction in oxygen pressure gradient from the alveoli to the capillary but also with a probable pulmonary vasoconstriction, which was not measured in the present study (for review, see (36)). Given that in the HN condition the participants were exposed to a normoxic amount of oxygen, it was expected that S_pO_2 would not be significantly different from NN despite the slight but significant decrease in blood PO_2 reported herein. As stated above, this slight decrease in PO_2 was accompanied by a decrease in PCO_2 and an increase in pH, therefore the Bohr effect likely countered the decrease in PO_2 (and the potential pulmonary vasoconstriction resulting from hypocapnia) so that SpO_2 did not change significantly between NN and HN. Therefore, the hypobaric effects on blood oxygen content are likely clinically irrelevant in a normoxic environment.

A decrease in blood PCO_2 with no significant increase in ventilation is a surprising result since altitude-induced hypocapnia and subsequent blood alkalosis are classically associated with altitude-induced hyperventilation (36). Interestingly, in a recent study measuring end-tidal PCO_2 and ventilation at maximal exercise in both HH and NH, the authors reported a higher maximal ventilation in the former condition but without any differences in end-tidal PCO_2. The latter has been shown a reliable surrogate of arterial PCO_2 in a large range of environmental conditions (37), indicating that the hyperventilation-driven hypocapnia may be influenced by confounding factors, including hypobaria. Indeed, the changes in ventilation may have been masked by a number of factors including a slight hyperventilation at rest across conditions (**Figure 1**), a rapid depressurization from sea level to 5000 m

inside the chamber, which may have negatively affected the measurements made by the gas analyser, and a short (five minutes) exposure to each condition at rest, which may not have allowed enough time for the ventilatory response to be complete.

Cerebral blood flow and cerebral oxygenation

In the present study, MCAv did not significantly change at rest despite a significant decrease in cDO_2 in the two hypoxic conditions compared with the two normoxic conditions (**Figure 2**). However, the interpretation of MCAv changes needs to be made with caution because there is no measure of the MCA diameter. In acute hypoxia, decreased arterial oxygen content typically induces cerebral vasodilation (38–40) whilst decreased arterial CO_2 content typically induces cerebral vasoconstriction (41, 42). The outcome of these two contradictory stimuli is that vasodilation likely prevails, as consistent increase in cerebral blood flow is commonly observed at altitude (43). Hypobaria *per se* did not seem to have any significant effect on cerebral oxygen delivery at rest or during exercise, the NN and HN being not significantly different on the one hand and the NH and HH conditions being not significantly different on the other hand. Previous studies reported changes in MCAv at rest (39, 44–46) contrarily to this study, however MCAv was assessed after five minutes of a very rapid ascent from sea level to 5000 m which may not have allowed enough time to reach a full MCAv response, or a modification of the MCA diameter interfered with the present measurements.

During exercise, MCAv was increased only in HH compared to the two normoxic conditions, the NH condition being not significantly different from the two normoxic conditions or HH. These findings may indicate that the additive effects of hypobaria and hypoxia on MCAv is unveiled only during hypoxic exercise and that this effect is small in magnitude compared with the ventilatory effects reported above. In the meanwhile, estimated cerebral oxygen delivery was decreased in the two hypoxic conditions compared with the two normoxic conditions largely because of the decrease in SpO_2. This was indicative that the additive effect of hypobaria in hypoxic condition is likely of negligible clinical significance for cerebral oxygen delivery regulatory mechanisms both at rest and during exercise.

Nevertheless, NIRS measurements showed significantly lower cerebral oxygenation in the two hypoxic conditions compared with the two normoxic conditions at rest and during exercise. Additionally, there were lower prefrontal TOI values in HH than in NH, which was indicative of a greater cerebral deoxygenation. Therefore, despite the cerebral autoregulation aiming at minimizing the effects of hypoxemia on cerebral oxygen delivery (47, 48), the decrease in arterial oxygen saturation affected prefrontal tissue oxygenation as assessed by NIRS and this decrease was greater in HH than in NH, which may be associated with the greater decrease in S_pO_2 and cDO_2.

Muscular oxygenation

Muscle oxygenation parameters assessed by NIRS indirectly reflect the metabolic changes that occur at the muscle level (49) but are also biased by many confounding factors (e.g. adipose tissue thickness) due to the non-invasive nature of the method (50). In the present study, muscle TOI was significantly lower in the two hypoxic conditions compared with the two normoxic conditions during exercise. Interestingly, muscle TOI was reduced to a greater extent in HH vs. NH, which indicates – once again – an additive influence of hypobaria in hypoxia (15). These changes may be associated with the changes in SpO_2, indicating that the additive effect of hypobaria in hypoxic condition is large enough to elicit significant changes all along the O_2 transport chain during exercise, from ventilation to blood oxygen saturation and muscle oxygenation. In normobaric conditions, there were no significant differences in muscle oxygenation, likely indicating that the effects of hypobaria are irrelevant in normoxia.

Effects of decreased cDO_2 on self-perceived sleepiness

One of the most known effects of high-altitude is the alteration of cerebral function (51) and it is likely the most feared by pilots during a flight. In the present study only hypoxia (NH) or combined

hypobaria and hypoxia (HH) decreased cDO_2, which may be associated with the greater sleepiness sensation reported in these two conditions (**Figure 5**).

Perspective

Although fewer individuals are exposed to the HN condition than the HH condition, the former remains essential in aviation medicine where pilots breath an oxygen-enriched gas mixture whilst flying in a depressurized cabin (52). In the case where HH induces lower blood oxygen saturation (14, 15) than NH, one may hypothesize an effect of hypobaria *per se*. This latter effect would mean that cerebral oxygen delivery (cDO_2) may be lowered, and the cognitive performance of the pilots may be altered in a depressurized cabin even though additional oxygen is added in the inspired gas (HN condition).

Limitations

The present study did not evaluate some ventilatory mechanisms which may have been different between HH and NH, including potential differences in oxygen consumption of the respiratory muscles, potential greater intravascular bubble formation and ventilation/perfusion disparity, greater alveolar dead space or greater changes in alveolar fluid permeability and chemosensitivity in HH than in NH (29, 32). These factors may further explain the observed differences between HH and NH.

The randomization of the order of the four hypoxic conditions was used to rule out any carry over effect from a condition to a subsequent one, yet we cannot exclude some carry over effects.

Each hypoxic exposure was just five minutes of rest and six minutes of exercise, which is a shorter time compared with most studies evaluating hypoxic exposure at 5000m and which may explain at least partially the discrepant results, particularly in terms of ventilation.

Traditionally, cDO_2 is assessed with volumetric flow, rather than MCAv which is flow velocity. As mentioned above, there is a strong potential for diameter changes in NH and HH, which would presently lead to an underestimation of cDO_2. A previous publication (53) observed similar cDO_2 during HH following partial acclimatization. This was largely attributed to an increase in flow but not velocity.

The relationship between cerebral blood flow, PCO_2, bicarbonates and pH is complex and goes beyond the scope of the present study. Yet, acute cerebral blood flow regulation is likely independent of arterial pH. CO_2 diffusion across the blood–brain barrier is rather key to alter perivascular extracellular pH, and changes in arterial bicarbonates acutely contribute to cerebrovascular acid–base regulation (54). Further studies are needed to assess the exact interplay between PCO_2, bicarbonates and pH on the alterations in cerebral blood flow in hypoxic and/or hypobaric environments.

Ear lobe capillary blood was used in the present study, while it is a surrogate for arterial blood (55) it is not perfect and may have introduced noise in the measurements. Future studies using arterial catheterisation are required.

Conclusion

To our knowledge, the present study was the first to evaluate the effect of hypobaria in both normoxic and hypoxic conditions on ventilatory, cardiovascular as well as cerebral and muscle oxygenation parameters during exercise. The present results demonstrate a specific effect of hypobaria *per se* on cerebral and muscular oxygenation during exercise that were observed in hypoxic conditions and to a lesser - and likely negligible - extent in normoxic conditions. This was attributed primarily to a larger decrease in blood oxygen saturation and a greater ventilatory response. The latter induced hypocapnia, which may have triggered pulmonary vasoconstriction affecting O_2 diffusion from the alveolar area to the blood in hypobaric hypoxia. These findings are essential for altitude physiology and aviation medicine where military pilots regularly train either in normobaric or hypobaric hypoxia whilst they may be exposed to hypobaric normoxia. To conclude, hypobaria led to greater decreases in

cerebral and muscular oxygenation during submaximal cycling exercise in hypoxia, whereas it had likely negligible effects in normoxia.

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Conflict of interest

The authors declare no conflict of interest and have no financial relationship to disclose.

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Author contribution

MRA, NB and GPM designed the study. MRA collected the data. MRA and NB analysed the data. NB and MRA wrote the article. DB and GPM reviewed the article. All the authors approved the final version of the manuscript.

Figure captions

*Figure 1: Respiratory frequency, tidal volume and minute ventilation in normobaric normoxia (NN); hypobaric normoxia (HN); normobaric hypoxia (NH); hypobaric hypoxia (HH). Square: rest; diamonds: exercise. * $p<0.05$ vs. NN; # $p<0.05$ vs. HN; + $p<0.05$ vs. NH.*

*Figure 2: Heart rate (HR), pulse oxygen saturation (SpO_2), middle cerebral artery velocity (MCAv), and estimated cerebral oxygen delivery (cDO_2) in normobaric normoxia (NN); hypobaric normoxia (HN); normobaric hypoxia (NH); hypobaric hypoxia (HH). Square: rest; diamonds: exercise. * $p<0.05$ vs. NN; # $p<0.05$ vs. HN; + $p<0.05$ vs. NH.*

*Figure 3: Prefrontal total haemoglobin (tHb), prefrontal tissue oxygenation index (TOI), Muscle total haemoglobin, and muscle tissue oxygenation index in normobaric normoxia (NN); hypobaric normoxia (HN); normobaric hypoxia (NH); hypobaric hypoxia (HH). Square: rest; diamonds: exercise. * $p<0.05$ vs. NN; # $p<0.05$ vs. HN; + $p<0.05$ vs. NH.*

*Figure 4: Capillary bood pH, oxygen partial pressure (PO_2) and carbon dioxide partial pressure (PCO_2) at rest in normobaric normoxia (NN), hypobaric normoxia (HN); normobaric hypoxia (NH) and hypobaric hypoxia (HH). Square: rest; diamonds: exercise. * $p<0.05$ vs. NN; # $p<0.05$ vs. HN; + $p<0.05$ vs. NH.*

Figure 5: Correlation between Karolinska Sleep Score (KSS) and estimated cerebral oxygen delivery (cDO_2) during rest and exercise across all four conditions. R: Pearson's coefficient of correlation.

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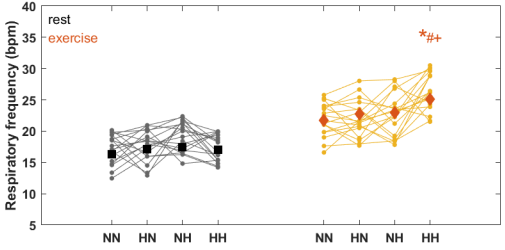
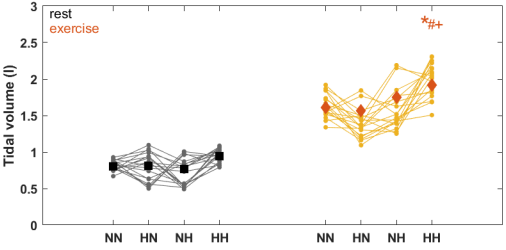
Figure 1


Respiratory frequency (bpm)
rest
exercise
*#+
NN HN NH HH
NN HN NH HH


Tidal volume (l)
rest
exercise
*#+
NN HN NH HH
NN HN NH HH

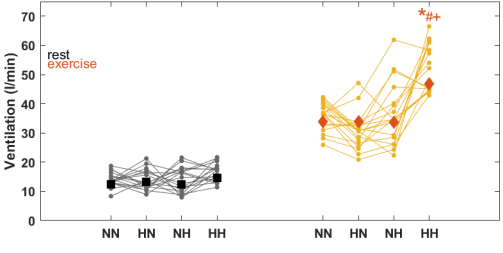

Ventilation (l/min)
rest
exercise
*#+
NN HN NH HH
NN HN NH HH

Figure 2

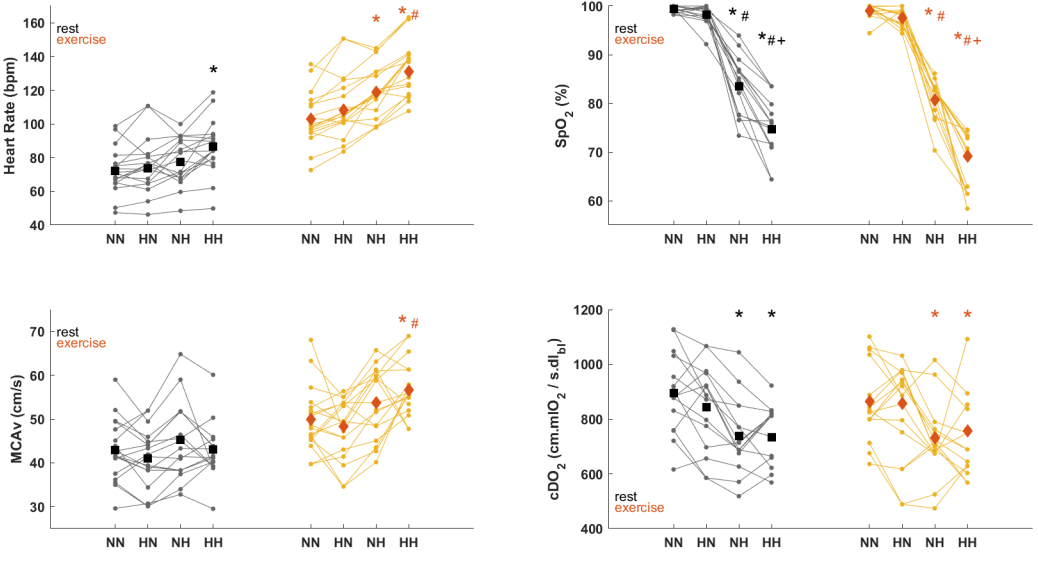
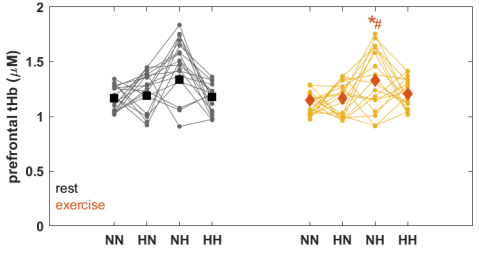
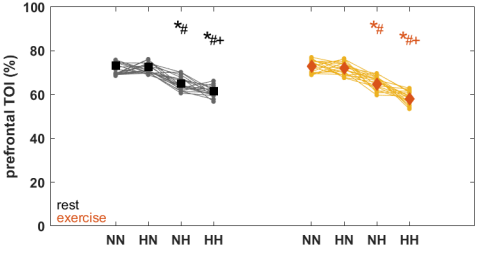
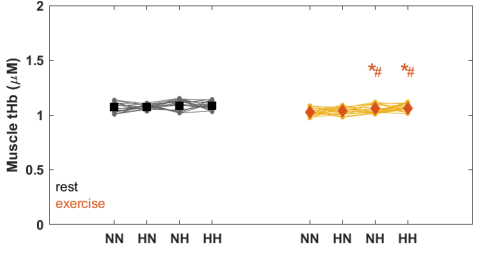

Heart Rate (bpm)
rest
exercise
NN HN NH HH
SpO2 (%)
MCAv (cm/s)
cDO2 (cm.mlO2 / s.dlbl)

Figure 3


prefrontal tHb (μM)
2
1.5
1
0.5
0
rest
exercise
NN HN NH HH
NN HN NH HH
*#


prefrontal TOI (%)
100
80
60
40
20
0
rest
exercise
NN HN NH HH
NN HN NH HH
*#
*#+


Muscle tHb (μM)
2
1.5
1
0.5
0
rest
exercise
NN HN NH HH
NN HN NH HH
*#

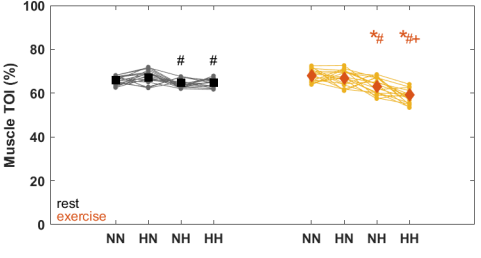

Muscle TOI (%)
100
80
60
40
20
0
rest
exercise
NN HN NH HH
NN HN NH HH
#
*#
*#+

Figure 4

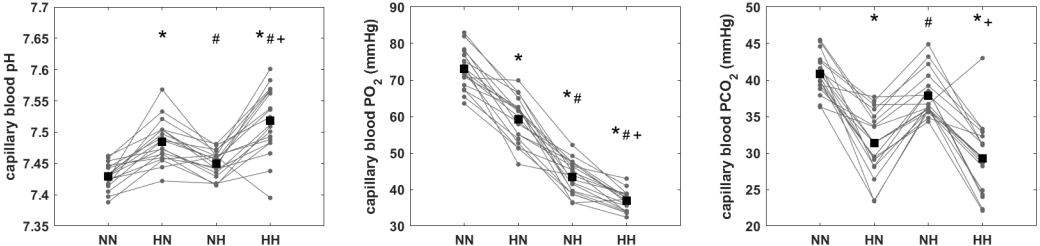

capillary blood pH
7.7
7.65
7.6
7.55
7.5
7.45
7.4
7.35
*
#
*#+
NN
HN
NH
HH
capillary blood PO2 (mmHg)
90
80
70
60
50
40
30
*
*#
*#+
NN
HN
NH
HH
capillary blood PCO2 (mmHg)
50
45
40
35
30
25
20
*
#
*+
NN
HN
NH
HH

Figure 5

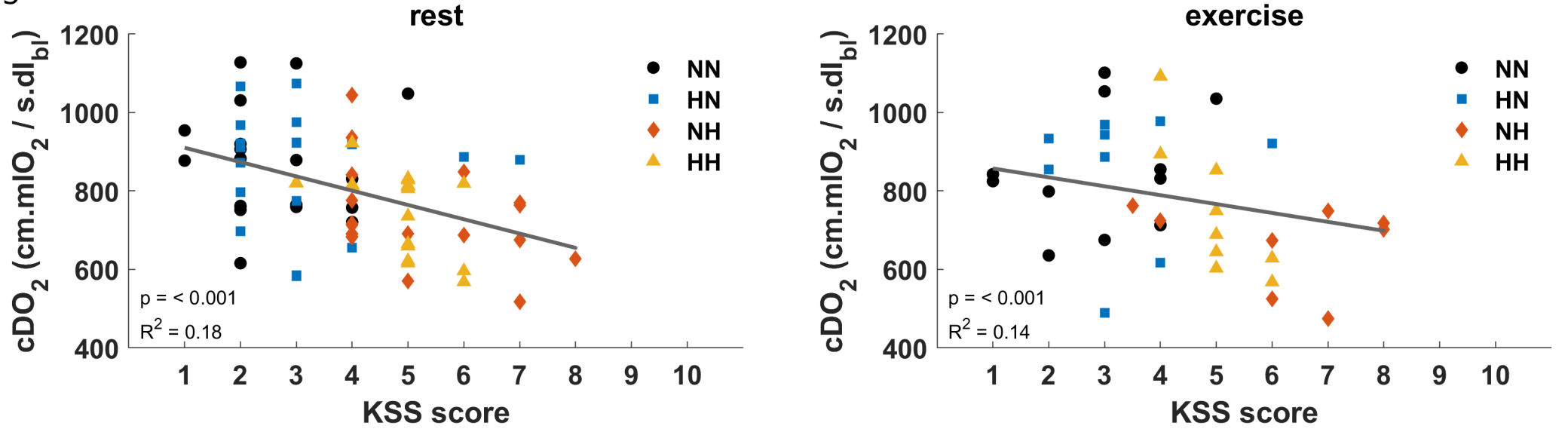
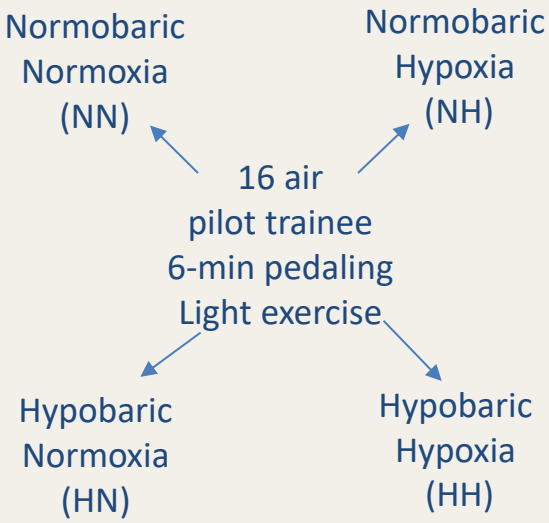

rest
exercise
NN
HN
NH
HH
p = < 0.001
R2 = 0.18
p = < 0.001
R2 = 0.14
cDO2 (cm.mlO2 / s.dlbl)
KSS score
1200
1000
800
600
400
1
2
3
4
5
6
7
8
9
10

*Table 1: barometric pressure (PB), inspired fraction of oxygen (F_IO2), and inspired oxygen pressure (P_IO2) in normobaric normoxia (NN), hypobaric normoxia (HN), normobaric hypoxia (NH) and hypobaric hypoxia (HH). ***p<0.001 vs. NN; # p<0.05, ### p<0.001 vs. HN; † p<0.05, ††† p<0.001 vs. NH.*

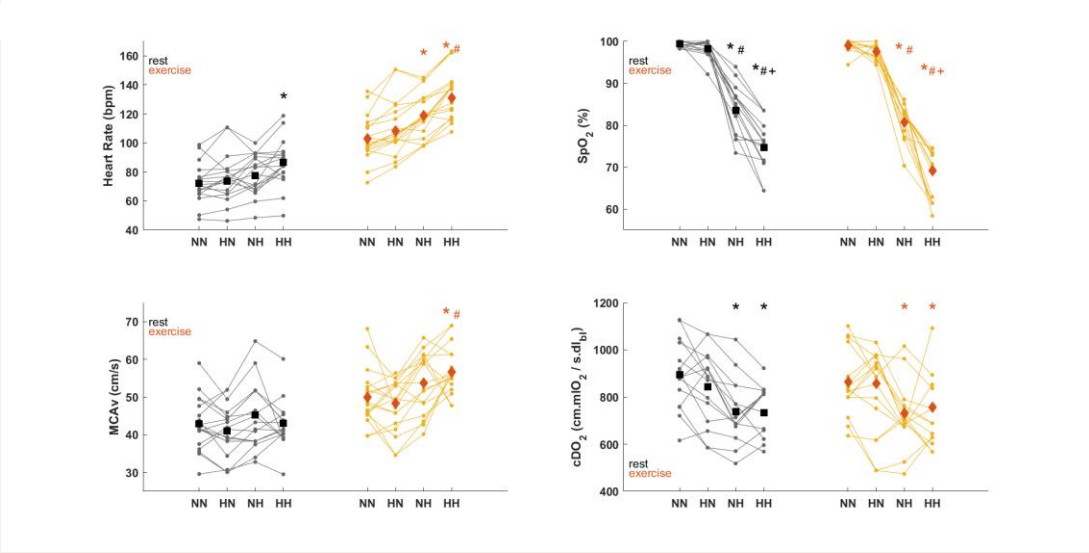
	NN	HN	NH	HH
P_B (mmHg)	723 ± 4	406 ± 4***	723 ± 4$^{###}$	403 ± 5$^{***\#\dagger\dagger\dagger}$
F_IO_2	0.209	0.394	0.112	0.209
P_IO_2 (mmHg)	141.2 ± 0.8	141.5 ± 1.5	75.7 ± 0.4$^{***\#\#\#}$	74.3 ± 1.0$^{***\#\#\#\dagger}$

Exercising in hypobaria and hypoxia

METHODS



OUTCOME Specific effects of hypobaria in normoxia was lesser than in hypoxia



CONCLUSION there is an additive effect of hypobaria on exercise in severe hypoxia