Cognitive Impairment During Combined Normobaric vs. Hypobaric and Normoxic vs. Hypoxic Acute Exposure

Mathias Roland Aebi; Nicolas Bourdillon; Philip Noser; Grégoire Paul Millet; Denis Bron

INTRODUCTION: Exposure to hypoxia has a deleterious effect on cognitive function; however, the putative effect of hypobaria remains unclear. The present study aimed to evaluate cognitive performance in pilot trainees who were exposed to acute normobaric (NH) and hypobaric hypoxia (HH). Of relevance for military pilots, we also aimed to assess cognitive performance in hypobaric normoxia (HN).

METHODS: A total of 16 healthy pilot trainees were exposed to 4 randomized conditions (i.e., normobaric normoxia, NN, altitude level of 440 m; HH at 5500 m; NH, altitude simulation of 5500 m; and HN). Subjects performed a cognitive assessment (KLT-R test). Cerebral oxygen delivery (cDO_2) was estimated based middle cerebral artery blood flow velocity (MCAv) and pulse oxygen saturation (S_pO_2) monitored during cognitive assessment.

RESULTS: Percentage of errors increased in NH (14.3 ± 9.1%) and HH (12.9 ± 6.4%) when compared to NN (6.5 ± 4.1%) and HN (6.0 ± 4.0%). Number of calculations accomplished was lower only in HH than in NN and HN. When compared to NN, cDO_2 decreased in NH and HH.

DISCUSSION: Cognitive performance was decreased similarly in acute NH and HH. The cDO_2 reduction in NH and HH implies insufficient MCAv increase to ensure cognitive performance maintenance. The present study suggests negligible hypobaric influence on cognitive performance in hypoxia and normoxia.

KEYWORDS: cognition, acute exposure, hypobaria, hypoxia.

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Military personnel, pilots, and mountaineers are often exposed to acute moderate or severe hypoxia. In hypoxia, arterial oxygen partial pressure (P_aO_2) is reduced.[27] Decreased oxygen availability at moderate and high-altitude [around 1500–7500 m (4921–24,606 ft)] has been shown to induce cognitive function impairments in human individuals.[1,9] In a narrative review, Taylor et al. demonstrated that cognitive function tended to be altered in acute hypoxia.[38] Another review on clinical neuropsychological parameters suggested a tendency for acute hypoxia to induce decrement in P300 latency and amplitude, with short-term memory impairment noticeable above 6000 m (19,685 ft).[40] When evaluating cognitive function, tasks are usually categorized as either “simple” or “complex,”[29] including memory (working, spatial, and verbal), attention, and executive function.[15] Taylor et al. presented a simplistic task categorization.[38] For instance, tasks including short-term memory and simple arithmetic are considered “simple cognitive tasks,” whereas arithmetic efficiency and working-memory tasks are “complex cognitive tasks.”[38] In the literature, because of inter- and intraindividual variations, the hypoxic effect on complex tasks remains unclear. The present study aimed to evaluate arithmetic efficiency, including working memory, defined as the ability to keep and process short-term information long enough to sustain attention to perform a cognitive task,[36] when acutely exposed to different combinations of hypoxic and hypobaric conditions.

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Altitude exposure can be simulated with the use of a hypobaric chamber by reducing the ambient barometric pressure (P_B) (i.e., hypobaric hypoxia, HH) or by decreasing the inspired oxygen fraction (F_IO_2) without changing P_B (i.e., normobaric hypoxia, NH). Various studies have reported cognitive performance impairment during acute exposure in HH[3,4,37] or in NH.[9,28] Recently, a review suggested that low P_aO_2 (30–60 mmHg) was the key predictor of cognitive performance impairment, independently of the type of hypoxic exposure (i.e., NH or HH).[20] More precisely, it was suggested that increased cerebral blood flow is unable to compensate for the lack of oxygen sufficiently enough for cognitive performance maintenance when P_aO_2 level is low (<60 mmHg).[20] Moreover, Ochi et al. reported a negative correlation between arterial oxygen saturation and executive function impairment during gradual simulated altitudes in normobaric hypoxia.[26] Nevertheless, hypoxic conditions with similar inspired oxygen pressure (P_IO_2) are not considered equivalent (i.e., normobaric and hypobaric hypoxia),[7] even if this point remained in debate.[21,30] For the last two decades, there are increased evidences that HH is a more severe environmental condition,[22] leading to larger hypoxemia.[32] Moreover, symptoms seem also qualitatively different in HH,[10] with increased acute mountain sickness in HH than NH.[31] Therefore, cognitive performance and symptoms may vary between NH and HH acute exposures. To our knowledge, there are very few studies that have investigated cognitive performance in NH vs. HH. Long ago, a study showed similar decrease in visual attention at an altitude of 3450 m (11,319 ft) in NH and HH when compared to sea level.[33] McMorris et al. suggested that NH may be associated with greater reductions in cognitive function; however, their findings regarding the use of normobaric vs. hypobaric hypoxic conditions were inconclusive.[20] Therefore, more studies comparing the effect of NH and HH on cognition are needed. The first aim of the present study was in fact to compare the effects of acute NH and HH exposure on cognitive performance and symptoms in pilot trainees.

The present study also aimed to better evaluate the specific effect of hypobaria, independently of hypoxia, on cognitive performance. By using a hypobaric normoxic (HN) condition, which allows comparing similar normoxic conditions with different P_B, one may therefore isolate the hypobaric effect from the hypoxic one. The HN consists of a low P_B environment combined with enriched oxygen gas mixture to obtain a comparable P_IO_2 than in normoxic normoxia (NN). Supplemental oxygen administration (35%) improved cognitive performance at 4300 m (14,108 ft; for two tests out of nine) on the first day of exposure in male soldiers.[8] Nevertheless, the effects of hypobaria in normoxia on cognitive performance remain unexplored.

The assessment of cognitive performance in hypobaric normoxia and hypoxia is, therefore, of interest in the context of both aviation [pilots exposed to hypobaria in the cockpit using supplemental oxygen (HN)] or workers at high terrestrial altitude with supplemental oxygen, for example, in dormitories (HN) vs. high-altitude residents/mountaineers/workers without supplemental oxygen (HH). More precisely, pilots during flights at high altitude may be exposed to hypobaria in unpressurized cabin aircraft,[25] in case of sudden cabin depressurization during commercial flights,[23] or in military aircraft while breathing a hyperoxic gas mixture (i.e., HN). In the present study, we aimed to evaluate the putative effect of hypobaria during acute exposure between conditions with comparable P_IO_2 (NH vs. HH and NN vs. HN) on cognitive performance. We first hypothesized that increased altitude level in HH would gradually decrease cognitive performance. Hypoxic conditions (NH and HH) would induce cognitive performance impairment, with possibly larger alteration in HH than in NH. Finally, we hypothesized that cognitive performance in HN would be similar to NN.

METHODS

Subjects

Participating voluntarily in this study were 16 healthy pilot trainees (13 men and 3 women, age 26 ± 4 yr; height 177 ± 7 cm; weight 71 ± 9 kg). None of the subjects had experienced hypoxic exposure before enrollment in the present study and/or altitude exposure in the days before the test visits. A physician screened the subjects during a familiarization visit to ensure that they were healthy and did not report any medical or altitude-related issues. Moreover, none of the subjects was on medication during the present study.

This study was performed according to the Declaration of Helsinki and was approved by the Swiss Ethics Committee of Zürich (Swissethics, BASEC ID: 2017-00,752). This clinical trial can be found on ClinicalTrials.gov (ID: NCT03303118). All subjects were informed about all procedures of this study and gave their written informed consent before participating in this study.

Equipment

The "Konzentrations Leistungs Test-Revidierte Fassung" (KLT-R) is a concentration-performance test on paper with the use of a pencil which evaluates both quantity and quality of the capacity of concentration.[12] The whole KLT-R test consists of 9 blocks, each including 20 separate arithmetic tasks. In the present study, subjects performed only two blocks in each condition. After exactly 2 min, the subjects have to progress to the second block whatever the progress. In the present study, the signals to start, continue, and finish the test were provided by the experimenter using a timer to allow precise intervals (total test duration of 4 min). In order to avoid any learning effects, subjects were given two blocks in a randomized order using different but complementary versions of the KLT-R in each condition. Before enrollment in the present study, subjects were first drilled with KLT-R during a familiarization visit.

Heart rate (HR, bpm) was monitored during the entire experimental procedure using a heart rate monitor (Polar RS800CX, FI-90,440, Kempele, Finland). Pulse oxygen saturation (S_pO_2, %) was monitored at the left earlobe using an oximeter (3100 pulse oximeter, Nonin, Plymouth, MN) and acquired at 0.5 Hz. A subset of these data has been previously published in a parallel article on cerebrovascular hypercapnic responses,[2] but the analyses were not performed over the same periods and the number of subjects was lower ($N = 9$). Mean HR and S_pO_2 were calculated during the last minute of cognitive assessment in each condition.

Middle cerebral artery velocity (MCAv) and cerebral oxygen delivery (cDO_2) were measured as described previously.[2] Mean MCAv and cDO_2 were calculated in each condition during the last minute of the cognitive assessment.

At the end of every condition and of every washout period in NN, subjects were asked to report any kind of symptoms they had experienced during the past condition. Acute mountain sickness was not measured in the present study. We asked the subjects to report their symptoms by answering a questionnaire in order to have more qualitative data regarding personal feeling during each condition. Subjects did not report persisting symptoms from a previous condition/exposure at the end of each NN period. Subjects attested being symptom-free before starting the next condition. Moreover, 1-factor RM-ANOVA showed no physiological changes across NN conditions for S_pO_2 [F(degree of freedom = 4) = 1.61; $P = 0.190$] and MCAv [$F(4) = 0.137$; $P = 0.968$]. Moreover, there was no significant difference across all NN conditions regarding cognitive performance since percentage of error (Err%) and number of errors during KLT also remained similar along NN conditions [$F(4) = 1.07$; $P = 0.379$ and $F(4) = 1.24$; $P = 0.307$, respectively]. Therefore, these results suggest that subjects had fully recovered after each condition and that there was minimal learning effect for the KLT test.

Procedure

This study was conducted at the Aeromedical Center of the Swiss Air Force. Subjects came for a test visit and underwent experimental trials near sea level [Dübendorf, 440 m (1444 ft), P_B: 727 ± 4 mmHg] and in hypobaric and/or hypoxic conditions. After material installation, subjects underwent a pretest in normobaric normoxia. Then, in a randomized order, all subjects ($N = 16$) undertook four experimental conditions of 30 min [NN as a control condition, HH at 5500 m (18,045 ft), NH to simulate 5500 m of altitude, and HN] in a hypobaric chamber interspersed with three washout periods of 30 min in NN for a total session duration of 5 h. Subjects undertook KLT-R after 5 min of acclimatization followed by 7 min of electroencephalography recording (i.e., from T+12 to T+16 min). After completing the KLT-R and in order to evaluate sleepiness, subjects had to rate their subjective sleepiness state on the 9-point scale using the Karolinska Sleepiness Scale (KSS). Subjects were asked to avoid physical exercise, heavy meals, and alcohol or caffeine consumption 24 h before the test visit.

In order to evaluate putative hypobaric effect between normoxic and hypoxic conditions, P_IO_2 between NN vs. HN (141 ± 1 vs. 133 ± 3 mmHg) and NH vs. HH (74 ± 1 vs. 70 ± 2 mmHg) were compared by adjusting P_B in the hypobaric chamber or F_IO_2 based on a known equation [$P_IO_2 = (P_B - 47) \times F_IO_2$], when 47 mmHg corresponds to water vapor pressure at 37°C.[7] Subjects breathed ≈11% and ≈40% O_2 gas mixture (0.03% CO_2) concentration for NH and HN, respectively, while P_B remained similar between NH and NN, but was similarly decreased in HN and HH. In order to achieve the NH condition, the hypobaric chamber was closed, but was not depressurized while subjects were switched to another gas cylinder containing 11% oxygen to simulate normobaric hypoxia. Regarding the experimental conditions, the altitude indicator (i.e., altimeter) in the hypobaric chamber was hidden and changes in pressure were unknown by the subjects. Moreover, gas concentrations in the mask were also unknown by the subjects.

Statistical Analysis

One-way repeated measures ANOVA were assessed for all parameters (KLT parameters, HR, S_pO_2, MCAv, cDO_2, and KSS absolute values) to evaluate significance between conditions using statistical software (Jamovi project 2018, version 0.9, https://www.jamovi.org). Pearson or Spearman correlations were calculated between absolute or relative differences with NN in physiological responses and cognitive parameters, respectively. Significant difference was set for $P < 0.05$.

RESULTS

Cognitive and physiological parameters in NN, HN, NH, and HH are displayed in **Table I**. Number of calculations assessed was lower only in HH when compared to NN [$F(3) = 5.35$; $P = 0.018$] and HN ($P = 0.011$). The number of right answers was decreased to the same extent in NH and HH when compared to normoxic conditions [NN and HN, $F(3) = 17.1$; $P < 0.001$]. %Err increased in the two hypoxic conditions when compared to normoxic conditions. Δ%Err was not significantly correlated with ΔS_pO_2 in NH ($r = -0.484$, $P = 0.097$). There was no significant difference between NN vs. HN and NH vs. HH regarding cognitive performance.

S_pO_2 decreased in NH and HH compared to normoxic conditions, with significantly lower values in HH than NH [$F(2.1) = 102$; $P = 0.008$]. HH induced higher HR value than NH [$F(3) = 11.2$; $P = 0.026$]. MCAv was greater in HH only than in all other conditions. ΔMCAv was significantly correlated with ΔS_pO_2 in HH ($r = -0.741$, $P = 0.008$). Moreover, absolute MCAv was correlated with cDO_2 in HH ($r = 0.698$, $P = 0.012$) and NH ($r = 0.589$, $P = 0.044$). Estimated cDO_2 was significantly lower in NH [$F(3) = 3.4$; $P = 0.033$] and HH ($P = 0.016$) than in NN. Nevertheless, there was no significant correlation between KLT-R parameters and MCAv, cDO_2, or S_pO_2.

All symptoms for each condition are reported in **Fig. 1**. Interestingly, some symptoms were more represented in hypoxic conditions (NH and HH), such as: dizziness, tiredness, and calculation difficulties. Subjects reported being dizzy, having postural alterations, cold hands, and nausea only in NH and HH. Globally, subjects reported more symptoms in HH than NH (46 vs. 25 observations in HH vs. NH, respectively). Finally, two subjects had red eyes in the hypobaric conditions (HH and

Table I. KLT-R Parameters and Physiological Data During Cognitive Assessment.

	NN	HN	NH	HH	STATISTICS
Calculations (nb)	20.9 ± 5.8	21.1 ± 5.9	19.7 ± 4.2	18.9 ± 5.9*‡	$F(3) = 5.35$ $P = 0.003$
Right (nb)	19.5 ± 5.5	19.9 ± 5.6	16.9 ± 4.5***‡‡‡	16.7 ± 6.0***‡‡‡	$F(3) = 17.1$ $P < 0.001$
Errors (nb)	1.4 ± 0.9	1.3 ± 0.9	2.7 ± 1.8*‡	2.2 ± 0.9	$F(3) = 5.25$ $P = 0.004$
Errors (%)	6.5 ± 4.1	6.0 ± 4.0	14.3 ± 9.1**‡‡	12.9 ± 6.4**‡	$F(3) = 8$ $P < 0.001$
Physiological responses during KLT					
S_pO_2 (%)	99.7 ± 0.4	98.5 ± 2.2	83.5 ± 5.6***‡‡‡	78.9 ± 5.8***‡‡‡§§	$F(2.1) = 102$ $P < 0.001$
HR (bpm)	77.2 ± 9.6	79.5 ± 7.6	87.2 ± 11.8***	94.8 ± 11.7***‡‡‡§	$F(3) = 11.2$ $P < 0.001$
MCAv ($cm \cdot s^{-1}$)	48.3 ± 8.1	48.5 ± 9.5	52.1 ± 10.0	55.5 ± 11.6***‡‡‡§	$F(3) = 12.3$ $P < 0.001$
cDO_2 (n.u.)	1007 ± 166	983 ± 170	904 ± 208*	827 ± 154*	$F(3) = 3.4$ $P = 0.03$
KSS score	2.97 ± 0.86	3.43 ± 0.95	4.50 ± 1.41***‡	4.83 ± 2.08***‡‡	$F(3) = 10.4$ $P < 0.001$

S_pO_2: pulse arterial oxygen saturation; HR: heart rate; MCAv: middle cerebral artery cerebral blood flow velocity; cDO_2: estimated cerebral oxygen delivery; NN: normobaric normoxia; HN: hypobaric normoxia; NH: normobaric hypoxia; and HH: hypobaric hypoxia. Data are mean ± SD ($N = 16$).
* $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ for difference with NN; ‡ $P < 0.05$, ‡‡ $P < 0.01$, and ‡‡‡ $P < 0.001$ for difference with HN; § $P < 0.05$ and §§ $P < 0.01$ for difference with NH.

HN). Regarding subjective sleepiness of the subjects, KSS score was higher in NH and HH when compared to NN [$F(3) = 10.4$; $P < 0.001$] and HN ($P = 0.022$ and $P = 0.006$ for NH and HH, respectively). KSS score remained similar between NN and HN ($P = 0.664$) and NN conditions [$F(3) = 0.808$; $P = 0.497$].

DISCUSSION

The main aim of the present study was to evaluate the putative effect of hypobaria during acute exposure in normoxia and hypoxia on cognitive performance. NH and HH conditions had a deleterious effect on cognitive performance. However, cognitive performance was maintained in HN when compared to NN. Overall, these results confirm the deleterious effect of hypoxia and add new insights regarding the negligible influence of hypobaria on cognitive performance.

In the present study, cognitive performance was deteriorated in acute HH, whereas MCAv was increased. This is in line with previous studies that have shown a deleterious effect of hypoxia on cognitive function in humans.[9,24] As individuals ascend to altitude above 5000 m (16,404 ft), cognitive impairments to, for example, working memory, have been observed.[6,17] Moreover, working memory was reduced in pilots exposed to acute HH at a simulated altitude level of 10,000 m (32,808 ft).[17] It was also suggested in a recent review that cognitive performance tends to become

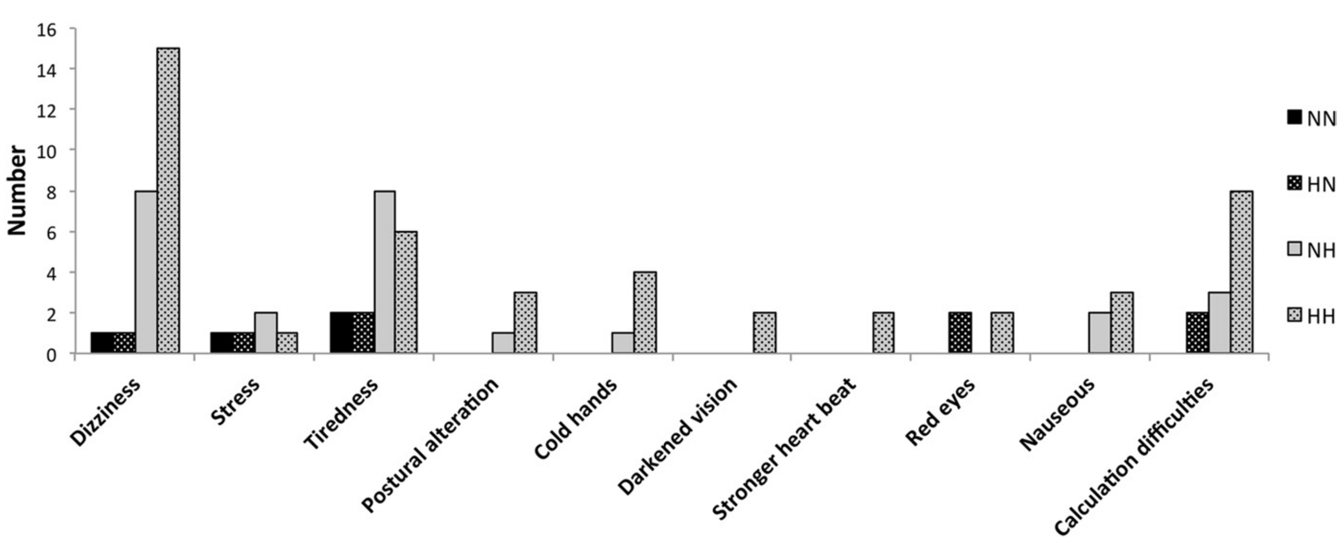

Fig. 1. Representation of the types of symptoms (X-axis) and number of symptoms reported by the subjects (Y-axis) for each condition: normobaric normoxia (NN), hypobaric normoxia (HN), normobaric hypoxia (NH), and hypobaric hypoxia (HH).

more impaired with increasing altitude, but with large interindividual variation among studies.[18] Ochi et al. reported a negative correlation between arterial oxygen saturation and executive function impairment during gradual simulated altitudes in NH.[26] However, ΔS_pO_2 was not significantly correlated with Δ%Err in NH in the present study.

The present study aimed to evaluate the putative hypobaric effect on cognitive performance in acute NH and HH. Both hypoxic conditions decreased cognitive performance to the same extent. McMorris et al. suggested that NH may be associated with greater reductions in cognitive function than HH.[20] However, NH induced comparable %Err than HH in the present study. Nevertheless, number of accomplished calculations decreased only in HH compared to NN. This suggests a slower speed in HH to assess the arithmetic task (i.e., lower arithmetic efficiency). Time to completion was greater at 5334 m (17,500 ft) and more than doubled at 7620 m (25,000 ft) in HH when compared to sea level,[3] which is in line with our results (i.e., decreased calculation numbers in HH). The mechanisms which explain how acute hypoxia negatively affects cognitive function are not completely understood, although it is likely a combination of factors, which may include neuronal damage[5] and fatigue.[40] Moreover, some physiological changes occur in the brain in HH, which can impair working memory tasks.[16] Surprisingly, we did not observe any correlations between changes in physiological responses to hypoxia (i.e., S_pO_2, MCAv, cDO_2) and cognitive performance.

To our knowledge, the present study is among the first studies to evaluate cognitive performance during acute exposure in NH vs. HH at high altitude. Overall, our results showed cognitive impairments in acute NH and HH when compared to NN, but with some slight differences (i.e., decreased speed in HH and higher number of mistakes in NH only).

The physiological differences between HH and NH (decreased S_pO_2 and increased heart rate in HH) are in line with several studies recently published.[21,22] In hypoxemia (i.e., decreased S_pO_2), the vasomotor tone enhances vasodilatation and consequently increases cerebral blood flow. In the present study, MCAv increased in NH and HH when S_pO_2 decreased in order to elevate cDO_2, which confirms cerebral vasodilation (i.e., in the MCA) in acute hypoxia to limit cDO_2 decrease.[13,41] However, the MCAv elevation in HH was insufficient to maintain cDO_2, resulting in putative cognitive performance reduction, whereas MCAv in NH remained similar to that in NN.

The present study aimed also to evaluate cognitive performance in acute HN in order to isolate the specific effect of hypobaria in the normoxic condition. Supplementary oxygen is known as a logical aid, which may counterbalance the negative side effects of hypobaric hypoxia on cognitive function, although literature on this topic scarcely exists.[38] One previous study showed cognitive performance improvement for two tests (out of a test battery of nine cognitive tests) at 4300 m (14,108 ft) in HH while breathing a supplemental oxygen gas mixture (35%).[8] The present results showed similar cognitive performance in HN and NN. One may speculate that the maintenance of S_pO_2 and cDO_2 in HN permitted the subjects to remain effective during cognitive task assessment.

In the present study, the subjects reported the symptoms they had experienced during each condition. The second aim of the present study was to collect qualitative data in order to evaluate the individual sensitivity and subjects' feelings when exposed to various acute hypoxic and hypobaric conditions. Interestingly, subjects reported more symptoms in HH than NH. Some symptoms seem representative of hypoxic exposure, such as dizziness, tiredness, postural alteration, cold hands, and nausea. Nevertheless, a few symptoms were reported only in HH (i.e., darkened vision, feeling of a stronger heartbeat), which may be related to hypobaria. Our observations are in line with previous studies in which acute mountain sickness differed qualitatively between NH and HH and was greater in HH than NH,[10,11,31] suggesting that NH and HH may be not completely interchangeable.[11]

The present study suggests that cognitive performance decreased in NH and HH to the same extent. However, the symptoms qualitatively differed between NH and HH. Military pilots often train in a flight simulator in NH. A recent study showed cognitive and flight performance impairment during training in normobaric hypoxia.[39] However, as previously recommended,[14,34,35] it remains paramount to regularly assess hypoxia awareness training, to teach military and civilian pilots to recognize their individual symptoms, in hypobaric hypoxia. Moreover, further research investigating the hypobaric normoxic environment are needed, as such circumstance may occur in flights during cabin depressurization at high altitude while breathing a hyperoxic gas mixture.

One may expect the differences in physiological parameters observed between conditions would be related to the differences in cognitive performance. However, no correlation was reported and this might be because the differences were not large enough or that the study was insufficiently powered. P_IO_2 was not perfectly matched between NN and HN or between NH and HH, corresponding to a slight difference of 400–500 m (1312–1640 ft) of altitude. This is less than the "natural" variation of "simulated altitude" due to the meteorological variability and, therefore, we argue that our results remain of practical significance. Finally, serial testing in a single day introduces significant confounders that need to be addressed, as cognitive impairment remains degraded for at least 2 h after acute hypoxia.[28] Moreover, the present study does not allow direct translation to prolonged exposure.[19]

In conclusion, the present study confirmed the detrimental effect of hypoxia on cognitive performance. Both normobaric and hypobaric hypoxia negatively affected cognitive performance with some slight differences, although the present results showed no additional deleterious effect of hypobaria on cognitive performance in hypoxia. However, symptoms seemed qualitatively different and more exaggerated in hypobaric than normobaric hypoxia. Finally, cognitive performance was unaffected in hypobaric normoxia when compared to normobaric normoxia, suggesting a negligible influence of hypobaria on cognitive performance in a normoxic environment.

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