Acute Mild Hypoxic Hypoxia Effects on Cognitive and Simulated Aircraft Pilot Performance

Fethi Bouak; Oshin Vartanian; Kevin Hofer; Bob Cheung

BACKGROUND: The effects of acute mild hypoxic hypoxia (HH) and physical activity on physiological measures, signs and symptoms, mood, fatigue, cognition, and performance on a simulated flight task were investigated between 8000 (8K; 2438 m) and 14,000 ft (14K; 4267 m).

METHOD: In a hypobaric chamber, 16 military helicopter pilots were randomly exposed to 4 altitudes and 3 physical exertion levels. After each exercise period, participants identified targets on a designated flight path on a desktop simulator and completed a cognitive test battery. Cerebral regional and finger pulse oxyhemoglobin saturation levels (rSO_2 and S_pO_2), heart and respiration rates were continuously monitored. Participants indicated their symptoms, mood and fatigue.

RESULTS: rSO_2 and S_pO_2 were affected by the increase of altitude and exercise level. Target identification accuracy and latency within the simulated flight task showed decrements at 8K, 10K (3048 m), 12K (3658 m), and 14K. Cognitive performance was degraded at 14K. More than 60% of the participants at 8K and 10K and more than 80% at 12K and 14K reported symptoms. Altitude increased symptoms, negative mood, general fatigue, and physical fatigue.

DISCUSSION: Our findings indicate a significant influence of mild HH on a number of outcome measures at altitudes above 10K, where operational restrictions are well established. In contrast, there was no clear influence of HH on performance at lower altitudes (i.e., 8K and 10K). The occurrence of HH symptoms and the decrements in target identification latency and accuracy at 8K and 10K may negatively impact flight performance and require further study.

KEYWORDS: hypobaric hypoxia, NIRS, cognitive performance, flight performance, mood, symptoms.

Bouak F, Vartanian O, Hofer K, Cheung B. *Acute mild hypoxic hypoxia effects on cognitive and simulated aircraft pilot performance*. Aerosp Med Hum Perform. 2018; 89(6):526–535.

Hypoxia can cause a number of subjective and objective signs and symptoms that can have serious and fatal consequences. At high altitude, the detrimental implications of hypoxic hypoxia (HH) on operations and flight safety are well documented in terms of gaseous exchange, times of useful consciousness, physical reaction, and performance levels.[10] In contrast, signs and symptoms onset and performance impairment below 15,000 ft (15K; 4572 m) are relatively less well characterized and difficult to quantify. Below 10K (3048 m), flight performance and safety are generally considered unaffected, and any HH symptoms experienced by aircrew are often seen as minor with no significant flight risks.[6,24] As a result, civilian and military authorities consider cabin altitudes below 10K to be safe, such that there is no requirement for supplemental oxygen (O_2) breathing by aircrew.

Nevertheless, there have been reports of hypoxic events in unpressurized and rotary-wing flights operating at altitudes below 10K. For example, Haerkens and Steen[9] reported that 31% of the Netherlands military helicopter pilots in Afghanistan experienced HH symptoms during a mission while 94% were convinced that reduced vision was likely due to hypoxia. In Canada, there have been anecdotal reports that physiological events similar to HH symptoms were experienced by military rotary-wing aircrew while operating without supplemental O_2 just under 10K. In a retrospective survey, Australian Army helicopter aircrew reported that symptoms consistent with hypoxia during operations at altitudes up to 10K might arise.[26] The incidence was higher for the physically active aircrew such

From Defence Research and Development Canada, Toronto Research Centre, Toronto, Ontario, Canada.

This manuscript was received for review in October 2017. It was accepted for publication in February 2018.

Address correspondence to: Fethi Bouak, Defence Research and Development Canada, Toronto Research Centre, 1133 Sheppard Ave. West, Toronto, ON, Canada M3K 2C9; fethi.bouak@drdc-rddc.gc.ca.

DOI: https://doi.org/10.3357/AMHP.5022.2018

as loadmasters when compared to pilots, suggesting that some of the symptoms might have been related to both the decrease of partial pressure of oxygen due to altitude and physical exercise, which further reduces arterial oxygenation.[17] Smith[27] suggested that physical activity at 7K (2133 m) may produce HH symptoms similar to that of a pilot resting at altitudes higher than 12K (3658 m). Thus, there are concerns over the possible negative effects of unprotected exposures on aircrew performance and safety in unpressurized aircrafts below 10K.

In the cognitive domain, a comprehensive literature review demonstrated that the effects of hypoxia [between 8K (2438 m) and 15K] on cognitive function extend to both elementary and higher-order cognitive tasks.[19] However, the results were generally inconsistent and difficult to quantify. The evidence suggesting a decrement of the pilot's flight performance was extrapolated largely from standard laboratory cognitive and psychomotor tests rather than from actual flight tasks in a simulator or in flight.[31] In addition, when cognitive performance was found to be affected by hypoxia, the decrements were relatively small and the operational significance unknown.[13,21] In fact, there is no evidence that cognitive tests were validated in advance as predictors of flight performance at altitude.[23] Recently, Cheung[3] questioned the usefulness of cognitive tasks in operational environments, arguing that because performance in operational settings is influenced by motivation, resilience, and individual compensatory responses of the aircrew, any performance decrement from cognitive test batteries would be difficult to interpret without validation in the operational environment, perhaps in conjunction with a simulator or in-flight investigation.

Few hypoxia research studies have been conducted in a flight simulation setting.[18] To our knowledge, the only previous study to have specifically reported any correlational results at low and moderate altitudes (i.e., 8K to 15K) found that cognitive decrements using the CogScreen®-Hypoxia Edition test battery under hypoxic conditions correlated with the degradation of flight performance at 15K.[23] Hypoxia studies using a flight simulator have demonstrated that the lowest altitude that can be associated with a measured decrease in pilot performance was 15K.[8,23] Nesthus et al.[18] found similar and consistent negative findings in terms of fixed-wing flight performance, but reported a significant increase in procedural errors due to hypoxia below 12.5K (3810 m). More recently, Steinman et al.[29] reported a significant difference in maintaining flight profile accuracy between 300 (91.4 m), 10K, and 15K ft in a fixed wing simulator. However, post hoc analysis revealed no significant difference in performance between 300 and 10K ft. Given that to date there has been no reported evidence of any performance decrement in a flight simulator at altitudes below 10K, it is possible that the effects of acute mild hypoxia could be subtle and difficult to detect, likely occurring only during novel and emergency situations.[12]

In this study, we attempted to investigate the acute effects of unprotected exposure to mild hypoxia on heart rate, respiration rate, subjective HH symptoms, subjective evaluation of mood and fatigue, cognitive performance (short-term memory, working memory, executive function), and flight simulator performance at altitudes between 8K and 14K (4267 m) with varying levels of physical exercise. Along with a decrease of cerebral oxyhemoglobin saturation due to diminishing oxygen content with increasing altitude, we hypothesized that cognitive performance, flight simulator performance, mood, and fatigue would be impaired by the increase of altitude from 8K to 14K. However, based on previous research, we expected that the impairments would likely be relatively subtle between 8K and 10K.

METHODS

Subjects

The study protocol was approved by the Defense Research and Development Canada's (DRDC) Human Research Ethics Committee. There were 16 male military helicopter pilots [age (mean ± SD): 32.5 ± 10.5 yr; weight: 80.1 ± 9.6 kg; height: 1.78 ± 0.07 m; flying experience: 860 ± 1329 h] who gave their written informed consent for participation as volunteers. A power analysis conducted prior to our study had indicated that a minimum sample size of 16 was required for testing our hypotheses.[7] Stress remuneration complied with the guidelines established by the Canadian Department of National Defense. All pilots had medical certification in accordance with Canadian Department of National Defense regulations and were screened by a medical officer for general health, medication use, and history of any condition that would exclude them from participation. Smokers were excluded.

Materials

The study was conducted in the DRDC hypobaric chamber at the Toronto Research Centre (TRC) with an elevation of 650 ft (198 m) above sea level, which corresponds to the ground level (GL).

Physiological monitoring. Oxyhemoglobin saturation level was monitored using pulse oxygen saturation (S_pO_2) at the fingertip and regional oxygen saturation (rSO_2) oximetry (Equanox by Nonin, Plymouth, MN) at the forehead. The placement of the two regional oximetry sensors on the forehead were aligned with the center of the right and left pupil, respectively. The sampling rate of both oximeters was set at 0.25 Hertz. Oximetry data were continuously collected throughout the experimental session, including baseline and post-altitude exposure. Data windows of 5 min from each of the physical exercise, simulation task, and cognitive testing portions of each signal were compiled together for 3 exercise intensities and 4 altitude levels for a total of 36 data windows for each of the 3 oximetry signals. Heart rate was obtained from pulse oximetry while respiration rate was obtained by using a strain-gauge across the chest of the participant (Hildalgo Limited, Cambridge, UK).

Flight simulation task. Flight simulation software developed at DRDC TRC was used to simulate one of the training mission profiles for CH-146 Griffon helicopter operation on a desktop computer with a 27″ flat panel screen. The software emulated and displayed flight instrumentation on the screen, and interacted with a physical cyclic control column, a collective, and rudder pedals. The participant was required to maneuver the aircraft along a predetermined route around an island while maintaining an altitude between 200 and 400 ft (61 to 122 m) above ground level with air speed maintained between 100 to 120 kn. Both altitude and airspeed were continuously recorded by the software. During each simulation run, the participants' task was to detect and correctly identify a single vehicle that appeared at a predetermined location along the flight route, unbeknownst to the subjects. The latency in detecting the vehicle was automatically inserted by event markers onto the data file while the accuracy of identifying the type of vehicle was recorded by the chamber's inside observer and the flight director. This flight simulation task took approximately 7 min to complete.

Cognitive test battery. A 30-min test battery of short-term memory (STM), working memory (WM), and executive function were conducted using the Cognitive Test Software (NTT Systems Inc., Toronto, ON, Canada). The following three tests were administered to each participant after the physical exercise phase at altitude:

1. The Delayed Matching-to-Sample Test (dMTS) is a classic measure of STM. It assesses spatial memory and pattern recognition skills and includes three phases: encoding, maintaining, and retrieving.[14] An 8×8 matrix of a red and green checkerboard pattern was presented for 10 s (encoding), removed, and then followed by a variable delay of 8 or 16 s. Two matrices were then presented side-by-side: the original matrix and a matrix with the color of two squares reversed. The participants were instructed to select the original matrix (retrieval) using the left or right arrow key. Accuracy, reaction time, and time-out errors (i.e., when the time of no response by the participant was reached) were recorded.
2. The adaptive dual n-back is a test of WM function that correlates with WM span.[5] The participant was presented with two types of stimuli: verbal (a series of letters) and on-screen (a series of positions of a square). He/she was prompted to report stimuli that were presented at earlier time points in the series. This task requires the participant to decide, on a trial-by-trial basis, whether a stimulus presented in the current trial matches a target stimulus presented a specific number of trials earlier in the sequence. The letter 'n' denotes the specific number of trials that separate the current trial from the target trial. Each session consisted of 10 blocks that took about 10–12 min to complete. The first block started with 1-back, but participants progressed forward, based on their performance, to the next level, i.e., to 2-back then 3-back and so on until the completion of 10 blocks, or remaining at the same level. After progressing forward, participants may also regress to a lower level (e.g., from 3-back to 2-back). For each session, the mean level of n-back (Average n) achieved by the participants was computed and used to represent their performance on this task. Each stimulus was presented for 500 ms. Interstimulus interval was a blank screen, presented for 2500 ms. Participants pressed the L-key for the auditory match (letters) and the A-key for the visual match (position).
3. The Stroop task is a classic task of executive function.[30] On each trial the participant was presented with a word and instructed to press one of four buttons corresponding to the color of the presented stimulus (i.e., red, blue, green, or yellow). Critically, on incongruent trials there is a mismatch between the color of the word and the content of the word (i.e., the word "BLUE" appears in green). In such cases there is a characteristic increase in reaction time and/or decrease in accuracy.

Self-reported, paper-and-pencil questionnaires assessing subjective signs and symptoms of HH, mood, and fatigue were administered at different stages of each experimental condition. No measures were collected at GL before altitude exposure. Their description is as follows.

1. Signs and symptoms (SSQ). Participants reported their subjective rating of hypoxia signs and symptoms using a questionnaire modeled after Smith.[26] In addition to obtaining a better understanding of the HH effect at altitude, the use of SSQ ensures that the participant was able to continue with data collection. The symptoms were grouped under five categories, each of which comprised of a number of items (shown within parenthesis): 1) Behavioral (change in mood, apprehension, euphoria); 2) Cognitive (impaired judgment, impaired memory/recall, mental confusion); 3) Physical (fatigue or drowsiness, feeling light-headed, headache, hot or cold flash, loss of muscle coordination, numbness, tingling of fingers or lips); 4) Psychological/Psychomotor (difficulty with communications, impaired manual dexterity, slowed reaction time); and 5) Visual (impaired peripheral vision, impaired visual acuity). The participant rated each item using the following scale: 0 for 'None,' 1 for 'Slight,' 2 for 'Moderate,' and 3 for 'Severe.'
2. The Positive and Negative Affect Schedule (PANAS) is a 24-item mood scale consisting of a number of words that describe different feelings and emotions.[32] Participants were asked to select the word that best described their current state.
3. The Multidimensional Fatigue Inventory (MFI) is a 20-item questionnaire to assess 5 dimensions of fatigue: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity.[25] Participants indicate how they feel on each of the five dimensions using a scale from 1 to 5.

Procedure

With the exception of the first two participants, all participants were grouped into pairs. Participants reported to the TRC on 5 consecutive days. On Day 1, they were given a consent form and were screened by a medical officer specialized in aerospace medicine. This was followed by a detailed briefing on the experimental protocol, procedures, and instrumentation before a full familiarization, including one practice session with the cognitive test battery and two practice sessions with the flight simulation task. The first session on the flight simulator was a familiarization with the flight path without target detection while the second included both detection and identification of a vehicle.

Data collection took place on Days 2–5. Participants in pairs were exposed to four levels of altitude: 8K, 10K, 12K, and 14K ft (2438, 3048, 3658, and 4267 m, respectively) above sea level on each of the 4 consecutive days. During each data collection, three physical exertion levels (Rest: 0W; Light: 30W; Moderate: 60W) on a bicycle ergometer (Monark, Model 818, Stockholm, Sweden) were employed, which correspond to the American College of Sports Medicine's "light" and "moderate" physical activity.[22] During physical exertion participants were instructed to maintain a target pedal rate of 30 $\pm$ 5 rotations per minute for 7 min. A single-blinded, within-subject design was employed. The order of presentation of the four levels of altitude was randomly assigned to each pair of participants, as was the sequence of presentation of the three levels of physical exertion to each participant during each altitude exposure. The random sequences for altitude and physical exertion were generated using the Research Randomizer software (www.randomizer.org). **Fig. 1** shows the sequence and the duration of each activity during Days 2–5. Data collection for all participants began at approximately the same time each day and was completed after approximately 4 h. The participants were instructed to refrain from actual flying between experimental sessions and for 24 h after completion of all sessions.

Each day upon arrival for the experimental session, participants completed a questionnaire on their daily physical activity, health condition, fatigue, and food and beverage intakes during the last 24 h. Physiological sensors were placed on the participants. As shown in Fig. 1, physiological measures were collected at GL for 15 min before and after hypoxic exposure. The participant was given a preflight briefing, including a review of the flight route. To check the participants' ear and sinuses, the chamber was depressurized to 5000 ft (1524 m) in 1 min then pressurized at 3000 ft/min (914 m/min). Upon reaching the randomly selected target altitude, participants remained at rest (denoted as 'Rest1' in Fig. 1) for 15 min before commencing physical exercise, followed by an assessment phase at rest (denoted as 'Rest2 + Assess'). The assessment included the flight simulator task, cognitive test battery (CTB), and subjective questionnaires. A single flight simulator was used, which necessitated creating two schedules to limit delays and potential visual distractions as participants completed iterations of the assessment phase inside the hypobaric chamber. For example, having two computers for CTB allowed both participants to complete portions of the CTB concurrently. However, at specific times, according to the schedules, Participant #1 would pause from the CTB and begin the simulation task while Participant #2 continued on with the CTB. Pauses from the CTB always occurred upon the completion of one of the three CTB tests. Upon completion of their tasks the participants switched, i.e., Participant #1 returned to his computer and continued with the CTB while Participant #2 paused from the CTB and began the simulation task. The two schedules were continuously alternated over the 12 assessment phases across Days 2–5. The entire activity sequence of 'Rest1,' 'Exercise,' and 'Rest2+Assess' (referred as 'Period' in Fig. 1) was repeated three times and was completed in approximately 1 h. The first two periods were followed by a recovery sequence of 7 min in which the participants breathed 100% O_2 via an aircrew oro-nasal mask (Gentex, MBU 12/P, Simpson, PA).

Statistical Analysis

A 4 (Altitude) $\times$ 3 (Exercise) repeated-measures Analysis of Variance (ANOVA) was used to analyze the effects of HH on each dependent variable (e.g., rSO_2 for oximetry, symptoms count, accuracy for dMTS, reaction time for Stroop, Average n for n-back, positive mood, and general and physical fatigue). When main effects for Exercise were not detected, the dependent variables were averaged across the three exercise levels and pooled at each altitude. The resulting means were compared using paired-samples t-tests across Altitude. Paired t-tests were used to examine the difference between GL and Altitude as well as between 'Before' and 'After' hypoxia exposure on all physiological measures. When the normality test failed, we used the Wilcoxon signed-ranks test or the Friedman repeated-measures ANOVA on ranks. The number of participants reporting HH symptoms was analyzed using McNemar's test. The correlation coefficient between cognitive performance and flight simulator performance was calculated using a Spearman's correlation test. Statistical significance was accepted at $P < 0.05$. All data are presented as mean $\pm$ SE of means (SEM).

RESULTS

All participants were able to complete the 5-d study. Their complete data sets were used in the analysis. Aside from reports of HH signs and symptoms (presented and discussed here), there were no appreciable issues or adverse effects reported during any of the experimental sessions.

Ground Level	Ascent	Altitude											Descent	Ground Level
		Period #1				Period #2				Period #3				
RestGL + Baseline		Rest1 + SSQ	Exercise	Rest2 + Assess	O_2 + SSQ	Rest1 + SSQ	Exercise	Rest2 + Assess	O_2 + SSQ	Rest1 + SSQ	Exercise	Rest2 + Assess		RestPost + Physiological measures
15 min		15	7	40	7	15	7	40	7	15	7	40		15 min

Fig. 1. Activity sequence and duration for each of the four altitude sessions.

Regional Oximetry

All the comparisons of oxyhemoglobin saturation levels were based on the last 5-min data of each activity window. There was no difference between the left and right regional oximetry measurements. The analysis of the right

rSO_2 is reported in this paper. The difference between daily baseline values and the difference between baseline and post-altitude exposure values for each day were not significant (**Table I**). Our results demonstrated a significant decrease in rSO_2 with increase in altitude from GL to any of the altitude levels ($P < 0.001$). Not surprisingly, a repeated measures ANOVA revealed a main effect of Altitude [$F(3, 45) = 56.4$, $P < 0.001$, partial $\eta^2 = 0.79$] and a main effect of Exercise [$F(2, 30) = 83.8$, $P < 0.001$, partial $\eta^2 = 0.85$]. The decrease in oxyhemoglobin saturation levels was amplified during the increase of either Exercise or Altitude. Once supplemental O_2 was administered, rSO_2 significantly increased beyond the corresponding values at GL ($P = 0.002$), Rest1 ($P < 0.001$), and Rest2+Assess ($P < 0.001$).

Similar to rSO_2, S_po_2 (see **Table II**) significantly decreased with the increase of altitude from GL ($P < 0.001$). At altitude, a repeated measures ANOVA revealed main effects of Altitude [$F(3, 45) = 219.0$, $P < 0.001$, partial $\eta^2 = 0.94$] and Exercise [$F(2, 30) = 26.5$, $P < 0.001$, partial $\eta^2 = 0.64$]. S_po_2 significantly increased with O_2 breathing at altitude (O_2 vs. Rest1: $P < 0.001$ and O_2 vs. GL: $P < 0.001$,). Heart rate increased with the increase of altitude and exercise (Table II). Specifically, there were significant increases from GL to altitude ($P < 0.05$), except between GL and 8K at Rest. At altitude, there were main effects of Altitude [$F(3, 45) = 5.5$, $P < 0.003$, partial $\eta^2 = 0.27$] and Exercise [$F(2, 30) = 65.7$, $P < 0.001$, partial $\eta^2 = 0.81$].

Hypoxic Hypoxia Signs and Symptoms

Our analysis was based on the cumulative (i.e., sum of) reported symptoms count (ΣS_p) over the 18 items of HH signs and symptoms regardless of the rating level. Participants gave their subjective ratings of HH at three conditions: 'End-Rest1' (before exercise), 'End-Assess' (after exercise, on completion of the test battery), and 'End-O_2' (during O_2 breathing) (Fig. 1). As shown in **Table III**, HH was reported at all altitudes and exercise levels. At End-Rest1, ΣS_p increased with Altitude, however, there were no significant Altitude effects, except between 10K and 12K or 10K and 14K ($P < 0.021$). There was a main effect between End-Rest1 and End-Assess such that ΣS_p increased ($P < 0.020$) and then decreased ($P < 0.021$) to the level of End-Rest1 values with the administration of supplemental O_2. A Friedman repeated measures ANOVA on ranks of ΣS_p at End-Assess indicated that there was a main effect of Altitude [$\chi^2(3) = 19.3$, $P < 0.001$], but showed no effect of Exercise at each altitude. To further investigate the effect of Altitude regardless of Exercise, ΣS_p was averaged across the three exercise levels and pooled at each altitude. The resulting means were compared using a series of Wilcoxon signed-ranks tests which showed that ΣS_p at End-Assess was significantly higher at 12K and 14K than at 8K or 10K (Table III). In contrast, there was no difference in ΣS_p between 8K and 10K. We also analyzed the number of participants reporting HH signs and symptoms (N_p) and the total count of their symptoms (S_{cat}) for each of the following categories: Behavioral, Cognitive, Physical, Psychomotor, and Visual. To compare S_{cat} between the five categories, we normalized S_{cat} by the number of symptoms in each category and then divided the result by the total count of symptoms across the five categories to obtain the percentage of reported symptoms by category. As shown in **Fig. 2** and **Fig. 3**, more participants ($P < 0.001$) reported more symptoms ($P < 0.001$) in each category at End-Assess than at End-Rest1. Physical symptoms were more common ($P < 0.001$) at End-Rest1 while cognitive symptoms were more common ($P < 0.001$) at End-Assess regardless of the altitudes. N_p at End-Assess was significantly higher at 12K and 14K than at 8K and 10K ($P < 0.001$).

Flight Simulation Task and Cognitive Performance

The helicopter simulator task and CTB were performed during 'Rest2+Assess', after physical exertion (Fig. 1). Each task was administered 12 times across Days 2–5. **Table IV** shows the mean (SEM) data for flight performance, target identification measurements, and the three cognitive tasks at GL and the four altitudes. Initial analysis indicated that there was no evidence of an order effect for any of the tasks. Friedman repeated measures ANOVA on ranks showed that the variables for which there were any statistical significant effects between GL and any of the altitude levels were the accuracy of target identification [$\chi^2(4, 16) = 14.9$, $P = 0.005$] and the latency (i.e., time between detection and identification) [$\chi^2(4, 16) = 27.1$, $P < 0.001$]. At altitude, neither the increase of Altitude from 8K to 14K nor Exercise had any effects on the accuracy of target identification and the latency.

Low scores on the dMTS, n back, and the accuracy of the Stroop task indicate greater impairments for short-term

Table I. Mean (SEM) Regional Blood O_2 Saturation (rSO_2) for All Conditions.

		ALTITUDE				
	GL BASELINE	REST1	EXERCISE	REST2 + ASSESS	O_2 BREATHING	GL POST-EXPOSURE
8K	73.6 (0.8)	70.6 (0.9)*	30W: 69.7 (0.8)*,‡	71.4 (0.8)*	77.9 (1.5)*,‡	73.3 (1.0)
			60W: 68.6 (1.0)*, ‡,‡‡			
10K	73.6 (1.0)	68.9 (0.9)*	30W: 67.2 (1.1)*,**,‡	69.6 (0.9)*,**	76.7 (1.5)*,‡	72.9 (1.2)
			60W: 65.9 (1.0)*,**, ‡,‡‡			
12K	73.7 (0.9)	66.4 (0.8)*,**,†	30W: 63.6 (0.9)*,**,†,‡	66.8 (0.8)*,**,†	77.1 (1.5)*,‡	73.6 (1.0)
			60W: 62.3 (1.0)*,**,†,‡,‡‡			
14K	73.7 (0.8)	63.0 (1.1)*,**,†,††	30W: 59.3 (1.1)*,**,†,††,‡	63.0 (1.1)*,**,†,††	76.2 (1.8)‡	73.7 (1.1)
			60W: 57.9 (1.0)*,**,†,††,‡,‡‡			

GL: ground level; Rest1: rest phase 1; Rest2 + Assess: rest 2 and assessment phase; 8K, 10K, 12K, 14K: four levels of altitude in thousands of feet; 30W, 60W: two levels of exercise in Watts.
* Significant difference from GL values (baseline and post-exposure) ($P < 0.01$); **significant difference to corresponding value at 8K ($P < 0.01$); †significant difference to corresponding value at 10K ($P < 0.01$); ††significant difference to corresponding value at 12K ($P < 0.01$); ‡significant difference to corresponding value at Rest1 before exercise ($P < 0.05$); ‡‡significant difference to corresponding value at 30W ($P < 0.05$).

Table II. Mean (SEM) for Pulse Blood O_2 Saturation (S_pO_2) and Heart Rate (HR) for All Conditions.

			ALTITUDE				
				EXERCISE			
		GL BASELINE	REST1	30W	60W	O_2 BREATHING	GL POST-EXPOSURE
8K	S_pO_2	96.7 (0.3)	91.8 (0.3)*	91.4 (0.4)*	91.0 (0.4)*,‡	98.6 (0.1)*,‡	96.7 (0.2)
	HR	74.9 (2.6)	75.2 (2.2)	92.7 (2.7)*,‡	109.4 (4.8)*,‡,‡‡	70.6 (2.1)*,‡	73.7 (2.6)
10K	S_pO_2	96.9 (0.3)	89.4 (0.4)*,**	88.1 (0.6)*,**,‡	87.0 (0.6)*,**,‡	98.7 (0.1)*,‡	97.0 (0.2)
	HR	75.4 (2.4)	77.7 (2.1)*	94.3 (3.0)*,‡	112.8 (5.5)*,‡,‡‡	71.6 (2.1)*,‡	75.0 (2.1)
12K	S_pO_2	96.8 (0.2)	85.7 (0.5)*,**,†	82.5 (0.9)*,**,†,‡	81.9 (0.9)*,**,†,‡	98.7 (0.1)*,‡	96.8 (0.2)
	HR	76.2 (2.9)	78.8 (2.7)*,**	95.3 (3.4)*,‡	114.4 (5.3)*,‡,‡‡	71.8 (2.6)*,‡	77.2 (3.2)
14K	S_pO_2	96.4 (0.3)	81.3 (0.9)*,**,†,††	77.4 (1.0)*,**,†,††,‡	76.8 (0.8)*,**,†,††,‡	98.4 (0.2)*,‡	96.5 (0.2)
	HR	77.2 (2.6)	84.2 (2.7)*,**,†,††	105.9 (3.7)*,**,†,††,‡	115.2 (6.3)*,‡	74.0 (2.6)*,‡	77.5 (2.3)

GL: ground level; Rest1: rest phase 1; 8K, 10K, 12K, 14K: four levels of altitude in thousands of feet; 30W, 60W: two levels of exercise in Watts.
* Significant difference from ground level (GL) values (baseline and post-exposure); **significant difference to corresponding value at 8K; †significant difference to corresponding value at 10K; ††significant difference to corresponding value at 12K; ‡significant difference to corresponding value at Rest1 before exercise; ‡‡significant difference to corresponding value at 30W.

memory, working memory, and executive functions, respectively. High scores on the reaction time of the Stroop task are indicative of reduced executive functions. dMTS data were analyzed using a within-subjects ANOVA where Altitude and Exercise were entered into the analysis as repeated-measures variables. The dependent variable was accuracy (i.e., number correct out of 25 trials). There were no effects of Altitude or Exercise on accuracy. To further investigate the effect of Altitude on accuracy, performance was averaged across the three exercise levels, pooled at each altitude level, and compared using paired-samples *t*-tests across Altitude. As shown in Table IV, the results demonstrated that accuracy at 14K was significantly worse than accuracy at 10K [$t(15) = 2.19$, $P = 0.045$]. Working memory data involving the adaptive dual n-back task were analyzed using a within-subjects ANOVA where Altitude and Exercise were entered as repeated-measures variables into the analysis. The dependent variable was Average n across all blocks in each session. Exercise had no effect on Average n. There was, however, a significant main effect for Altitude [$F(3, 45) = 3.15$, $P = 0.034$, partial $\eta^2 = 0.17$]. To further investigate the effect of Altitude on Average n, we averaged performance for each altitude level across the three exercise levels, and compared the means using paired-samples *t*-tests across Altitude levels. The results demonstrated that Average n at 14K was significantly worse than Average n at 8K [$t(15) = 2.67$, $P = 0.017$] and 10K [$t(15) = 2.31$, $P = 0.035$]. In other words, there are no significant differences at the lower altitudes of 8K and 10K. Stroop data were analyzed using a within-subject ANOVA where Altitude, Exercise, and Congruency (congruent, incongruent) were entered as repeated-measures variables into the analysis. The dependent variable was accuracy (i.e., percent correct). Exercise and congruency had no effects on accuracy. There was, however, a significant main effect for Altitude [$F(3, 45) = 2.81$, $P = 0.050$, partial $\eta^2 = 0.16$].

Subjective Measures of Affect (PANAS) and Fatigue (MFI)

These two questionnaires were administered during the assessment period, after physical exercise. A Friedman repeated-measures ANOVA on ranks of mood and fatigue data indicated that there was a main effect of Altitude on positive mood and general and physical fatigue ($P < 0.001$), but showed no effect of Exercise at each altitude. To further investigate the effect of Altitude regardless of Exercise, both mood and fatigue data were averaged across the three exercise levels and pooled at each altitude (Table III). Participants reported significantly lower positive mood ($P < 0.001$) and significantly greater general and physical fatigue as a function of Altitude ($P < 0.05$). A series of Wilcoxon signed-ranks tests between altitude levels demonstrated that whereas there was no difference in positive mood and general fatigue between 8K and 10K, those two levels exhibited significant differences vs. 12K and 14K ($P < 0.05$ for either dependent variable), which in turn did not differ among themselves. Physical fatigue was significantly lower at 8K compared to 12K ($P < 0.02$) and 14K ($P < 0.02$).

DISCUSSION

The main findings from this study is that mild HH significantly increased signs and symptoms and general and physical aspects

Table III. Mean (SEM) Data for Cumulative Count of HH Symptoms (ΣS_p) Per Participant, Positive Mood, and Fatigue (Both General and Physical).

	HH SIGNS AND SYMPTOMS (ΣS_p)					
	END-REST1	END-ASSESS	END-O_2	POSITIVE MOOD	GENERAL FATIGUE	PHYSICAL FATIGUE
8K	0.7 (0.3)	1.8 (0.4) †,‡	0.7 (0.2)	34.5 (2.0)	6.7 (0.4)	6.1 (0.5)
10K	0.5 (0.2)	1.8 (0.5) †,‡	0.5 (0.2)	34.7 (2.1)	7.1 (0.5)	6.5 (0.5)
12K	1.2 (0.3)**	3.8 (0.7)*,**,†,‡	0.8 (0.3)	31.9 (2.1)*,**	8.3 (0.6)*,**	7.0 (0.6)*
14K	1.6 (0.4)**	4.2 (0.8)*,**,†,‡	1.2 (0.3)	32.8 (2.2)*,**	8.3 (0.6)*,**	7.3 (0.6)*

HH: hypoxic hypoxia; End-Rest1: end of rest phase 1; End-Assess: end of assessment phase; End-O_2: end of recovery/oxygen-breathing phase; 8K, 10K, 12K, 14K: four levels of altitude in thousands of feet.
* Significant difference to corresponding value at 8K ($P < 0.05$); **significant difference to corresponding value at 10K ($P < 0.05$); †significant difference to corresponding value at Rest1 before Exercise ($P < 0.05$); ‡significant difference to corresponding value at End-O_2 ($P < 0.05$).

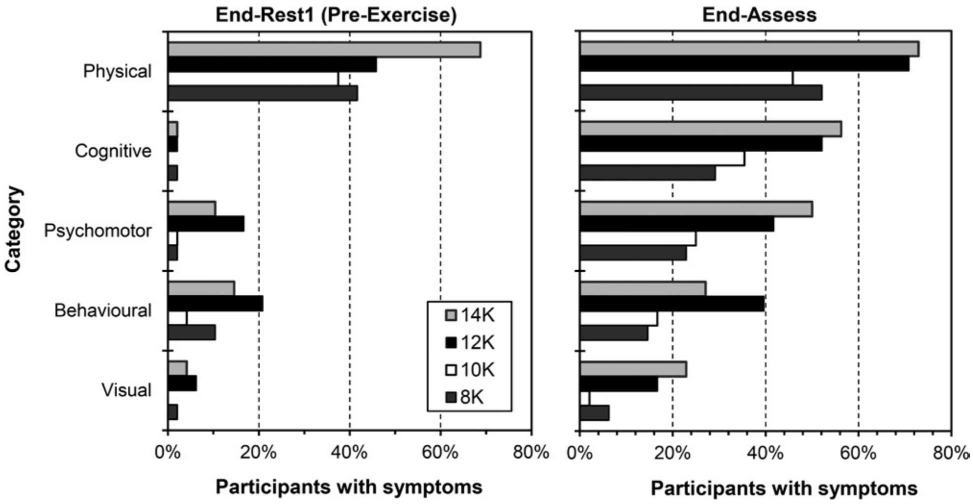

Fig. 2. Percentage of participants with HH symptoms in each category at the end of the rest period (left) and at the end of the assessment period (right).

of fatigue and decreased positive mood at 12–14K. More than 60% of the participants at 8K and 10K and more than 80% at 12K and 14K reported symptoms. These findings are similar to that found by Legg et al.,[12] who reported a reduction of vigor and an increase of fatigue at 12K. In the simulated flight task, target identification accuracy and latency were significantly affected between GL and altitude (8–14K). Cognitive performance was significantly degraded at 14K only. As expected, our results showed a significant reduction of S_pO_2 and rSO_2 at altitude, and this reduction was exacerbated with physical exercise in all conditions (except between 10K and 8K at rest for rSO_2, and between rest and 30W at 8K and 30W and 60W at all altitudes for S_pO_2). With oxygen content of the atmosphere diminishing with increasing altitude, rSO_2 and S_pO_2 levels were consistent with published data, suggesting that the hypoxic environment in this study was appropriate.[16,20,21] On average, all oxygen saturation data returned to baseline levels 5–10 min following all altitude exposures (8–14K). Cerebral regional oximetry provides a convenient and noninvasive method in tracking changes in cerebral tissue oxygenation during hypoxia, and offers a more sensitive measure of oxygen level than pulse oximetry, notwithstanding certain limitations and assumptions.[4]

Although participants reported significantly fewer symptoms at 8–10K compared to 12–14K, they did nevertheless report some symptoms at 8–10K as well. The increase of the reported HH symptoms during the rest period after altitude exposure was similar to the increase during the rest period after exposure to exercise. Current findings confirm the anecdotal and surveyed reports of the occurrence of classic HH signs and symptoms by Royal Canadian Air Force and other helicopter pilots at low altitude levels,[9,28] and are consistent with published studies.[2,21] Regardless of altitude or exercise level, more participants reported a higher number of symptoms after the assessment activity (End-Assess) vs. the symptoms reported before exercise (End-Rest1). There are two likely explanations. First, given that the second set of symptoms was reported 50 min later, we suspect that a host of possible reasons, including physical exertion, fatigue, time-on-task tiredness, and boredom may have led to the negative effects, generating more symptoms that are comparable to HH symptoms. The second explanation is that the participants may have actually been affected by staying longer at altitude given that symptoms were significantly less frequent after only 6 min of breathing supplemental O_2 at altitude (the SSQ questionnaire was administered at the 6th minute of the 7-min period of supplemental O_2). We suggest that the combination of these two reasons may have contributed to the current findings.

The helicopter simulation task designed for this study was an attempt to elucidate the effects of mild hypoxia on specific aspects of cognition hypothesized to be required for task performance. Simulated flight performance measures (maintaining altitude and air speed) showed no statistically significant differences between GL and altitude exposure, or across altitudes from 8K to 14K. Task requirements in maintaining altitude and air

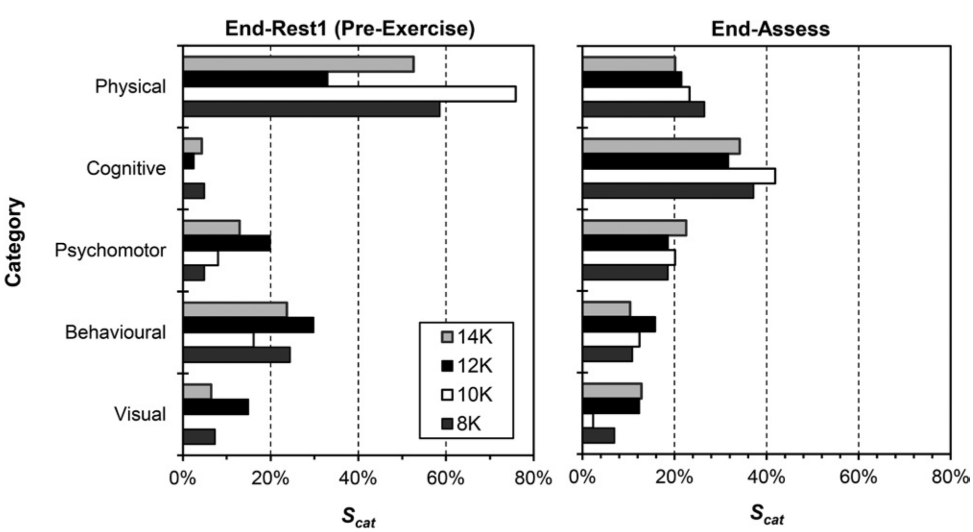

Fig. 3. Percentage of reported HH symptoms count in each category (S_{cat}) at the end of the rest period (left) and at the end of the assessment period (right).

Table IV. Mean (SEM) Data for the Flight Simulator Task and the Cognitive Test Battery.

	GL	8K	10K	12K	14K
Flight Performance:					
Percentage of time in maintaining correct airspeed	74 (3)	71 (3)	72 (3)	72 (3)	71 (3)
Percentage of time in maintaining correct altitude	77 (3)	81 (2)	78 (3)	79 (2)	76 (3)
Target Detection and Identification:					
Accuracy in target identification (%)	100 (0)	88 (5)*	90 (4)*	81 (6)*	77 (6)*
Misses – no detection, no identification (%)	0.0	0.0	0.0	8.3 (4.8)	6.3 (3.4)
Latency: Time between detection and identification (s)	16.4 (4.0)	33.1 (5.6)*	43.6 (14.8)*	76.3 (24.7)*	62.8 (22.7)*
dMTS: Accuracy (Max = 25)		20.3 (0.3)	20.0 (0.4)	19.4 (0.6)	18.9 (0.4)†
Adaptive Dual n-back: Average n		2.8 (0.1)	2.7 (0.1)	2.7 (0.1)	2.5 (0.1)**,†
Stroop:					
Accuracy (%)					
Congruent		98.1 (0.5)	98.2 (0.4)	98.1 (0.4)	96.9 (0.7)**,†,††
Incongruent		98.1 (0.3)	98.3 (0.3)	97.5 (0.5)†,‡	97.4 (0.5)†
Reaction time (s)					
Congruent		0.81 (0.03)	0.79 (0.03)	0.80 (0.03)	0.82 (0.03)
Incongruent		0.86 (0.03)‡	0.85 (0.04)‡	0.86 (0.04)‡	0.90 (0.04)‡

GL: ground level; 8K, 10K, 12K, 14K: four levels of altitude in thousands of feet.
* Significant difference from Ground Level (GL) values ($P < 0.05$); **significant difference to corresponding value at 8K ($P < 0.05$); †significant difference to corresponding value at 10K ($P < 0.05$); ††significant difference to corresponding value at 12K ($P < 0.05$); ‡significant difference between congruent and incongruent data at the same altitude ($P < 0.01$).

speed within a range appeared not to have been affected by the degree of hypoxia induced in this study. Although target identification appeared to be significantly affected between GL and altitude, there were no significant differences between levels of altitude; however, trends were observed which showed decrement in target performance may exist with the increase in altitude. While only a small number of studies have reported a clear hypoxia-related performance deficit in the flight simulator,[8,29,31] none of these studies have demonstrated any significant effects between GL and altitudes below 15K. Although Nesthus et al.[18] found no difference in simulated flight performance between GL and altitudes below 12.5K, they reported a noticeable rise of unsafe and high risk flying errors during the cruise phase and the descent phase of flights from 10K and 12.5K. In our study, the only procedural errors that we consistently captured were 'target misses.'

In this study we combined three cognitive tasks (i.e., dMTS, n-back, and the Stroop) that broadly covered various aspects of cognitive function to assess performance decrements due to hypoxia at low altitude. Two interesting results are worth mentioning. First, none of the tasks exhibited any significant change due to hypoxia between 8K and 10K, or between these two altitudes and 12K in WM. Second, the results suggest that the altitude that appears to bring about performance decreases is found between 10K and 12K for STM and WM, and between 12K and 14K for executive functions. Our findings are consistent with many previous studies described in the introduction in that they showed only a slight or no effect of mild hypoxia on cognitive performance at altitudes lower than 12K. It is possible that different aspects of cognitive function may be susceptible to impairments at different altitudes, in turn contributing to a diversity of results across studies linking HH to cognition. The presence and significance of hypoxia on cognitive impairment at or below 10K or 12K remain contentious and inconsistent for various reasons, including the use of different types of cognitive tests, training and or exposures durations, and individual compensatory mechanisms, among others.[19] In addition, the type of cognitive tests that were used in laboratory studies have not been validated against performance tasks that are employed in simulated and actual flight environments.[3] It has been suggested that the lack of impaired cognitive performance during mild hypoxia exposure may be due to less demanding tests that are insufficiently susceptible to low altitudes.[11,15,20] Another explanation could be the relatively small sample sizes in most studies.

To arrive at a clearer picture of the relationship among various outcome measures, correlations were computed to assess the relationship between performance measures from the flight simulator and cognitive tests, and between subjective measures of HH symptoms, mood, and fatigue. There were correlations between the flight simulator task and WM, between mood measures and STM, and between HH symptoms and both STM and MFI measures. Specifically, increases of the mean percentage of correct target identification were correlated with increases of Average n ($P = 0.005$) in the WM task. However, count of HH signs and symptoms (ΣS_p) at End-Assess were negatively correlated with correct matching ($P = 0.009$) while positively correlated with general fatigue ($P = 0.015$). Finally, increases of positive mood were correlated with increases in correct matching ($P = 0.046$) and decreases of both general and physical fatigue ($P < 0.001$ for general and $P < 0.001$ for physical). With the exception of the correlations between positive mood and fatigue, all the other correlations coefficients were low and weakly predictive of one another.

Limitations and Recommendations

Limitations of this study include primarily 1) the lack of comparison between GL and Altitude in some of the subjective and cognitive measurements; 2) not monitoring acute hypoxic ventilatory response known to manifest between 8K and 18K where there is a complex interplay between hypoxia, hyperventilation, hypocapnia, cerebral blood flow responses, and cognitive performance; and 3) small sample size. We offer the following considerations for the interpretation of our findings. First, no conclusion can be drawn regarding any impairment of cognitive function, or increase of HH signs and symptoms, negative mood, or fatigue between GL (both pre- and postexposure) and Altitude. With respect to HH signs and symptoms, participants were only asked about their physical activities, alcohol consumption, food, medication, fatigue level, and any concern when they first reported to the chamber each morning. None of the participants reported any concerns at GL. However, Pilmanis et al.[21] showed that minor to no differences in symptoms was found between GL and 8K, while differences between GL and 12K were found to be significant. Balldin at al.[2] observed a significant increase in reported hypoxia and acute mountain sickness symptoms at 10K vs. those reported at GL. In comparing mood between baseline and altitude (8K and 12K), Legg et al.[12] observed significant changes of fatigue and vigor at 12K only. Baseline subjective measures at GL should be included in future empirical investigations.

Second, with respect to the small sample size, our power analysis had indicated that this number was the minimum adequate for this type of experiment, and our resources and timing for the experiment did not allow us to have additional participants. A larger sample size would have enabled us to explore individual differences in a way that was not feasible with our rather limited sample size.[1,13,21] In addition, our sample size was relatively "homogeneous" as all the participants were male helicopter pilots. The use of different genders and roles (e.g., flight engineers) could contribute to our understanding of the impact of mild hypoxia on different populations. Third, physical exertion is known to lower the altitude at which hypoxia effects manifest. Except for the physiological measures, this study did not find any statistically significant effects of physical exertion on the other dependent measures at altitudes 8–14K. One of the reasons could be that the different tasks were not administered during exercise but only postexercise, at which point the effects of exertion may have diminished. To replicate cockpit workload, future studies could be extended to have the participants exercising during the different performance evaluations. In addition, flying and procedures errors should be explicitly captured to investigate HH effects on flight performance. More demanding and realistic scenarios should be used in a flight simulator that includes advanced features, such as better visual flight performance variables.

In conclusion, our findings indicate significant effects of mild HH on a number of subjective and objective measures at altitudes at 12–14K compared to 8–10K. At lower altitudes (i.e., 8–10K), our results are consistent with previous studies for the physiological measures and reported HH symptoms. The absence of baseline measurements at GL does not enable us to draw any additional conclusion for the cognitive tasks in comparison to any altitude level.

ACKNOWLEDGMENTS

This study was funded by the Canadian Department of National Defence (Portfolio: Air-Navy; Project: 03aa – Air Human Effectiveness).

The authors would like to thank the study participants for their dedication and commitment. The technical and data analyses support provided by Robert Miles and Kristen Thompson, and the support of various other groups within DRDC–Toronto Research Centre and other CAF Units is much appreciated. The authors also acknowledge the assistance of the members of the Canadian Forces Environmental Medicine Establishment (CFEME). We would also like to thank Madeleine D'Agata and Jenna Crocker for help with data analysis.

Authors and affiliations: Fethi Bouak, MASc, Ph.D., Oshin Vartanian, B.Sc., Ph.D., and Kevin Hofer, B.Sc., M.A., Defence Research and Development Canada (DRDC), Toronto Research Centre, and Bob Cheung, M.Sc., Ph.D., University of Toronto, Toronto, Ontario, Canada.

REFERENCES

1. Asmaro D, Mayall J, Ferguson S. Cognition at altitude: impairment in executive and memory processes under hypoxic conditions. Aviat Space Environ Med. 2013; 84(11):1159–1165.
2. Balldin UI, Tutt RC, Dart TS, Whitmore J, Fischer J, Harrison RT, et al. Effects of 12 hours of low-grade hypoxia at 10,000 ft at night in special operations forces aircraft operations on cognition, night vision goggle vision and subjective symptoms. San Antonio (TX): U.S. Air Force Research Laboratory; 2007. Report No.: AFRL-HE-BR-TR-2007-0047.
3. Cheung B. Relevance of elemental cognitive performance tasks to operational environments [abstract]. Aerosp Med Hum Perform. 2016; 87(3):176–177.
4. Cheung B, Bouak F, Vartanian O, Hofer K. Acute effects of mild hypoxia between 8,000 to 14,000 feet: a pilot study. Toronto (Canada): Defence Research and Development Canada; 2015. Report No.: DRDC-RDDC-2015-R161.
5. Conway AR, Kane MJ, Bunting MF, Hambrick DZ, Wilhelm O, Engle RW. Working memory span tasks: a methodological review and user's guide. Psychon Bull Rev. 2005; 12(5):769–786.
6. Ernsting J. Prevention of hypoxia—acceptable compromises. Aviat Space Environ Med. 1978; 49(3):495–502.
7. Faul F, Erdfelder E, Lang AG, Buchner AG. *Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007; 39(2):175–191.
8. Gold RE, Kulak LL. Effect of hypoxia on aircraft pilot performance. Aerosp Med. 1972; 43(2):180–183.
9. Haerkens MHTM, Steen J. The possible need for supplementary oxygen in AH-64D night operations. Proceedings of the NATO Human Factors and Medicine Panel HFM-141 Symposium on Human Factors and Medical Aspects of Day/Night All Weather Operations: Current Issues and Future Challenges; April 23–25, 2007; Crete, Greece. Brussels (Belgium): NATO RTO; 2007.
10. Harding RM, Gradwell DP. Hypoxia and hyperventilation. In: Ernsting J, Nicholson AN, Rainford DJ, editors. Aviation medicine. Oxford (England): Butterworth-Heinemann; 1999:43–58.
11. Hewett KJ, Curry IP, Rath E, Collins SM. Subtle cognitive effects of moderate hypoxia. Fort Rucker (AL): U.S. Army Aeromedical Research Laboratory; 2009. Report No.: USAARL 2009-17.
12. Legg SJ, Gilbey A, Hill S, Raman A, Dubray A, et al. Effect of mild hypoxia in aviation on mood and complex cognition. Appl Ergon. 2016; 53(Pt. B):357–363.
13. Legg S, Hill S, Gilbey A, Raman A, Schlader Z, Mündel T. Effect of mild hypoxia on working memory, complex logical reasoning, and risk judgment. Int J Aviat Psychol. 2014; 24(2):126–140.
14. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss and stress on cognitive performance and mood during U.S. Navy SEAL training. Psychopharmacology (Berl). 2002; 164(3):250–261.
15. Linde L, Gustafsson C, Ornhagen H. Effects of reduced oxygen partial pressure on cognitive performance in confined spaces. Mil Psychol. 1997; 9(2):151–168.

16. McFarland RA. Psychophysiological implications of life at altitude and including the role of oxygen in the process of aging. In: Yousef M, Horvath SM, Bullard RW, editors. Physiological adaptations. New York (NY): Academic Press; 1972:157–181.
17. Muhm JM, Rock PB, McMullin DL, Jones SP, Lu IL, et al. Effect of aircraft-cabin altitude on passenger discomfort. N Engl J Med. 2007; 357(1): 18–27.
18. Nesthus TE, Rush LL, Wreggit SS. Effects of mild hypoxia on pilot performances at general aviation altitudes. Washington (DC): Office of Aviation Medicine; 1997. Report No.: DOT/FAA/AM-97/9.
19. Petrassi FA, Hodkinson PD, Walters PL, Gaydos SJ. Hypoxic hypoxia at moderate altitudes: review of the state of the science. Aviat Space Environ Med. 2012; 83(10):975–984.
20. Phillips JB, Hørning D, Funke ME. Cognitive and perceptual deficits of normobaric hypoxia and the time course to performance recovery. Aerosp Med Hum Perform. 2015; 86(4):357–365.
21. Pilmanis AA, Balldin UI, Fisher JR. Cognition effects of low-grade hypoxia. Aerosp Med Hum Perform. 2016; 87(7):596–603.
22. Pollock ML, Gaesser GA, Butcher JD, Després J-P, Dishman RK, et al. American College of Sports Medicine position stand: the recommended quantity and quality of exercise for developing and maintaining cardio-respiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc. 1998; 30(6):975–991.
23. Rice GM, Vacchiano C, Moore JL. Correlation of simulated flight and neuropsychological performance at simulated altitude [abstract]. Aviat Space Environ Med. 2006; 77(3):274.
24. Sheffield PJ, Heimback RD. Respiratory physiology. In: DeHart RL, editor. Fundamentals of aerospace medicine. Baltimore (MD): Williams & Wilkins; 1996:69–108.
25. Smets EM, Garssen B, Bonke B, De Haes JC. The multidimensional fatigue inventory: psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995; 39(3):315–325.
26. Smith A. Hypoxia symptoms reported during helicopter operations below 10,000 feet: a retrospective survey. Aviat Space Environ Med. 2005; 76(8):794–798.
27. Smith A. The impact of short-duration light and moderate physical activity at 7,000 ft and 9,000 ft on the development of hypoxia [abstract]. Aviat Space Environ Med. 2006; 77(3):274.
28. Smith AM. Acute hypoxia and related symptoms on mild exertion at simulated altitudes below 3048 m. Aviat Space Environ Med. 2007; 78(10):979–984.
29. Steinman Y, van den Oord MHAH, Frings-Dresen MHW, Sluiter JK. Flight performance during exposure to acute hypobaric hypoxia. Aerosp Med Hum Perform. 2017; 88(8):760–767.
30. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935; 18(6):643–662.
31. Temme LA, Still DL, Acromite MT. Hypoxia and flight performance of military instructor pilots in a flight simulator. Aviat Space Environ Med. 2010; 81(7):654–659.
32. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988; 54(6):1063–1070.