Oculometric Feature Changes During Acute Hypoxia in a Simulated High-Altitude Airdrop Scenario

Gaurav N. Pradhan; William Ottestad; Anders Meland; Jan Ivar Kåsin; Lars Øivind Høiseth; Michael J. Cevette; Jan Stepanek

BACKGROUND: Severe acute hypoxia results in a rapid deterioration of cognitive functioning and thus poses a risk for human operations in high altitude environments. This study aimed at investigating the effects of oxygen system failure during a high-altitude high-opening (HAHO) parachute jump scenario from 30,000 ft (9144 m) on human physiology and cognitive performance using a noncontact eye-tracking task.

METHODS: Nine healthy male volunteers (ages 27–48) were recruited from the Norwegian Special Operations Commandos. Eye-tracking data were collected to derive information on cognitive performance in the context of rapid dynamic changes in pressure altitude while performing a modified King-Devick test. The baseline data was collected at 8000 ft (2438 m) while breathing 100% oxygen during decompression. For every test, the corresponding arterial blood gas analysis was performed.

RESULTS: The study subjects endured severe hypoxia, which resulted in significant prolongations of fixation time (range: 284.1–245.6 ms) until 23,397 ft (131 m) and fixation size (range: 34.6–32.4 mm) until 25,389 ft (7739 m) as compared to the baseline (217.6 ± 17.8 ms and 27.2 ± 4.5 mm, respectively). The increase in the saccadic movement and decrease in the saccadic velocity was observed until 28,998 ft and 27,360 ft (8839 and 8339 m), respectively.

DISCUSSION: This is the first study to investigate cognitive performance from measured oculometric variables during severe hypobaric hypoxia in a simulated high-altitude airdrop mission scenario. The measurement of altered oculometric variables under hypoxic conditions represents a potential avenue to study altered cognitive performance using noncontact sensors that can derive information and serve to provide the individual with a warning from impending incapacitation.

KEYWORDS: oculometric, acute hypoxia, cognitive performance, high-altitude high opening.

Pradhan GN, Ottestad W, Meland A, Kåsin JI, Høiseth LØ, Cevette MJ, Stepanek J. *Oculometric feature changes during acute hypoxia in a simulated high-altitude airdrop scenario*. Aerosp Med Hum Perform. 2021; 92(12):928–936.

Hypobaric hypoxia can be assessed by methods reflecting oxygenation either globally (e.g., arterial blood gases, blood oxygen saturation) or regionally (e.g., cerebral oxygenation using near-infrared spectroscopy[16]). While these measurements are associated with cerebral functioning, they do not adequately assess the complexities of cognitive performance. The intriguing aspect of using a dynamic task and noncontact eye-tracking tools is the possibility of quantifying alterations in oculometrics. These alterations occur in the multiple neural pathways that control eye movements (motor cortex, visual cortex, numerous ocular nuclei, autonomic nervous system, and cranial nerves). Furthermore, a visual task is frequently an important component of human cognition, especially in the aerospace environment, be that a pilot scanning instruments, or a parachutist checking for malfunctions in their equipment, or the altitude and direction of flight, making it a potentially valuable target of further study. The unobtrusive nature of eye tracking and the presence of computers and screens demanding visual scanning tasks of operators in many environments potentially further adds to the value of pursuing investigations in this domain.

From Mayo Clinic, Scottsdale, AZ, USA.

This manuscript was received for review in May 2021. It was accepted for publication in September 2021.

Address correspondence to: Gaurav N. Pradhan, Ph.D., Mayo Clinic, 13400 E. Shea Blvd, Scottsdale, AZ 85259, USA; pradhan.gaurav@mayo.edu.

DOI: https://doi.org/10.3357/AMHP.5930.2021

Changes in several oculometric variables have been reported to correlate with cognitive performance.[8,23,25] Our objective was to assess oculomotor paradigms related to fixation and saccadic eye movements as descriptors for cognitive performance. Fixation and saccadic behavior play vital roles in the cognitive tasks that involve reading or scanning, which is common in military flight operations. Fixation relates to the cognitive processing required to maintain a gaze and visually process and construe the target of interest.[9] Increased fixation times have been associated with neurological impairments and a state of impaired cognitive functioning during alcohol intoxication.[14] Saccadic eye movements are related to attention and can be affected by injury to the underlying oculomotor reflex.[5] Thus, the present study aimed to evaluate cognitive performance from the measured oculometric variables during severe hypobaric hypoxia in a simulated high-altitude airdrop mission scenario.

METHODS

Subjects

The study protocol was approved by the Regional Committees for Medical and Health Research Ethics (REC South East, reference 2014/469; https://rekportalen.no/#hjem/home). Each subject provided written informed consent before participating. Nine healthy men were recruited among personnel qualified for performing high-altitude high-opening (HAHO) procedures in the Norwegian Special Operations Commando. All were healthy nonsmokers, with a mean age of 31 (27–48) yr [mean (range)]. Subjects abstained from solid foods for 4 h, clear liquids for 2 h, and physical exercise and any analgesics for 24 h before the hypobaric exposure and none were acclimatized to altitude.

Equipment and Materials

Hypobaric chamber and flight profile. The experiment was conducted in a hypobaric chamber (Aeroform Poole, Dorset, UK) at the Institute of Aviation Medicine, Oslo, Norway. To facilitate denitrogenation and to decrease the risk of decompression sickness, a 60-min oxygen prebreathe started at ground level [1017 hPa (763 mmHg)]. The 60-min prebreathe complies with both standard operational procedures during hypoxia training in the Norwegian army and in NATO. The subjects breathed 100% oxygen using an oxygen mask (Gentex MBU 20, Gentex, Carbondale, PA) on a pressure demand regulator (CRU-73, Cobham Life Support, Davenport, IA). Approximately 40 min into the denitrogenation, pressure was reduced to 753 hPa [565 mmHg, 8000 ft (2438 m)], simulating standard cabin pressure during flight. All baseline measurements were completed and a safety brief performed. When the 60-min prebreathe was completed, the chamber was decompressed from 753 hPa (565 mmHg) to 301 hPa [226 mmHg, 30,000 ft (9144 m)] at 4000 ft · min^{-1} (1219 m · min^{-1}). At 301 hPa (226 mmHg) while breathing oxygen, each subject was instructed to do 30 deep squats and then to sit down, to simulate the workload associated with exiting the airplane. To simulate parachute drop and flight, the chamber was repressurized from 30,000 ft to 28,998 ft (9144 to 8839 m) in 15 s at 4000 ft · min^{-1} to simulate the free fall phase, followed by a descent from 28,998 ft to ground level at 1000 ft · min^{-1} (305 m · min^{-1}) to simulate descent under a canopy. Supplemental oxygen was removed at the start of chamber recompression and subjects breathed ambient air throughout the descent profile. Ottestad et al.[15] presents the same flight profile methodology to discuss physiological responses, while this study specifically aimed for greater detail of the cognitive performance and altered oculometric variables during acute severe hypoxia. The overall aim of the study was to explore the risks associated with a loss of supplemental oxygen during HAHO operations. The broader purpose of the study was thus to reduce the risk of such training/operations.

Eye tracking setup. During the experiment, the subjects were seated in a chamber facing a 19″ computer screen (resolution of 1440 × 900 pixels) and positioned to maintain a viewing distance of approximately 65–70 cm, a distance within the recommended reading range. A noninvasive eye-tracking device (Tobii x1 Light, Tobii Technology, Stockholm, Sweden) was affixed to the bottom of the computer screen. The Tobii x1 tracker consists of infrared cameras, which capture eye movements by tracking the corneal reflections of infrared reference lights. The eye tracking data was collected at a sampling rate of 40 Hz with an accuracy of 0.5°. The lighting in the chamber was consistently maintained at the same level (240 lx) throughout the experiment for all subjects. To ensure accurate tracking of eye movements, equipment calibration was performed for each subject prior to the data collection.

Mental workload task. A mental workload task was created by modifying the King-Devick (K-D) test[4] due to its proven efficacy in describing altered cognitive performance in the concussion[3,20] and hypoxia domains.[21,22] The original K-D test requires reading numbers aloud arranged from left to right in sequential lines shown on three different test cards or screens (40 numbers per card/screen). Based on our previous studies,[21,22] the entire K-D test completion time during normoxia was 46.3 ± 10.4 s and in a hypoxic exposure [i.e., 8% oxygen with balance nitrogen gas mixture; equivalent altitude of 23,300 ft (7102 m) for 3 min], it was 54.5 ± 12.4 s. However, the current flight profile was dynamic with rapid recompression and the goal was to measure cognitive performance during changes in ambient pressure every 2 min throughout the profile [corresponding to approximately every 2000 ft (610 m) descent]. To perform the entire K-D test with all three cards that consisted of reading out loud 120 numbers every 2 min more than 10 times continuously would have been an extremely tiring process for the subjects. This would have potentially led to difficulty in quantifying cognitive performance and oculometric measurements purely due to hypoxia. In addition, in a recent study,[17] we have established the normative values of oculometrics separately for all three K-D cards. We discovered that the "baseline" oculometrics and reading times were significantly different across all

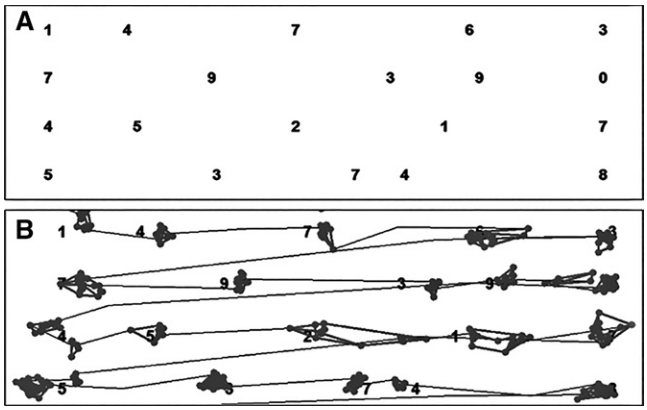

Fig. 1. A) The mental workload task in the form of a modified King-Devick (K-D) test card (only middle 4 rows of Card #2 consisting of 20 numbers). B) The raw eye-tracking scan-paths with saccades (lines) and fixations (grouped dots).

three cards because they offered varying cognitive loads by presenting the numbers to read in different formats. Hence, presenting three cards with different cognitive loads would have been another potential confounding factor. As a result, we had to modify the K-D test by reducing the test to only 1 card with 20 numbers from the center 4 rows of the middle card (as shown in **Fig. 1A**). The described flight profile provided an ideal platform to keep mental workload consistent while measuring raw eye movements during acute and severe hypoxia.

Procedures

The baseline eye-tracking data during the modified K-D test was collected at 8000 ft while breathing 100% oxygen. It should be noted that the hyperoxic baseline measurements were performed from a HAHO operating conditions perspective and may not represent normoxic performance at sea level equivalent since hyperoxia will result in alterations to central nervous system blood flow (vasoconstriction) and altered carbon dioxide metabolism. To familiarize the subject with the test procedure and desensitize potential learning effects, 10 practice trials reading the modified K-D card were performed 10 min prior to the baseline test. During the flight profile, 11 K-D tests and simultaneous eye movements were collected at every 2000 ft descent (i.e., every 2 mins) from 30,000 ft to ~9000 ft (2743 m). The first K-D test during the flight profile was performed at 28,998 ft. At the end of the experiment, a post baseline test was performed at ground level. For every K-D test, the corresponding arterial blood gas analysis was performed using Radiometer 133 ABL 90 FLEX (Radiometer, Brønshøj, Denmark).

The raw eye movement captured by the eye-tracking device is represented as the scan-path plotted on the modified K-D test card (**Fig. 1B**) that was presented as a mental workload. The eye-tracking device transformed the relative position of the corneal reflection and the pupil center in each frame to pixel coordinates (x, y) on the presented computer screen. All saccadic movements were calculated based on the Euclidean distance between eye positions on two consecutive frames. To identify fixations (maintenance of visual gaze within a specific area of the screen or region of interest) and saccades (rapid eye movements between fixations), we used an algorithm[17] that required two input parameters: 1) "saccadic threshold", defined as the threshold for the length (or size) of the saccade represented on the screen; and 2) "minimum sample for fixations", defined as the threshold for the number of eye-tracking data points sampled in the fixation, which is the amount of time spent within a specific area of the screen. The input values for saccadic threshold and minimum sample for fixations were set to 14 mm (i.e., less than 1° amplitude) and four eye-tracking data points, respectively, for classifying fixations and saccades during the reading of all three test cards. The saccadic movements above the saccadic threshold (i.e., greater than 1°) were classified as saccades. Further, a cluster of at least four consecutive microsaccades (i.e., less than 1°) between two consecutive saccades were classified as fixations. The classified saccades were converted later into degrees based on the visual angle between screen and eye.

Statistical Analysis

The measures related to fixations were fixation time (ms; time looking at a target), and fixation size (mm; total eye movement, i.e., microsaccadic small eye movements within a fixation). The measures related to saccades were total saccadic amplitude (degrees), average horizontal saccadic velocity ($° \cdot s^{-1}$), i.e., transitioning between numbers on a line, and average oblique saccadic velocity ($° \cdot s^{-1}$), i.e., transitioning between lines. The arterial blood gas partial pressures of oxygen and carbon dioxide (P_aO_2 and P_aCO_2) and all oculometric data related to fixations and saccades at baseline and different altitudes during the flight profile were tested for normality using Shapiro-Wilk's test to find no significant departure from the normal distribution. Hence, we analyzed the changes in the individual oculometrics related to fixations and saccades between baseline and different altitudes during the flight profile using the parametric, one-way repeated measures ANOVA test for statistical significance. Statistical analysis was performed using MATLAB software. The values are presented as mean ± SD. Statistical significance was set at $P \leq 0.05$. Due to the small number of subjects, Cohen's d was computed to evaluate the effect size. We also presented these changes against the major environmental stressor of hypoxia as measured by arterial blood gas (P_aO_2 and P_aCO_2) at the tested altitudes.

RESULTS

Eight subjects completed the entire flight profile and performed a mental workload at predetermined tested altitudes throughout the entire exposure. One subject experienced loss of consciousness at 25,400 ft (7742 m) and was excluded from the analyses due to lack of data. However, early and striking prolongations of fixation time, well beyond the other subjects, were recorded in the subject who lost consciousness.

Fig. 2A and 2B show the P_aO_2 and P_aCO_2 values, respectively, across eight subjects during baseline at 8000 ft (2438 m; breathing 100% oxygen before recompression) and then descent,

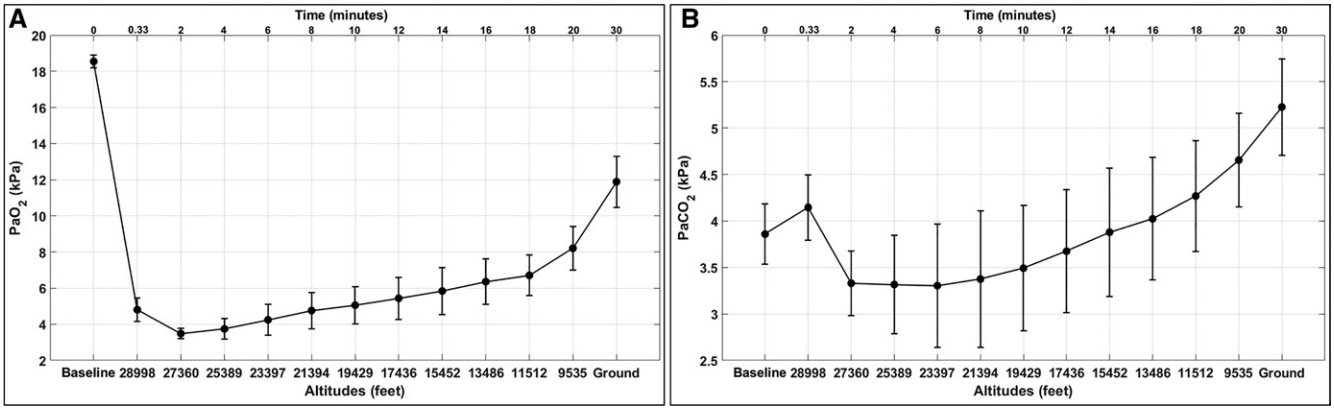

Fig. 2. A) P_aO_2 and B) P_aCO_2 levels through the simulated flight profile ($N = 8$) from 30,000 ft (9144 m) to ground level (recompression) in 30 min. The data points indicate mean and error bars indicate 1 SD.

breathing ambient air, from 30,000 ft to ~9000 ft (9144 to ~2743 m) at every ~2000 ft (610 m) during descent and one at ground level. In descent, P_aO_2 dropped instantly from baseline [18.5 ± 0.36 kPa (95% CI: 18.2–18.9 kPa)], at 28,998 ft [8839 m; 4.8 ± 0.35 kPa (95% CI: 4.3–5.3 kPa)], and further worsened at 27,360 ft [8339 m; 3.5 ± 0.28 kPa (95% CI: 3.2–3.7 kPa)]. P_aO_2 gradually increased for the remaining part of the descent from 25,389 ft (7739 m) and finally reached 11.9 ± 1.4 kPa (95% CI: 10.7–13.1 kPa) at ground level, still statistically lower than the baseline because baseline P_aO_2 was markedly hyperoxic, while ground level P_aO_2 during descent was approaching normoxic. Similarly, due to hyperoxia during baseline, P_aCO_2 baseline values [3.9 ± 0.33 kPa (95% CI: 3.6–4.1 kPa)] were lower than normal levels (5.3 kPa). In descent, P_aCO_2 slightly increased at 28,998 ft [4.1 ± 0.35 kPa (95% CI: 3.8–4.4 kPa)] because subjects performed 30 deep squats before hypoxic exposure that might have resulted in production of CO_2 due to the metabolic needs of the muscle tissue. However, P_aCO_2 levels at 27,360 ft [3.3 ± 0.34 kPa (95% CI: 3–3.6 kPa)] decreased soon due to severe hypoxia and maybe also due to hypocapnia from attempted compensation by increased ventilation.

Fixation Time

The fixation time indicates the average amount of time required for the subject to fixate on the number to read it. During the severe hypoxic exposure endured in this flight profile, we recorded significant alterations in fixation times from baseline to 28,998 ft [$F(1,7) = 16.2$, $P = 0.005$], 27,360 ft [$F(1,7) = 13.9$, $P = 0.007$], 25,389 ft [$F(1,7) = 8.9$, $P = 0.02$], and 23,397 ft [7131 m; $F(1,7) = 6.7$, $P = 0.036$] (**Fig. 3A** and **Table I**). These findings suggest a decline in cognitive performance during severe hypoxia at altitudes of 28,998 ft, 27,360 ft, 25,389 ft, and 23,397 ft followed by subsequent values approaching baseline levels with further descent, as seen in Fig. 3A. From 19,429 ft (5922 m) to ground level, the fixation times were numerically almost identical to baseline with no significant differences.

Fixation Size

The fixation size indicates the total eye movement within the fixation, i.e., small saccadic movements that represent the spatial characteristic of the fixation. The fixation sizes during severe hypoxia at high altitudes of 28,998 ft (34.6 ± 10.7 mm), 27,360 ft (34.3 ± 9.4 mm), and 25,389 ft (32.4 ± 9.3 mm) were significantly larger than the baseline fixation size (27.2 ± 4.4 mm) (**Fig. 3B** and Table I). The alterations in fixation sizes at altitudes from 23,397 ft (7131 m) to the ground level were not statistically different from baseline. However, significantly higher intersubject variability in fixation size was observed throughout the flight as compared to the baseline (Fig. 3B).

Saccadic Amplitudes and Velocities

The saccadic amplitude signifies the sum of total saccadic eye movement transitioning between all the numbers on the modified K-D card (i.e., horizontal saccades) and total saccadic eye movement transitioning between all the lines on the card (return sweep, i.e., oblique saccades). The saccadic amplitude was increased immediately from 58.6 ± 9.1° at baseline to 74.8 ± 18.9° [$F(1,7) = 6.8$, $P = 0.035$] at 28,998 ft (Table I). During remaining descent, there was no significant difference in saccadic amplitudes due to high intersubject variability during hypoxic exposure. However, as it can be noticed in **Fig. 4A**, variabilities in saccadic amplitudes across subjects are more stable in altitudes closer to the ground and at ground level as compared to high altitudes (i.e., the hypoxic environment). Similar to saccadic amplitudes, the horizontal saccadic [$F(1,7) = 24.53$, $P = 0.0017$] and oblique [$F(1,7) = 9.3$, $P = 0.01$] velocities were instantaneously reduced at 28,998 ft from baseline (**Fig. 4B and 4C**, and Table I).

DISCUSSION

Visual performance measures represent a direct physiological sign of cognitive activity;[10] therefore, oculometric measures are now being studied as indicators to detect hypoxia-induced cognitive performance decrements.[22,28,30] All studies to date have tested the changes in oculometric measures in a steady state hypoxic environment, that is, at a particular altitude or by simulating low oxygen levels with hypoxic gas mixtures. This study is the first to systematically examine the continuous changes in

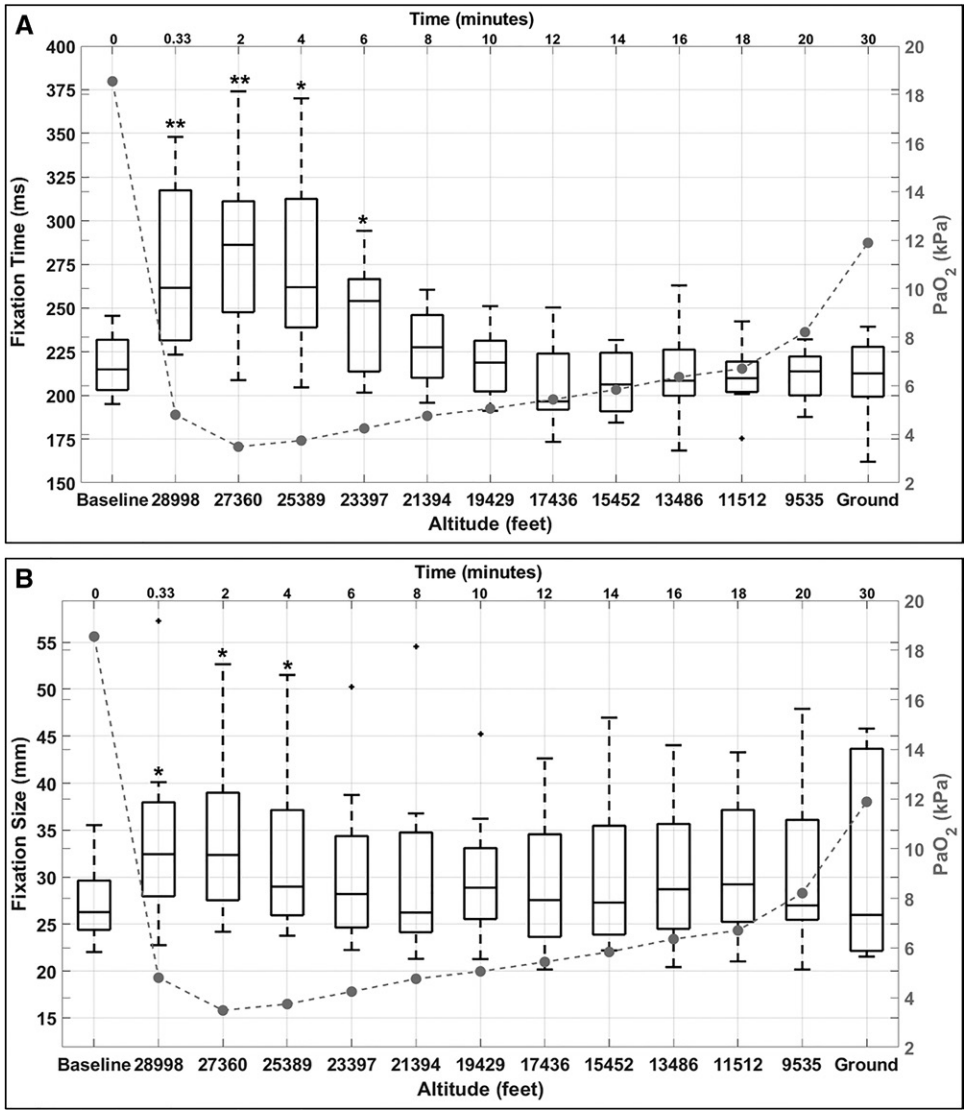

Fig. 3. The relationship between fixation-related features (left Y-axis) and P_aO_2 (right Y-axis) during the simulated flight profile from 30,000 ft (9144 m) to ground level (recompression) in 30 min. A) Fixation time and B) fixation size. *$P \leq 0.05$; **$P < 0.01$. In each box, the central mark indicates the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points.

oculometric measures during severe hypoxia and rapidly changing ambient pressure.

Across all tested individuals, the completion time of the modified K-D test until ~25,000 ft (7620 m) was significantly longer than the overall baseline (5.6 ± 0.8 s), which was performed before jumping while breathing 100% oxygen (as seen in Table I). Severe hypoxia will result in compensatory increased ventilation, which results in cerebral vasoconstriction and a left shift of the oxy-hemoglobin dissociation curve. These mechanisms will create further decreases in tissue oxygen delivery and independently decrease human performance and functioning, which may have an impact on cerebral perfusion of the oculomotor centers. This suggests the relevant importance of exploring the alterations of oculometric measures during a cognitive workload task (i.e., reading numbers) to detect an early decline in cognitive performance.

A previous study using a similar methodology has related fixation time to cognitive performance,[18] suggesting the increase in fixation time was associated with a decline in cognitive performance. Consistent with this finding, we observed a significant increase in fixation time until ~23,000 ft (7010 m), where P_aO_2 levels were lowest during that period of the flight profile, and P_aCO_2 levels were around 3.3 kPa (Fig. 2), which is a departure from normal levels of 5.3 kPa, corresponding to a potential vasoconstriction effect of up to 30–40%, suggesting a decline in cognitive performance. Given the K-D structure, the duration of fixation on each number plays a crucial role in assessing cognitive function since it involves the integration of information for reading, verbalizing, planning the motor movement, and directing attention to the next number.[7,20] Such types of cognitive tasks involve brain regions that are responsible for executive functions and attention, which have also been

Table I. Comparing Changes in Oculometric and Cognitive Performance Throughout the Flight Profile at Predetermined Altitudes.

ALTITUDES (ft); TIME ELAPSED (min)	TIME AND OCULOMETRIC PERFORMANCE DURING MODIFIED K-D TEST MEAN ± SD (95% CI) COHEN'S *d* VALUE, *P*-VALUE (REPEATED-MEASURE ONE-WAY ANOVA)					
	TIME (s)	FIXATION TIME (ms)	FIXATION SIZE (mm)	TOTAL SACCADIC AMPLITUDE (°)	HORIZONTAL SACCADIC VELOCITY (° · s^{-1})	OBLIQUE SACCADIC VELOCITY (° · s^{-1})
Baseline	5.7 ± 0.8 (5–6.3)	217.6 ± 17.8 (202.7–232.5)	27.2 ± 4.5 (23.5–31)	58.7 ± 9.1 (51.1–66.3)	47.3 ± 5 (43.1–51.5)	143.4 ± 11.8 (133.5–153.3)
28,998; 0.33	7.9 ± 1.2* (6.9–8.8) 2.2, 0.0009	274.1 ± 49.1 * (233–315.1) 1.7, 0.005	34.6 ± 10.7 * (25.7–43.5) 0.96, 0.037	74.8 ± 18.9 * (59–90.6) 1.15, 0.035	40.8 ± 5.1 * (36.5–45.1) 1.28, 0.0017	123.8 ± 14.7 * (111.5–136) 1.48, 0.01
27,360; 2	7.7 ± 1.8 * (6.2–9.1) 1.6, 0.01	284.1 ± 52 * (240.6–327.6) 1.9, 0.007	34.3 ± 9.4 * (26.4–42.2) 1, 0.009	61.5 ± 8.5 (54.4–68.6) 0.32, 0.44	44.3 ± 3.5 * (41.4–47.2) 0.7, 0.05	132.8 ± 17.9 (117.8–147.8) 0.7, 0.25
25,389; 4	7.1 ± 1.4 * (5.9–8.3) 1.3, 0.04	275.2 ± 53.9 * (230.2.5–320.2) 1.6, 0.02	32.4 ± 9.3 * (24.6–40.2) 0.75, 0.04	63 ± 9.4 (55.2–70.9) 0.47, 0.26	45.5 ± 5.4 (40.9–50) 0.35, 0.3	134.4 ± 18.1 (119.3–149.5) 0.6, 0.29
23,397; 6	6.2 ± 1.2 (5.2–7.3) 0.6, 0.29	245.6 ± 32.8 * (218.1–273.1) 1.1, 0.036	30.9 ± 9.3 (23.1–38.6) 0.52, 0.13	62.2 ± 10.8 (53.1–71.2) 0.35, 0.41	46.2 ± 4.4 (42.5–49.9) 0.23, 0.49	131.4 ± 9.5 (123.5–139.3) 1.1, 0.06
21,394; 8	5.6 ± 0.8 (4.9–6.3) 0.05, 0.8	228 ± 23.4 (208.4–247.6) 0.51, 0.2	30.7 ± 10.9 (21.7–39.9) 0.46, 0.22	63.8 ± 11.7 (54–73.6) 0.49, 0.26	46.6 ± 4.5 (42.9–50.4) 0.14, 0.49	138.4 ± 14.7 (126.1–150.7) 0.38, 0.34
19,429; 10	5.8 ± 0.5 (5.4 – 6.2) 0.24, 0.52	218.4 ± 20.4 (201.4 – 235.5) 0.04, 0.85	30.2 ± 7.5 (23.9 – 36.5) 0.49, 0.095	65.3 ± 11.3 (55.8 – 74.7) 0.64, 0.17	44.1 ± 5.9 (39.2 – 49) 0.58, 0.1	131.2 ± 16.9 * (117–145.3) 0.85, 0.037
17,436; 12	5.5 ± 0.7 (5–6.2) 0.12, 0.76	206.1 ± 26.9 (183.6–228.6) 0.5, 0.09	29.3 ± 7.6 (22.9–35.6) 0.34, 0.29	63.3 ± 8.6 (56.1–70.5) 0.52, 0.26	43.3 ± 5.2 (38.9–47.6) 0.78, 0.052	128.3 ± 29.1 (104–152.6) 0.74, 0.12
15,452; 14	5.7 ± 0.8 (5–6.3) 0.02, 0.96	207.5 ± 18.4 (192.1–222.8) 0.56, 0.05	30.3 ± 8.9 (22.9–37.8) 0.45, 0.16	62.9 ± 10.7 (53.9–71.8) 0.42, 0.34	44.3 ± 6.7 (38.6–49.9) 0.51, 0.19	130.3 ± 29.5 (105.6–154.9) 0.64, 0.14
13,486; 16	5.6 ± 0.8 (4.9–6.2) 0.14, 0.69	212.6 ± 27.5 (189.6–235.6) 0.2, 0.52	30.3 ± 8 (23.6–37) 0.48, 0.17	60.4 ± 7.6 (54.1–66.8) 0.21, 0.61	46.2 ± 7 (40.3–52) 0.18, 0.52	135.1 ± 16.2 (121.5–148.7) 0.6, 0.13
11,512; 18	5.2 ± 0.8 (4.6–5.9) 0.52, 0.1	210.1 ± 19.3 (193.9–226.3) 0.4, 0.18	30.9 ± 7.7 (24.5–37.4) 0.6, 0.085	60.4 ± 6.6 (54.9–65.9) 0.22, 0.53	44.2 ± 6.4 (38.8–49.5) 0.54, 0.13	132 ± 22.2 (113.4–150.6) 0.67, 0.12
9535; 20	5.8 ± 0.9 (5–6.5) 0.09, 0.81	211.5 ± 15.1 (198.9–224.2) 0.37, 0.39	30.6 ± 9.4 (22.8–38.5) 0.49, 0.14	59.3 ± 7.1 (53.3–65.3) 0.08, 0.77	45.7 ± 6 (40.7–50.8) 0.29, 0.3	136.7 ± 17.4 (122.2–151.3) 0.46, 0.12
Ground; 30	5.8 ± 1.2 (4.8–6.8) 0.1, 0.81	210.2 ± 24.2 (189.9–230.4) 0.35, 0.43	31.4 ± 11 (22.2–40.6) 0.53, 0.22	61.8 ± 11.6 (52.2–71.5) 0.31, 0.27	46.1 ± 4.8 (42.1–50.1) 0.24, 0.68	130.2 ± 24.1 (110.1–150.3) 0.74, 0.16

*$P \leq 0.05$ in comparison with baseline.

reported to be affected in mild traumatic brain injury.[24] In line with this, prolonged fixation time has also been reported in concussed vs. healthy adults.[20] This suggests that monitoring increases in fixation time during cognitive workload has the potential to provide signs of cognitive decline during military operations like our tested flight profile.

Fixation size is the total length of the small-amplitude involuntary eye movements, i.e., microsaccades within the fixation.[17] The increase in fixation size indicates a reduction in fixation stability. These microsaccadic eye movements provide information on brain function and related oculomotor circuits concerning cognition and attention.[6,11] We found a significant increase in the fixation size until ~25,000 ft. There have been no studies that analyze microsaccadic eye movements within the fixation in terms of total length, except one study that documented fixation size as an indicator of fixation stability and perceptual learning that indicated the maturation process in healthy youth athletes.[18] We believe that fixation size represents a good reflection of cognitive processes associated with mental attention, i.e., performance during a cognitive workload task such as reading.[19] This supports the importance of monitoring the changes in fixation size during the cognitive or attentional task to assess focus in military operations to detect acute cognitive impairment. In this study, as seen in the bar plot of Fig. 3B, the range of deviation of fixation size across tested individuals is much larger during the entire test profile as compared to baseline while breathing oxygen before flight. The differences are not statistically significant because of the observed high intersubject variability as well as high intrasubject variability at different altitudes (Table I). This indicates that acute severe hypoxia has caused fixation instability due to the involuntary nature of microsaccadic eye movements. Our finding is aligned

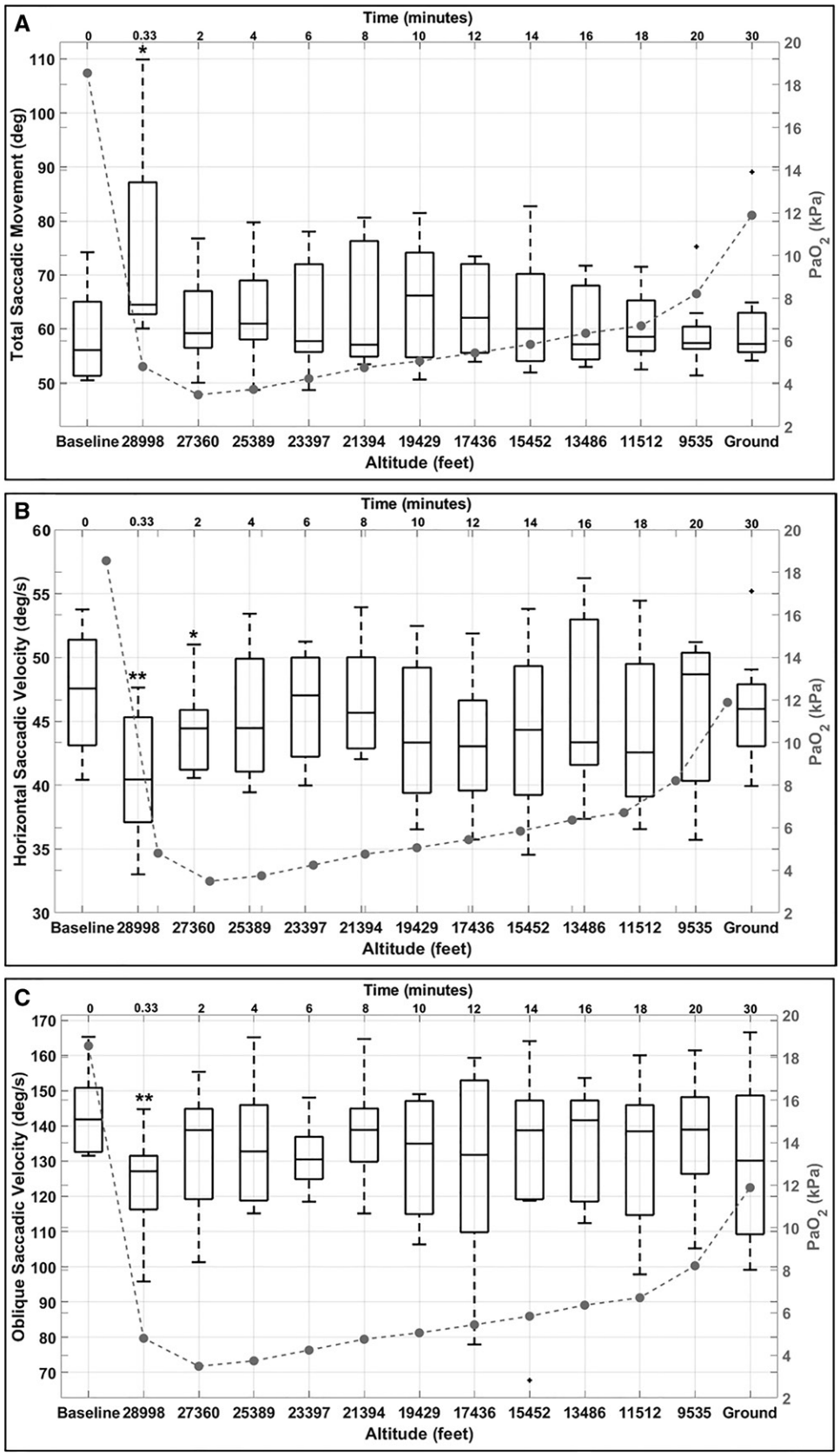

Fig. 4. The relationship between saccade-related features (left Y-axis) and P_aO_2 (right Y-axis) during the simulated flight profile from 30,000 ft (9144 m) to ground level (recompression) in 30 min. A) Total saccadic movement; B) horizontal saccadic velocity (in-between numbers); and c) oblique saccadic velocity (in between lines) $*P \leq 0.05$; $**P < 0.01$. In each box, the central mark indicates the median and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points.

with the work that observed an increment in intersaccadic drift velocity due to hypoxia that caused diminishing eye stability.[2]

Previous findings[1,12,22] have revealed either no significant changes in saccadic velocities due to acute hypoxia, while a few other studies[26,28] have observed a decrease in saccadic velocity due to hypobaric hypoxia, mainly in larger amplitude saccadic[28] and finer gaze movements during free-viewing.[26] In this study, we observed a significant increase in total saccadic movement (Fig. 4A) and significant decrease in saccadic velocities (Figs. 4B and 4C) in finer horizontal saccades (between numbers) as well as larger oblique saccades (between lines) during the first K-D test in the flight profile at ~29,000 ft (8839 m; i.e., immediately after sudden hypoxic exposure). Also, throughout the entire flight profile, significant variance in both the horizontal and oblique saccadic velocities was observed (Table I). These findings in saccadic movements during the performance of a cognitive workload task in a hypoxic flight profile may indicate visual instability[26] and serve to detect early signs of acute cognitive impairment.

There are several limitations to this study, first the small number of highly selected subjects may limit the external validity of our data. The eye-tracking hardware used in this study uses a 40-Hz sampling rate, which may lead to difficulty in adequately describing saccadic performance. We anticipate improved detection of subtle changes in oculometric performance with improved sampling rates in the future. The repetitive nature of the K-D test may have introduced fatigue and boredom effects, confounding our results; however, since all oculometric variables normalized within ~23,000 ft, these effects should be marginal. As far as learning effect[29] as a confounding factor is concerned, the task was not to remember the digits, and subjects would have no real benefit by learning the task by heart. Also, the raw eye-tracking scan path data (e.g., Fig. 1B) disproves such effects as the gaze data shows that all subjects moved their eyes to every digit throughout the experiment. Furthermore, humans are limited to holding up to seven digits in working memory under normoxic conditions,[13] while hypoxia impairs short-term memory and may introduce learning effects during cognitive testing.[27] Even though the K-D test is widely used in sideline concussion testing in contact sports to identify severe cognitive impairment in athletes, it has yet to be clinically proven to be effective in detecting mild cognitive impairment. Oculometric performance during the K-D test may have limited value as a proxy for cognitive performance in more complex real-life scenarios, especially during less severe hypoxia.

In this study, the flight profile set up in a controlled hypobaric chamber was designed to collect oculometric measures to assess cognitive performance in a dynamic extremely hypoxic emergency situation (oxygen system failure). It should be noted that the ability to perform such standardized testing in a laboratory setting may not predict the ability to perform a correct action in an emergency in a real setting. During flights or operations such as HAHO, the operator continuously receives sensory and cognitive inputs in the form of cognitive mental workload tasks. This requires attention, extensive information processing, and a level of executive functioning. During the performance of real-life emergency situations (e.g., HAHO and oxygen system failure), eye movements can represent early signs of cognitive impairment. Hence, such studies may reveal the oculometric patterns that need to be monitored or detected to deliver early warning signs to the operator. In addition, it gives important insights for the operators on what to expect in such emergency situations, which could inform training regimes and improve mental readiness.

Severe hypoxia during the HAHO simulated scenario resulted in consistent prolongations of fixation time, fixation size, and increased saccadic movement, whereas saccadic velocity decreased. These unobtrusively measured oculometrics warrant further large-scale trials to investigate the detection of cognitive performance decline due to the influence of acute hypoxia. We also found that these oculometric measures were significantly different from baseline in severe hypoxic high altitudes, but not in moderate or mild hypoxic lower altitudes. These findings may encourage further investigation of the use of oculometric measures in advancing field testing capability to detect mild cognitive impairment as well as early changes in cognitive performance.

ACKNOWLEDGMENTS

We give special thanks to the Norwegian Special Operations Commando for facilitating the study and to the operators who participated. We are grateful for the support granted by the Norwegian Defence Medical Services, Institute of Aviation Medicine, Oslo, Norway.

Financial Disclosure Statement: No conflicts of interest, financial or otherwise, are declared by the authors.

Authors and Affiliations: Gaurav N. Pradhan, M.S., Ph.D., Michael J. Cevette, M.S., Ph.D., and Jan Stepanek, M.D., M.P.H., Aerospace Medicine and Vestibular Research Laboratory, Mayo Clinic, Scottsdale, AZ, USA; and William Ottestad, Ph.D., Air Ambulance Department, Division of Prehospital Services, and Lars Ø. Høiseth, M.D., Ph.D., Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, and Anders Meland, Ph.D., Norwegian School of Sport Sciences, Department of Sport and Social Sciences, and Jan I. Kåsin, Ph.D., Department of Research, Education, and Working Environment in Flight Operations, Institute of Aviation Medicine, Norwegian Defence Medical Services, Oslo, Norway.

REFERENCES

1. Cymerman A, Muza SR, Ditzler D, Sharp M, Friedlander A, et al. Oculomotor and pupillary reflexes during acute exposure to hypobaric hypoxia. Natick (MA): USARIEM; 2003. Technical report.
2. Di Stasi LL, Cabestrero R, McCamy MB, Ríos F, Catena A, et al. Hypobaric hypoxia increases intersaccadic drift velocity. J Vis. 2014; 14(10):113.
3. Galetta KM, Barrett J, Allen M, Madda F, Delicata D, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. Neurology. 2011; 76(17):1456–1462.
4. Galetta KM, Brandes LE, Maki K, Dziemianowicz MS, Laudano E, et al. The King-Devick test and sports-related concussion: study of a rapid visual screening tool in a collegiate cohort. J Neurol Sci. 2011; 309(1–2): 34–39.
5. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Halszka J, van de Weijer J. Eye tracking: a comprehensive guide to methods and measures.

Oxford (UK): Oxford University Press; 2011. http://ukcatalogue.oup.com/product/9780199697083.do.
6. Kapoula Z, Yang Q, Otero-Millan J, Xiao S, Macknik SL, et al. Distinctive features of microsaccades in Alzheimer's disease and in mild cognitive impairment. Age (Dordr). 2014; 36(2):535–543.
7. Kulp MT, Schmidt PP. Effect of oculomotor and other visual skills on reading performance: a literature review. Optom Vis Sci. 1996; 73(4):283–292.
8. Liversedge SP, Findlay JM. Saccadic eye movements and cognition. Trends Cogn Sci. 2000; 4(1):6–14.
9. Luna B, Velanova K, Geier CF. Development of eye-movement control. Brain Cogn. 2008; 68(3):293–308.
10. Marshall SP. Identifying cognitive state from eye metrics. Aviat Space Environ Med. 2007; 78(5, Part II):165–175.
11. Martinez-Conde S, Macknik SL, Troncoso XG, Hubel DH. Microsaccades: a neurophysiological analysis. Trends Neurosci. 2009; 32(9):463–475.
12. Merz TM, Bosch MM, Barthelmes D, Pichler J, Hefti U, et al. Cognitive performance in high-altitude climbers: a comparative study of saccadic eye movements and neuropsychological tests. Eur J Appl Physiol. 2013; 113(8): 2025–2037.
13. Miller G. Human memory and the storage of information. IEEE Trans Inform Theory. 1956; 2(3):129–137.
14. Moser A, Heide W, Kömpf D. The effect of oral ethanol consumption on eye movements in healthy volunteers. J Neurol. 1998; 245(8):542–550.
15. Ottestad W, Hansen TA, Pradhan G, Stepanek J, Høiseth LØ, Kåsin JI. Acute hypoxia in a simulated high-altitude airdrop scenario due to oxygen system failure. J Appl Physiol. 2017; 123(6):1443–1450.
16. Ottestad W, Kåsin JI, Høiseth LØ. Arterial oxygen saturation, pulse oximetry, and cerebral and tissue oximetry in hypobaric hypoxia. Aerosp Med Hum Perform. 2018; 89(12):1045–1049.
17. Pradhan GN, Bogle J, Kleindienst S, Cevette MJ, Stepanek J. Correlating multi-dimensional oculometrics with cognitive performance in healthy youth athletes. J Healthc Inform Res. 2018; 2(1–2):132–151.
18. Pradhan GN, Bogle JM, Cevette MJ, Stepanek J. Discovering oculometric patterns to detect cognitive performance changes in healthy youth football athletes. J Healthc Inform Res. 2019; 3(4):371–392.
19. Rayner K. The role of eye movements in learning to read and reading disability. Remedial Spec Educ. 1985; 6(6):53–60.
20. Rizzo J-R, Hudson TE, Dai W, Berkemeier J, Pasculli RM, et al. Rapid number naming in chronic concussion: eye movements in the King-Devick test. Ann Clin Transl Neurol. 2016; 3(10):801–811.
21. Stepanek J, Cocco D, Pradhan GN, Smith BE, Bartlett J, et al. Early detection of hypoxia-induced cognitive impairment using the King-Devick test. Aviat Space Environ Med. 2013; 84(10):1017–1022.
22. Stepanek J, Pradhan GN, Cocco D, Smith BE, Bartlett J, et al. Acute hypoxic hypoxia and isocapnic hypoxia effects on oculometric features. Aviat Space Environ Med. 2014; 85(7):700–707.
23. Sussman ES, Ho AL, Pendharkar AV, Ghajar J. Clinical evaluation of concussion: the evolving role of oculomotor assessments. Neurosurg Focus. 2016; 40(4):E7.
24. Barker-Collo S, Jones K, Theadom A, Starkey N, Dowell A, et al. Neuropsychological outcome and its correlates in the first year after adult mild traumatic brain injury: a population-based New Zealand study. Brain Inj. 2015; 29(13–14):1604–1616.
25. Thomas ML, Russo MB. Neurocognitive monitors: toward the prevention of cognitive performance decrements and catastrophic failures in the operational environment. Aviat Space Environ Med. 2007; 78(5, Suppl.): B144–B152.
26. Thropp JE, Buza PW. Modeling oculomotor variability during slow cabin decompression using infrared technology. International Journal of Aviation, Aeronautics, and Aerospace. 2018; 5(5):6. [Accessed Oct. 8, 2021]. Available from https://commons.erau.edu/ijaaa/vol5/iss5/6.
27. Turner CE, Barker-Collo SL, Connell CJW, Gant N. Acute hypoxic gas breathing severely impairs cognition and task learning in humans. Physiol Behav. 2015; 142:104–110.
28. van der Post J, Noordzij LAW, de Kam ML, Blauw GJ, Cohen AF, van Gerven JMA. Evaluation of tests of central nervous system performance after hypoxemia for a model for cognitive impairment. J Psychopharmacol. 2002; 16(4):337–343.
29. Wesnes K, Pincock C. Practice effects on cognitive tasks: a major problem? Lancet Neurol. 2002; 1(8):473.
30. Wilson MH, Edsell M, Imray C, Wright A; Birmingham Medical Research Expeditionary Society. Changes in pupil dynamics at high altitude—an observational study using a handheld pupillometer. High Alt Med Biol. 2008; 9(4):319–325.