Early Detection of Hypoxia-Induced Cognitive Impairment Using the King-Devick Test

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Introduction: Hypoxic incapacitation continues to be a significant threat to safety and operations at high altitude. Noninvasive neurocognitive performance testing is desirable to identify presymptomatic cognitive impairment, affording operators at altitude a tool to quantify their performance and safety. ***Methods:*** There were 25 subjects enrolled in this study. Cognitive performance was assessed by using the King-Devick (K-D) test. The performance of the subjects on the K-D test was measured in normoxia followed by hypoxia (8% O_2 equivalent to 7101 m) and then again in normoxia. ***Results:*** K-D test completion time in hypoxia for 3 min was significantly longer than the Baseline Test (54.5 ± 12.4 s hypoxic vs. 46.3 ± 10.4 s baseline). Upon returning to normoxia the completion time was significantly shorter than in hypoxia (47.6 ± 10.6 s post test vs. 54.5 ± 12.4 s hypoxic). There was no statistically significant difference between baseline test and post test times, indicating that all subjects returned to their normoxic baseline levels. S_pO_2 decreased from 98 ± 0.9% to 80 ± 7.8% after 3 min on hypoxic gas. During the hypoxic K-D test, S_pO_2 decreased further to 75.8 ± 8.3%. ***Conclusions:*** In this study the K-D test has been shown to be an effective neurocognitive test to detect hypoxic impairment at early presymptomatic stages. The K-D test may also be used to afford a reassessment of traditional measures used to determine hypoxic reserve time.

Keywords: hypoxia, cognitive performance, King-Devick test, altitude, presymptomatic hypoxic state.

EXPOSURE TO HIGH altitude reduces oxygen supply to the central nervous system due to hypoxia from the reduced ambient partial pressure of oxygen. This may affect cognitive performance. Based on field studies and laboratory experiments in hypobaric chambers, we know that 10,000–12,000 ft (3048–3658 m) is the zone in which cognition, sensory, physiological, and psychological functions begin to be significantly impaired due to hypoxia (2). Physiological and psychological alterations increase with altitude and particularly with extreme altitudes (e.g., 23,000–26,000 ft or 7010–7925 m), including memory deficits that may persist after returning to normoxia (7). Time spent in hypoxia is also considered an aggravating factor for decline in memory performance, verbal expression, and ability to concentrate (3). Cahoon et al. (6) reported that at 15,000 ft (4572 m) cognitive tasks such as complex decision making were more affected than psychomotor tasks. Impaired judgment and decision-making capacity may increase the risk of accidents in challenging environments such as high altitude flight or climbing in dangerous terrain at altitude (13).

The review by Cable (5) reported 656 hypoxia incidents from 1976 to 1990 in the U.S. Air Force and 40 aircraft mishaps with 67 fatalities as revealed by the U.S. National Transportation Safety Board. The problem of hypoxia remains a major physiological and flight safety concern. Because of a possible problem with the On-Board Oxygen Generating System associated with incidents suspicious for hypoxic incapacitation, the F-22 fleet was recently grounded by the USAF.

High altitude impairment of judgment and muscular coordination along with poor acclimatization have been observed in mountaineering. Over a 5-yr period in the Sierra Nevada, McLennan et al. (17) reported 215 hypoxia related accidents in climbers.

Acute mountain sickness (AMS) and hypothermia were documented in 104 individuals, the majority of whom sustained injuries resulting from errors in judgment with 17 deaths ultimately attributed to head injury.

Based on these and other observations, training to familiarize aviators and mountaineers with hypoxic symptoms and physiologic changes are carried out using mixed gas (hypoxic gas mixtures) or hypobaric chamber exposures (18,24). The training may involve psychomotor, visual, and/or memory tests (1,21) to demonstrate to the individual exposed to hypoxia the concept of acute hypoxia tolerance up to the appearance of common hypoxic symptoms (e.g., paresthesia, increased rate and/or depth of breathing, headache, drowsiness, tachycardia, light-headedness, loss of muscle coordination, impaired vision, and others). These training and demonstration tests are not designed to detect early signs of hypoxia which occur before the appearance of the aforementioned common hypoxic symptoms. In fact the presence of definite hypoxic

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symptoms represents an advanced stage of hypoxic incapacitation with significant alterations in decision making capacity. The purpose of this current study is to introduce a simple and reproducible tool allowing detection of early cognitive impairment in the presymptomatic phase of an acute exposure. We propose a validated cognitive screening test, the "King-Devick (K-D) test," which is in clinical use as a sensitive diagnostic assessment tool to identify cognitive alterations due to sports-related concussion. Galetta et al. showed that 90% of collegiate athletes who had concussion have a significant difference in K-D test performances from their baseline when evaluated on the sideline immediately after the injury (12). Similarly, the same significant differences were reported in boxers and mixed martial arts athletes in the post-fight K-D tests performed after concussion. In this group, worse scores were observed in cases of head trauma followed by loss of consciousness (11). The K-D test also showed its utility in identifying unrecognized concussions during the sideline standard evaluation in rugby players (15). A significant correlation between K-D test performance and sleep deprivation has also been reported (9). The K-D test is based on the detection of impaired eye movements known to be robust discriminators for the identification of a mild traumatic brain injury (15). Since oculometric measures have also been recognized as highly sensitive to hypoxia (8), K-D testing may also be useful as an indicator of hypoxic incapacitation at high altitudes. The aim of this paper is to study the effect of mixed gas induced hypoxia on K-D test performance (completion time, error rate) in comparison to test performance under normoxic conditions.

METHODS

Study Participants

There were 25 subjects, 14 men and 11 women, enrolled in this study approved by the Mayo Clinic Institutional Review Board. Healthy nonsmokers between 18 and 55 yr of age with no significant medical illnesses were recruited (specific exclusions were history of obstructive/restrictive respiratory and cardiovascular diseases, epilepsy, diabetes, chronic headaches or migraines, or hematologic disorders). All the subjects were Caucasian and all of them were residents of the Phoenix metropolitan area (elevation of 1500–2000 ft / 457–609 m above sea level).

A negative urine pregnancy test was required for female subjects. Written informed consent was obtained from all subjects prior to enrollment. The cohort was of mean age 32.4 ± 9.8 yr, mean height 1.74 ± 0.12 m, mean weight 73.9 ± 16.3 kg, and mean BMI of 24.3 ± 4.1.

The King-Devick (K-D) Test

The K-D test is based on sequential rapid number reading aloud with performance based on time needed to complete the task and number of errors made by the subject. The procedure involves reading aloud a series of single digit numbers from left to right on three test cards (**Fig. 1**), and requires less than 2 min to administer, including one demonstration card and three actual test cards. Subjects are asked to read aloud the numbers on each card from left to right as quickly as possible without making errors. The sum of the three test card times constitutes the completion time for the entire test. The number of errors made in reading the test cards is also recorded by research personnel. The K-D test satisfies psychometric properties, including objectivity, standardization, reliability, validity, and discrimination (12).

Study Design

All studies were carried out in a quiet, climate-controlled room in the Mayo Clinic Aerospace Medicine and Vestibular Research Laboratory. A finger sensor for pulse oximetry recordings (Nonin Medical, Inc., Plymouth, MN) was placed on the tip of a finger of each subject. For the entire experiment, each subject wore an aviation helmet. The K-D test cards (as shown in Fig. 1) were shown on a computer display screen one at a time during the experiment. After reading each card, the subject was instructed to press the keyboard "space" key to proceed to the next card. The time required to complete the entire test (all three cards) was recorded by using a digital stop-watch. The number of errors made during each experiment was recorded. At the beginning of the experiment, baseline measures of S_po_2 were collected for about 1 min. Subjects were asked to perform the K-D test twice to gain familiarity with the test procedures. The S_po_2 was continuously monitored and recorded throughout the experiment.

Normoxia was tested by providing room air to the subject through the mask. Hypoxia was induced by providing a hypoxic premixed gas mixture of 8% O_2 (partial pressure 24.3 mmHg) balance N_2 (equivalent to 23,300 ft or 7101 m) through the aviator mask.

The sequence of the study protocol was designed as follows:

Step 1. Two practice K-D tests were performed to familiarize the subject with the test procedures.
Step 2. The first K-D test was performed when the subject was normoxic (i.e., breathing normal room air through the mask). This test was considered the "Baseline Test."
Step 3. The subject was then exposed to the hypoxic gas mixture for 3 min.
Step 4. After breathing the hypoxic gas mixture for 3 min, the K-D test was performed. This test represents the "Hypoxic Test."
Step 5. After completing the K-D test, the subject was allowed to breathe normal room air through the mask for 3 min to return to normoxia.
Step 6. A repeat K-D test was performed. This test was considered as the "Post Test" to quantify the return of performance to baseline level.

After the experiment was completed each subject provided a verbal report in order to document the incidence and severity of any subjective hypoxic symptoms.

Power Analysis

Power analysis showed that an average K-D test time of 46 s in the Baseline Test, with a standard deviation of 10 s, and a sample size of 25 subjects would provide 80%

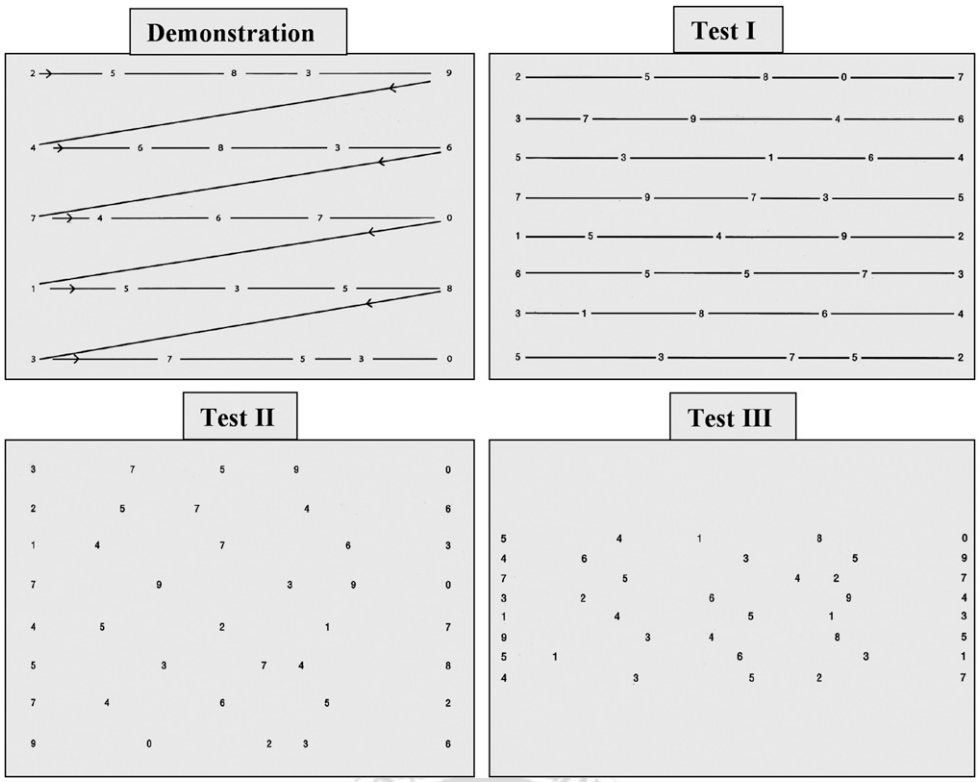

Fig. 1. Demonstration and test cards for the King-Devick (K-D) test.

power, if it showed at least 6 s (i.e., 13%) incremental change in the K-D test time in the Hypoxic Test. Based on these results, we chose at least a 13% increment in the K-D test time to be considered as a significant change from performance in normoxia versus hypoxia, which we desired to be able to detect in this study. The differences in K-D test time from Baseline Test to Hypoxic Test, and Hypoxic Test to Post Test were calculated. The number of errors recorded during the different test conditions were compared using a one-way ANOVA analysis. We also monitored and compared arterial oxygen saturation (S_pO_2 levels) across all three test conditions for all subjects. Statistical analysis was performed using MATLAB software. All results are presented as means ± SE. The level of statistical significance was chosen to be 5%.

RESULTS

All 25 subjects participating in the study completed the experiment performing the K-D test in all three conditions. Merely mild hypoxic symptoms were reported by participants: 4 (16%) light-headedness, 4 (16%) dizziness, 2 (8%) increased rate and/or depth of breathing, and 2 (8%) loss of concentration, and finally, 1 (4%) warmth, 1 (4%) lip paresthesia, and 1 (4%) blurred vision.

Baseline Test completion time in normoxia was measured after all subjects were familiar with the K-D test by practicing it twice. The 1st practice K-D test completion time during the familiarization/learning process was longer than the following Baseline Test [50 vs. 46.3 s, F(1,48) = 1.25, P = 0.27, one-way ANOVA] with no statistical significance. The average difference of 3.7 s reflected a slight learning effect before the start of the experiment. There was no difference in completion time between the 2nd practice K-D test and Baseline Test [46.6 vs. 46.3 s, F(1,48) = 0.01, P = 0.93, one-way ANOVA], which showed that learning was achieved in all subjects prior to the first recorded baseline test. These results confirm that the learning effect did not influence subsequent results between baseline normoxic and hypoxic conditions.

From **Fig. 2**, the K-D test completion time during 3 min of hypoxia was significantly longer (worse) than on the Baseline Test [54.5 ± 12.4 s hypoxic vs. 46.3 ± 10.4 s baseline, F(1,48) = 6.23, P = 0.016, one-way ANOVA]. Upon returning to normoxia (i.e., breathing normal air for 3 min), the completion time was significantly shorter than on the Hypoxic Test [47.6 ± 10.6 s Post Test vs. 54.5 ± 12.4 s hypoxic, F(1,48) = 4.42, P = 0.04, one-way ANOVA]. There was no statistically significant difference between Baseline Test and Post Test [F(1,48) = 0.1, P = 0.75], showing that all subjects returned to their normoxic baseline levels. The slight increase in the average K-D completion time in the Post Test vs. Baseline Test may indicate either a subtle post-hypoxia effect and/or experiment related fatigue.

Fig. 3 shows an 18% increase in K-D completion time from the Baseline Test to the Hypoxic Test with a statistical power of 95%. The effect of hypoxia is associated with a clinically and statistically significant change with the effect size of Cohen's d = 0.8 (large effect) on the K-D test completion time.

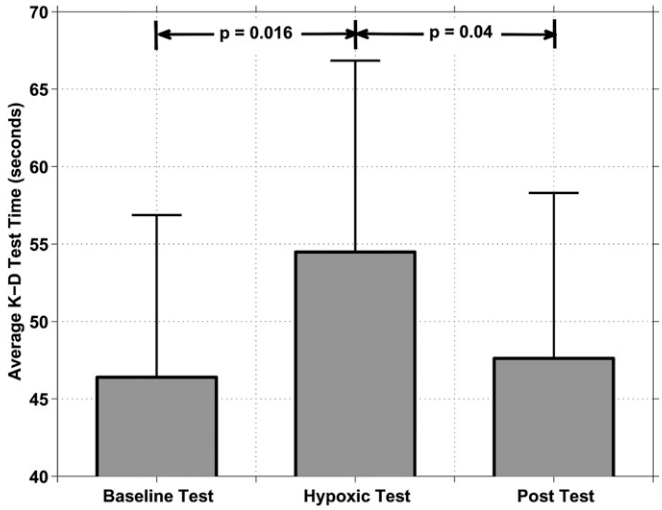

Fig. 2. Comparing average K-D test completion time in baseline normoxic, hypoxic, and post test normoxic conditions.

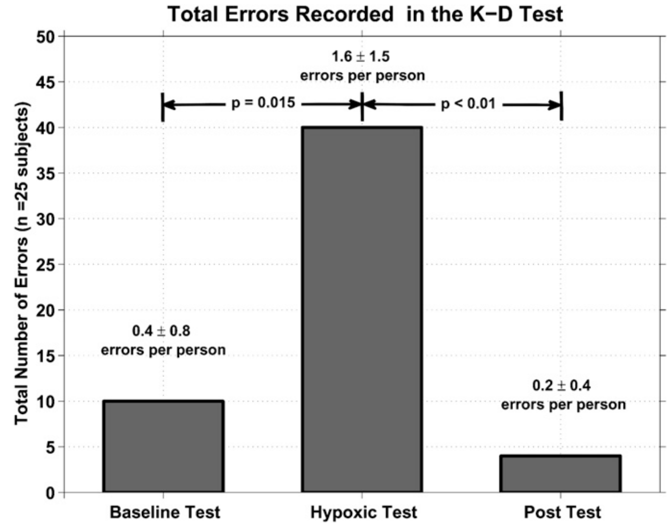

Fig. 4. Total number of errors by 25 subjects in performing the K-D test in baseline normoxic, hypoxic, and post test normoxic conditions.

To indicate an appropriate contribution of the completion time of each test card to the overall K-D test time, we analyzed the internal consistency reliability (12) by measuring the respective correlations [Cronbach's alpha] of 0.98 (test card 1), 0.98 (test card 2), and 0.97 (test card 3) between individual test card completion time and the total K-D test time during baseline.

The number of errors in the K-D test was significantly higher in hypoxia than in the baseline normoxia (**Fig. 4**). The total of 10 errors per 25 subjects during the Baseline Test (rate of 0.4 ± 0.8) is significantly lower than the 40 errors per 25 subjects (rate of 1.6 ± 1.5) during the Hypoxic Test [$F(1,48) = 11.37$, $P = 0.015$]. In post testing errors were minimal and significantly fewer than the number of errors during hypoxia [$F(1,48) = 19.64$, $P < 0.01$].

Fig. 5 shows the S_po_2 values across all 25 subjects throughout the experimental conditions. The S_po_2 decreased from 98 ± 0.9% to 80 ± 7.8% after 3 min on the hypoxic gas mixture (8% O_2 balance N_2, equivalent to 23,300 ft or 7101 m). During the hypoxic K-D test, S_po_2 decreased further to 75.8 ± 8.3%. All subjects recovered to their near normal baseline S_po_2 levels (96.3 ± 2.6%) in the first 2 min after hypoxia while breathing room air and recovered fully by the end of 3 min to baseline S_po_2 levels (97 ± 2%).

DISCUSSION

Neurocognitive impairment in hypoxia affects multiple neurological functions. Hochachka et al. (14) reported a reduction in brain activity in three frontal areas, the left occipital lobe and the right thalamus, and observed a bilateral increase in the cerebellum activity after extreme altitude exposure by evaluating the brain glucose metabolism with Positron Emission Tomography. The most commonly studied effect of hypoxia is the impact on the reaction time (RT). RT is a sensitive index of exposure at altitudes above 8000 ft (2438 m).

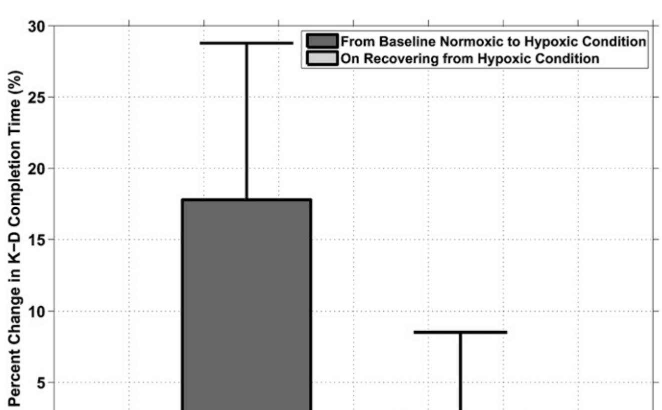

Fig. 3. Percent change in K-D test completion time during hypoxic and post test normoxic conditions in reference to prebaseline time.

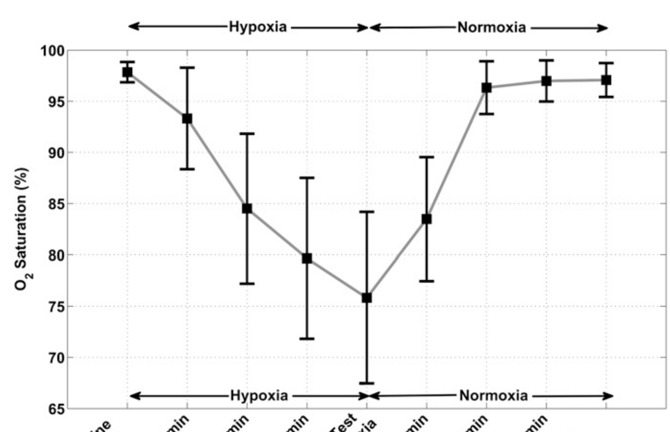

Fig. 5. Arterial oxygen saturation level during all stages of the experiment across all 25 subjects.

Auditory and visual stimuli have been used in order to evaluate the impact of hypoxia on the RT. In both cases a dose-dependent rise in the threshold of detecting the stimuli has been shown (10).

Impairment in language and verbal fluency has also been repeatedly reported (20). West (23) showed alterations in language production and an increase in aphasic errors. Deficits in the speech motor control and in syntax comprehension were observed as five members of the 1993 American Sagarmatha Expedition ascended Mt. Everest (16). The time needed to comprehend simple spoken English sentences increased by 50% at higher altitudes, and was correlated with deterioration of motor speech. The authors concluded that this pattern of deficits was similar to that noted for Parkinson disease and may reflect dysfunction of subcortical pathways to the prefrontal cortex.

Even though hypoxia produces measurable impairment in a number of cognitive domains, one of the limitations in interpreting past research is the diversity in methods used to study the problem. Viruès-Ortega et al. (22) proposed four criteria as a requirement for a standardized neuro-cognitive test: known psychometric properties, low practice and ceiling effect, suitability of administration by a nonexpert, and being affected by altitude in at least one study. The K-D test meets the first three criteria. Galetta et al. (12) demonstrated that the K-D test is a sensitive neuro-cognitive tool able to detect the deleterious effect of concussion on visual tracking. The K-D test assesses vision, attention, language, and other areas that correlate functions of brainstem, cerebellum, and cerebral cortex. The K-D test is portable and easily adaptable, requiring less than 1-2 min to complete without need for a medical professional or trainer to administer it. To date, no clinical studies have been performed to evaluate the utility of the K-D test in detecting and quantifying hypoxic impairment. The present study is the first to demonstrate altered cognitive performance in hypoxia using the K-D test. We showed an 18% increase in K-D completion time from Baseline Testing to Hypoxic Testing with a statistical power of 95%. This confirms that hypoxia induced a clinically and statistically significant change on K-D test performance, satisfying the fourth criteria of Viruès-Ortega et al. (22) and making the K-D test an applicable neuro-cognitive test for hypoxic impairment.

A limitation of neuro-cognitive tests is the learning effect, as task performance may improve over the course of the testing (4). The K-D test shows a decrease in time (improved performance by 2.5 s) over the course of two testing sessions, with an interval of 15 min (12). Based on this observation, we considered beginning the experimental session only after two practice tests. Our results indicate that the 2nd practice test and Baseline Test showed no significant difference in completion time ($P = 0.93$) across all subjects, suggesting that the test learning process was completed before the experimental condition began. Our results also demonstrate that K-D completion time between Baseline and Post Test (46.3 ± 10.4 s baseline vs. 47.6 ± 10.6 s post test, $P > 0.05$) did not decrease (i.e., improved), indicating that post test performance was not influenced by a learning effect. A slight increase in completion time in the Post Test could be the effect of fatigue. Galetta et al. (12), however, found no evidence of fatigue effect in a team of basketball players tested immediately after an intense 2-h scrimmage, but instead noted an average performance improvement of 3.6 s from baseline values. The rise in the completion time in our Post Test therefore may reflect a transient aftereffect of hypoxia even though the S_pO_2 values recovered to baseline (97–98%) 1 min before the Post Test was administered.

The number of errors in the K-D test showed a fourfold increase in the Hypoxic Test compared to the Baseline Test (Fig. 4) in all subjects. This finding represents an early effect on cognitive performance even after short exposures to hypoxia (3 min) in the absence of any reported major clinical hypoxic symptoms. The psychomotor component was also evaluated by asking subjects to take control of the progression of the test by pressing the "space" key on the keyboard to proceed to the next card. In our hypoxia test condition, none of the subjects showed psychomotor impairment (i.e., premature or delayed action or pressing keys other than the "space" key to advance to the next test card) during the K-D test. Based on our previously reported results and observations (6), we posit that cognitive impairment represents a testable presymptomatic phase of hypoxic incapacitation. We propose the K-D test as a reproducible and quantitative tool to detect early signs of hypoxia associated cognitive impairment.

In conclusion, in this study the K-D test has been shown to be an applicable and effective neurocognitive test to detect impairment of cognitive performance at a presymptomatic stage of hypoxia. Further testing and study is warranted using this tool in acute hypoxic exposures that may be of relevance in the operational aerospace environment.

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REFERENCES

1. Bahrke MS, Hale-Shukitt B. Effect of altitude on mood, behaviour, and cognitive function. Sports Med 1993; 16:97–125.
2. Bonnon M, Noel-Jorand MC, Therme P. Psychological changes during altitude hypoxia. Aviat Space Environ Med 1995; 66: 330–5.
3. Bonnon M, Noel-Jorand MC, Therme P. Effect of different stay durations on attentional performance during two mountain expeditions. Aviat Space Environ Med 2000; 71:678–84.
4. Braude D, Goldsmith T, Weiss SJ. Assessing air medical crew real-time readiness to perform critical tasks. Prehosp Emerg Care 2011; 15:254–60.

5. Cable GG. In-flight hypoxia incidents in military aircraft: causes and implications for training. Aviat Space Environ Med 2003; 74:169–72.
6. Cahoon RL. Simple decision making at high altitude. Ergonomics 1972; 15:157–63.
7. Cavaletti G, Garavaglia P, Arrigoni G, Tredici G. Persistent memory impairment after high altitude climbing. Intl J Sports Med 1990;11:176–8.
8. Cymerman A, Muza SR, Friedlander AL, Fulco CS, Rock PB. Saccadic velocity and pupillary reflex during acclimatization to altitude (4300 m). Aviat Space Environ Med 2005; 76:627–34.
9. Davies EC, Henderson S, Balcer LJ, Galetta SL. Residency training: the King-Devick test and sleep deprivation: study in pre- and post-call neurology residents. Neurology 2012; 78(17):e103–6.
10. Fowler B, Prlic H. A comparison of visual and auditory reaction time and P300 latency thresholds to acute hypoxia. Aviat Space Environ Med 1995; 66:645–50.
11. Galetta KM, Barret 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; 76:1456–62.
12. 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):34–9.
13. Harris GA, Cleland J, Collie A, McCrory P. Cognitive assessment of a trekking expedition to 5100 m: a comparison of computerized and written testing methods. Wilderness Environ Med 2009; 20:261–8.
14. Hochachka PW, Clark CM, Matheson GO, Brown WD, Stone CK, et al. Effects on regional brain metabolism of high-altitude hypoxia: a study of six US marines. Am J Physiol 1999; 277:R314–9.
15. King D, Brughelli M, Gissane C. Concussion in amateur rugby union identified with the use of a rapid visual screening tool. J Neurol Sci 2013; 326:59–63. Epub ahead of print.
16. Lieberman P, Protopapas A, Kanki BG. Speech production and cognitive deficits on Mt Everest. Aviat Space Environ Med 1995; 66:857–64.
17. McLennan JG, Ungersma J. Mountaineering accidents in Sierra Nevada. Am J Sports Med 1983; 11:160–3.
18. Morgagni F, Autore A, Landolfi A, Torchia F, Appiani G. Altitude chamber related adverse effects among 1241 airmen. Aviat Space Environ Med 2010; 81:873–7.
19. Nunnally J. Psychometric theory, 2nd ed. New York: Mc Graw-Hill. 1978.
20. Petiet CA, Townes BD, Brook RJ, Kramer JH. Neurobehavioral and psychosocial functioning of woman exposed to high altitude in mountaineering. Percept Mot Skills 1988; 67:443–52.
21. Qin Z, Hu H, Ding L, Xiao H, Li J. Hand performance changes under acute exposure to moderate and mild hypobaric hypoxia. In: Remote Sensing, Environment and Transportation Engineering (RSETE) 2011 International Conference. 2011 June 24-26; Nanjing, China. IEEE; 2011. P.7617-7622,
22. Viruès-Ortega J, Buela-Casal G, Garrido E, Alcazar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychol Rev 2004; 14:197–224.
23. West JB. Human physiology at extreme altitude on Mt. Everest. Science. 1984; 223:784–8.
24. Yoneda I, Tomoda M, Tokomure O, Sato T, Watanabe Y. Time of useful consciousness determination in aircrew member with reference to prior altitude chamber experience and age. Aviat Space Environ Med 2000; 71:72–6.