Real-Time Effects of Normobaric, Transient Near-Anoxia on Performance

James C. McEachen; Amine N. Issa; Jan W. Marck; Lawrence W. Steinkraus; Bruce D. Johnson

INTRODUCTION: Recent physiological incidents involving pilots of high performance fighter aircraft have raised the question of whether inadvertent, short bursts of significantly reduced oxygen could negatively impact real-time performance. This study evaluated normobaric, real-time performance in the setting of transient near-anoxia to inform future countermeasure development.

METHODS: The study was performed on 12 healthy subjects without significant medical history. Following collection of baseline data, real-time performance changes were evaluated during sequentially increasing periods of near-anoxic gas exposure ($F_IO_2 = 1\%$) using a computer-based performance assessment tool. Both room air and 100% oxygen were used as the prebreathe/recovery gases. Statistical analysis was performed on the results.

RESULTS: Under normobaric conditions, subjects inspiring up to five near-anoxic breaths showed no significant performance decrement in either accuracy or effective actions per minute. Mean accuracy up to five near-anoxic breaths was 0.67 (SD = 0.01) as compared to a baseline mean of 0.68 (SD = 0.02). Hyperoxia had a protective effect on subject physiological response to near anoxia.

DISCUSSION: These normobaric findings offer an assessment of real-time performance changes in the setting of transient, near-anoxic gas exposure. Overall, the results help inform the design of increasingly complex aircraft oxygen delivery systems in terms of how tightly such systems must match the sea-level gas equivalent with increasing altitude. This is particularly relevant as such systems are being called upon to ensure safe aircrew operations across an expanding operational flight envelope.

KEYWORDS: transient hypoxia, cognitive performance, altitude, hyperoxia, borderline hypoxia.

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As the flight envelope of high performance aircraft continues to expand, many aerospace medicine specialists are calling for a deeper understanding of the real-time cognitive and physiological performance changes that govern human tolerance in such extreme environments.[17] Recent physiological incidents involving pilots of high performance fighter aircraft have raised the question of whether inadvertent, short bursts of significantly reduced oxygen could negatively impact an individual's real-time performance.

Throughout the 20th century, the literature is replete with research demonstrating the effects that acute and chronic hypoxia can have on an aviator's visual, motor, somatosensory, and neuropsychological function.[7,10,18] Advances in neurophysiology have shown that complex behaviors are regulated by neural circuits linking activity in different parts of the brain and that subcortical structures support these neural circuits by helping sequence motor and cognitive processes.[13] As seen in functional imaging studies and high altitude research, subcortical structures such as the basal ganglia and hippocampus are especially vulnerable to reduced oxygen.[2,8,12] With regard to anoxia, neuropsychologists have shown that nearly all persons surviving 5 or more minutes of complete oxygen deprivation sustain permanent brain damage.[12,19] Less studied in the literature is the impact that a transient exposure to near-anoxia

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can have on the real-time performance of an individual in terms of hand eye coordination, speed, and accuracy.

The focus of this project was to evaluate real-time performance in the setting of transient, normobaric near-anoxia to help inform future countermeasure development. This project used a computer-based assessment tool which allowed for near instantaneous evaluation of a subject's motor executive function during sequentially increasing bouts of transient near-anoxia. Concurrent monitoring of physiological metrics was also employed to obtain correlative indicators of subject health status. Based on a review of the literature, it was hypothesized that a sudden transient exposure of five or less breaths of near-anoxic gas would result in a significant difference ($p < 0.05$) in performance from baseline.

METHODS

Subjects

Enrolled in this study, which was approved by the Institutional Review Board of the Mayo Clinic (Rochester, MN), were 12 healthy, nonsmoking adult subjects (9 men, 3 women). Subjects were of moderate to high general fitness, participated in regular physical activity, and reported no significant medical history ($N = 12$, mean $\pm$ SEM, age $= 27 \pm 6$ yr, height $= 179 \pm 6$ cm, weight $= 77 \pm 13$ kg, BMI $= 24 \pm 3$ kg $\cdot$ m^{-2}). Exclusion criteria included any personal medical history of obstructive/restrictive respiratory disease, cardiovascular disease, metabolic disease, anemia (< 12 g $\cdot$ dl^{-1} for men, < 11g $\cdot$ dl^{-1} for women), migraines, current pregnancy, current tobacco use, or a body mass index in excess of 30 kg $\cdot$ m^{-2}. Informed consent was obtained from all of the test subjects. The cutoff threshold for stopping administration of hypoxic gas was an oxygen saturation of 65%.

Equipment

Subject performance was determined using a computer-based assessment tool developed by physiologists and neuropsychologists at the Mayo Clinic (Rochester, MN). This rapid cognitive assessment tool (RCAT) provided a real-time measure of executive performance with an overall test duration of approximately 1 min. The RCAT incorporated a combination of executive function tasks integrated into a spawning visual target model allowing for real-time evaluation of an individual's accuracy, response time, speed, and overall performance. The RCAT user interface used a mouse and keyboard. With the aid of an eye-tracking device (X60 Eye Tracker, Tobii, Danderyd, Sweden), the RCAT was also able to separate reaction time from movement time.

In a recent high-altitude research effort involving cognitive evaluation, the RCAT was evaluated against the Stroop test.[9] Both the RCAT and Stroop test successfully demonstrated the onset of a performance decrement with altitude as well as significantly predicting the presence of acute mountain sickness. In addition, results from this study showed strong test reproducibility with no significant difference in the variation between repeated attempts in a given RCAT testing session.

The primary metrics being reported in the RCAT analysis interface are: response time, accuracy, speed, and overall performance. Each individual's RCAT performance was evaluated in terms of their actions per minute (APM) to assess for any trends relative to baseline. This included an assessment for any change in the subject's good APM, bad APM, total APM, or a combination of the above. More specifically, good APM reflects the number of correct actions taken by an individual during the RCAT which resulted in an increase in their overall score. Similarly, bad APM reflects actions taken during the RCAT which resulted in a decrease in score. Total APM refers to the sum total of all actions (correct or incorrect) taken by an individual during the course of the RCAT to arrive at their score. Collectively these values provided a more detailed look at the impact a physiological stressor (such as near-anoxic gas) may have on the subject's executive function, including response rate, response pattern, and accuracy. Throughout the course of testing, performance metrics were sampled continuously at 10 samples per second, recorded, and analyzed in MATLAB.

Physiological data were monitored, collected, and analyzed in conjunction with the performance results. A pneumotachograph (MedGraphics preVent Pneumotach, Medical Graphics, St. Paul, MN) and a mass spectrometer (Marquette 1100 Medical Gas Analyzer, Perkin-Elmer, St. Louis, MO) were used to collect continuous gas exchange data. A two-way switching valve (Hans Rudolph 4285 series, Hans Rudolph, Kansas City, MO) was used to deliver gas mixtures to the subject. Cardiopulmonary metrics were noninvasively assessed using a hemodynamic monitor (Nexfin, BMEYE B.V., Amsterdam, The Netherlands). Arterial oxygen saturation data was noninvasively collected using reflectance pulse oximetry from the forehead (Nellcor N-595, Tyco Healthcare Group, Nellcor Puritan Bennett Division, Pleasanton, CA) and fingertip (Model 3150, Nonin Medical Inc., Plymouth, MN). Cerebral tissue oxygenation was monitored noninvasively using Near Infrared Spectroscopy (Equanox 7600, Nonin Medical Inc.).

Procedure

A pretest screening visit was conducted with all test subjects whereby they underwent hemoglobin testing and, if female, a urine pregnancy test. The subjects then practiced the RCAT and gained familiarity with its mechanics over the course of about 30 min. This was to minimize the effects of learning on the results and to establish a baseline for their skill level.

With the commencement of formal testing, subjects engaged in the RCAT performance assessment tool three times to establish a baseline at the start of the study (see **Fig. 1**). Subjects were advised to breathe normally rather than control the duration/volume of their breath to help avoid disruption of their performance evaluation. Once a baseline was established, the subject inspired two breaths of 1% oxygen (with return to room air by the next breath) while simultaneously beginning the RCAT performance task. After a minute of gameplay, the subject rested for 3 min and repeated the game without a gas transition. This sequence was repeated, adding another breath to the total, until the subject either reached five

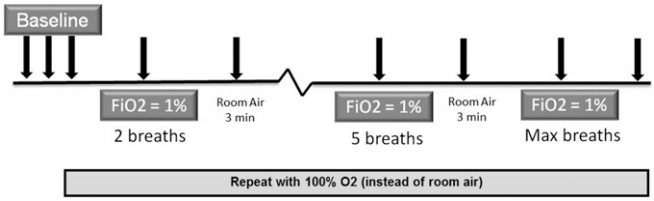

Fig. 1. Transient near-anoxia (F_IO_2 = 1%) test protocol. Following a baseline evaluation using the rapid cognitive assessment tool (RCAT), subjects received a sequentially increasing number of near-anoxic breaths as indicated in the figure above while performing the RCAT performance test (black arrows). A 3-min rest break was provided between all bouts. If the subject completed five breaths of 1% oxygen exposure without reaching the S_pO_2 cutoff threshold of 65%, a final bout was offered whereby the subject inspired the maximum number of near-anoxic breaths until they approached a S_pO_2 of 65%. The entire test sequence was conducted first using room air as the prebreathe/recovery gas followed by the use of 100% oxygen.

breaths of 1% oxygen or had a S_pO_2 of 65%. If the subject completed five breaths of 1% oxygen without reaching the 65% S_pO_2 cutoff threshold, the next test involved inspiring the maximum number of breaths until a S_pO_2 of 65% was achieved. These breaths were not randomized in the interest of safety. The entire trial was then repeated using 100% oxygen in place of room air as the prebreathe/recovery gas.

Statistical Analysis

All physiological data were gathered using PowerLab (ADInstruments, Colorado Springs, CO) then anonymized and imported into MATLAB (Mathworks Inc., Natick, MA) for analysis. Finger and forehead pulse oximetry data were initially viewed using Nonin software and then exported into MatLab for subsequent analysis. NIRS data were recorded directly into MatLab and analyzed. Eye tracking metrics were recorded using the Tobii system software and then exported into MatLab for analysis. All data streams (inclusive of physiological and performance metrics) were time synchronized and stored in a secure, local network computer cluster.

Statistical analysis was accomplished with each subject serving as their own control through accomplishment of a baseline evaluation before exposure to the formal transient hypoxia test procedure. All metrics were plotted for visual inspection of artifacts or missing data. Baseline and formal test data were acquired for each subject. Means and SDs were calculated for the RCAT metrics during each baseline and formal test sequence. These are referred to as the absolute values. To allow for examination of within subject variation, all absolute values were divided by their mean values during corresponding baseline games. These values are referred to as the relative values. To check if conditions result in significant differences within an experiment the Mann Whitney *U*-test was used.

RESULTS

Each study took approximately 3 h to complete from the time of initial set up and instrumentation to removing sensors and being dismissed. The baseline RCAT performance mean accuracy and SD while breathing room air was 0.68 and 0.02, respectively. Corresponding mean and SD performance scores for near-anoxic breath test sequences along with relative scores as compared to baseline and associated *P*-values are presented in **Table I**. With 21% oxygen used as the prebreathe/recovery gas, the mean RCAT performance accuracy score ranged from 0.67 to 0.69. Similarly, with 100% oxygen used as the prebreathe/recovery gas, the mean accuracy score ranged from 0.67 to 0.68. Transient, near-anoxic exposure to five or less breaths of 1% oxygen exhibited no significant difference in performance relative to baseline.

A composite summary of the subjects' APM data relative to each near-anoxic breath test sequence is presented in **Table II**. The data includes mean and SD total APM, good APM, and bad APM along with a comparison relative to baseline. The baseline value for total APM while breathing room air was 102 APM with a SD of 16. With regard to good APM and bad APM, the baseline values were 87 APM (SD = 14) and 15 APM (SD = 7), respectively. No significant performance decrement in terms of total APM, fewer good APM, or an increased number of bad APM was seen among subjects exposed to five or less breaths of near-anoxic gas as compared to baseline values.

Eight subjects underwent testing to assess the maximum number of breaths until desaturation approaching 65% using both room air and 100% oxygen as the prebreathe/recovery gases while performing the RCAT assessment task. Hyperoxia had a protective effect on subject response to anoxia as shown in **Fig. 2**. With room air as the prebreathe/recovery gas, subjects endured an average of 10 near-anoxic breaths (SD = 1) for an average duration of 39 s (SD = 9) until oxygen desaturation approaching 65%. With 100% oxygen used as the prebreathe/recovery gas, subjects inspired an average of 31 near-anoxic breaths (SD = 7) for an average duration of 100 s (SD = 29) prior to oxygen desaturation approaching 65%. Collectively, the results showed an average 61-s increase in performance duration with hyperoxia used as the prebreathe/recovery gas during normobaric, transient exposure to near-anoxic gas. While nearly all individuals were exhibiting signs of impaired performance by the time an oxygen desaturation of 65% was achieved, the use of oxygen saturation alone did not singularly define impaired performance in all individuals. This was most aptly demonstrated by a subject who endured 156 s of near-anoxic gas exposure prior to oxygen desaturation (using 100% oxygen as the prebreathe/recovery gas) and continued to demonstrate excellent RCAT performance and accuracy.

DISCUSSION

Under normobaric conditions at rest, this study evaluated real-time performance during and up to 1 min after inspiring near-anoxic gas. Subjects inspiring less than five breaths of near-anoxic gas showed no significant change in real-time performance accuracy within the 1-min evaluation window regardless of the prebreathe/recovery gas used (i.e., 21% oxygen

Table I. Performance Accuracy.

PRE-BREATHE/ RECOVERY GAS	NUMBER OF 1% OXYGEN BREATHS	ACCURACY		
		MEAN (SD)	MEAN ACCURACY RELATIVE TO BASELINE	*P*-VALUE
21% Oxygen	0 (Baseline)	0.68 (0.02)	1.00	--
	2	0.69 (0.02)	1.01	1.00
	3	0.68 (0.02)	0.99	1.00
	4	0.68 (0.03)	1.00	0.73
	5	0.67 (0.01)	0.99	0.06
100% Oxygen	2	0.68 (0.04)	1.00	0.73
	3	0.68 (0.02)	0.99	0.26
	4	0.68 (0.03)	1.00	0.73
	5	0.67 (0.03)	0.99	0.26

For each prebreathe/recovery gas, the RCAT mean and SD scores for near-anoxic breath test sequences are presented along with relative scores as compared to baseline and associated *P*-values.

or 100% oxygen). In addition, no significant decrement in total APM, good APM, or bad APM was apparent until after five near-anoxic breaths were inspired. A trend toward improved performance was noted in terms of increasing good APM and fewer bad APM at the more intense levels of transient hypoxia regardless of the prebreathe/recovery gas. This may suggest a learning effect, increased focus, or a compensatory physiological response in anticipation of the impending increased physiological stressor. When subjects were asked to inspire a maximum number of 1% oxygen breaths until achieving a 65% oxygen desaturation, the use of hyperoxia (i.e., 100% oxygen) as a prebreathe/recovery gas had a protective effect, allowing subjects to perform significantly longer during bouts of near-anoxia.

The computer-based performance assessment tool used in this study placed a high focus on motor executive function: specifically hand eye coordination, speed, accuracy, and reflexes. This is only a portion of total cognitive function. Dating back to the 1930s, several neurocognitive tests have been used to demonstrate the resultant impact of induced altitude hypoxia on cognitive tasks.[4,11,14] Cognitive and linguistic tests such as the Wisconsin Card Sorting Task (WCST), the Odd-Man-Out test (OMO), and the Mini-Cog have been cited for their utility in assessing hypoxia-induced cognitive impairment.[13,15,16] During brief exposures to oxygen levels comparable to an altitude of 16,000 ft, deficits on a symbol substitution task and in motor speed were apparent while vigilance, verbal fluency, and immediate memory remained intact.[1] In a longer duration hypoxia study of Mount Everest climbers, speech motor sequencing errors increased as climbers ascended, reflecting degraded basal ganglia activity.[3,13] The variety of tests used by these other studies allude to different aspects of cognitive function that have varying degrees of sensitivity to hypoxia. Future work should consider a combination of these tests in the setting of transient hypoxia to explore such effects.

The findings in this study complement the work of Dr. Ernsting's team with regard to assessing performance during and immediately following a rapid, transient exposure to a near-anoxic altitude (i.e., rapid decompression from 8,000 ft to 40,000 ft). Specifically, his team noted that when air was breathed before and for 8-10 s after a rapid decompression in 2 s from 8,000 ft to 40,000 ft, no decrement in the subject's ability to recall a learned sequence was seen until about 12-14 s after exposure to near-anoxic gas.[5,6] Our normobaric results provide a demonstration of retained performance with up to five breaths of 1% oxygen based on near instantaneous assessments of accuracy, response time, speed, and overall performance.

Dr. Ernsting's team also demonstrated that the severity of hypoxia was directly influenced by the composition of the gas breathed prior to decompression.[5,6] More specifically, as

Table II. Performance in Terms of Actions per Minute (APM).

		RECOVERY GAS = 21% OXYGEN				RECOVERY GAS = 100% OXYGEN			
	BASELINE	2 BREATHS	3 BREATHS	4 BREATHS	5 BREATHS	2 BREATHS	3 BREATHS	4 BREATHS	5 BREATHS
APM (mean/SD)									
Total	102 (16)	102 (15)	101 (16)	105 (17)	107 (15)	103 (15)	107 (15)	104 (14)	106 (16)
Good	87 (14)	90 (12)	89 (14)	93 (13)	95 (11)	88 (14)	92 (11)	89 (11)	94 (15)
Bad	15 (7)	12 (5)	12 (5)	12 (7)	12 (6)	15 (7)	15 (8)	15 (7)	12 (6)
APM (relative to baseline)									
Total	--	1.00	1.00	1.02	1.05	1.00	1.04	1.02	1.04
Good	--	1.03	1.02	1.05	1.08*	1.01	1.06*	1.03	1.08*
Bad	--	0.87	0.93	0.81	0.83	0.95	0.89	0.98	0.77*

F_{IO_2} = 1% for each set of breaths. For each prebreathe/recovery gas, the mean and SD total APM, good APM, and bad APM are listed. Also shown are the APM relative to baseline for each prebreathe/recovery gas along with associated *P*-values.
* Refers to $P < 0.05$.

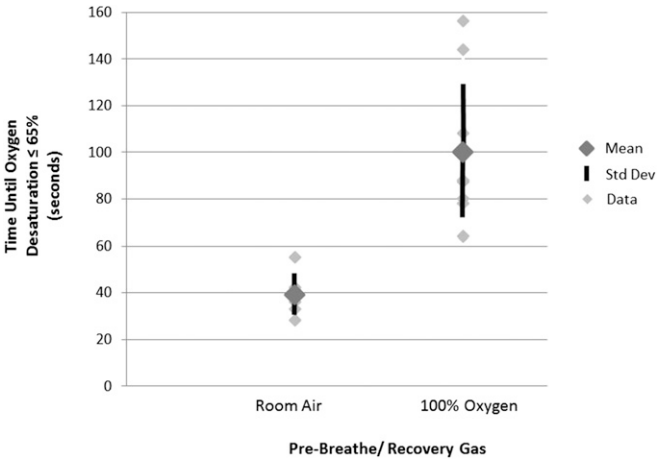

Fig. 2. Impact of prebreathe/recovery gas selection on the duration of time a subject engaged in the performance task before oxygen desaturation approaching 65%.

the concentration of oxygen breathed prior to decompression was increased from 21 to 100%, the magnitude of hypoxia produced by the rapid decompression decreased.[5,6] Our normobaric results lend further credence to the use of hyperoxia as a prebreathe/recovery gas, allowing an individual to tolerate an increased duration of near-anoxia before the onset of desaturation and performance decrements. The findings in this study also attest to the importance of accounting for individual variability as seen in the performance of subjects who desaturated during the maximum near-anoxic inspiration test, but continued to perform well on the performance task versus other subjects who desaturated and performed poorly. Further research in this regard is recommended.

A notable limitation of this study is the absence of hypobaria, for which additional research is currently planned and certainly recommended. In addition, the study population was limited in both size and scope, with a focus on young, healthy individuals without significant past medical history. Expanding the size and scope of the subject population under evaluation could potentially add an additional measure of generalizability to the results. A third limitation concerns the lack of exercise as an operational analogue in the test protocol. Additional real-time cognitive performance research studies involving near-anoxic gas exposure in the setting of hypobaria and exercise are recommended to further assess the robustness of these results.

In summary, these results offer insight toward assessing whether inadvertent, short bursts of significantly reduced oxygen could negatively impact real-time performance. The use of transient near-anoxic gas exposure in this study provides an extreme example of such an occurrence paired with a real-time evaluation of subject performance along with a demonstration of the protective nature of hyperoxia as a prebreathe/recovery gas. These real-time performance results also help to inform the development of advanced aircraft oxygen delivery systems in terms of how tightly such systems must match the sea-level gas equivalent with increasing altitude. This has a direct impact on the complexity of oxygen delivery system design, which is particularly relevant as such systems are being called upon to ensure safe aircrew operations in a cost-effective manner across an expanding operational flight envelope.

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