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Hypoxia: Exposure Time Until Significant Performance Effects

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Hypoxia: Exposure Time Until Significant Performance Effects

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ABSTRACT

Previous research has shown that hypoxia affects the ability of an operator to take corrective action or enact emergency procedures, and this may occur prior to the times outlined in the Time of Useful Consciousness (TUC) table. The quality of and decline in performance preceding total incapacitation has so far not been examined. Thus, the aim of the current work was to complement the existing TUC table by examining the rate of cognitive decline. Three altitudes (20, 22, 25k ft) were simulated by a Reduced Oxygen Breathing Device (ROBD). Performance was tested with simple and choice reaction time tasks and analyzed as single minute time periods compared to performance at a sea-level baseline. An analysis of the third quartile of reaction time values revealed significantly slower responses during the hypoxia exposure trials when compared to their baseline counterparts, generally ahead of the times specified in the TUC table. Results from the current study suggest that hypoxia exposure can lead to a rapid destabilization of performance earlier than those times put forward by the TUC table. By focusing on the point of incapacitation, the TUC table does not capture the performance degradation experienced before loss of consciousness.

Key Words: Hypoxia, Time of Useful Consciousness Table, Human Performance

The effects of hypoxia while piloting modern tactical aircraft have been implicated in a substantial number of filed hazardous reports (HazReps) in addition to several mishaps involving the losses of planes and aircrew. Ambient air pressure decreases with altitude, leading to a lower concentration of oxygen by volume; an auxiliary oxygen supply is therefore necessary in order to maintain performance at high altitudes. Without such a supply, hypoxia leads to a sharp decline in alertness, attention, and cognitive functioning. While this phenomenon is not a recent development, the issue has become more pronounced with the current generation of aircraft. In the event of a failure within an oxygen delivery system such as the Liquid Oxygen (LOX) system, or the newer On Board Oxygen Generating System (OBOGS), pilots and aircrew have an extremely limited amount of time before yielding to the physiological stress accompanying hypoxia. The range of times that operational performance is able to be maintained can be found in the Time of Useful Consciousness (TUC) table, which specifies a temporal interval for specific altitudes above sea-level elevations (DeHart, 1985). Noted in the TUC table, as altitude increases, the time an operator can reasonably expect to maintain coherent function decreases.

Table 1

Standard Time of Useful Consciousness Values.

Effective Performance Time at Altitude		
Altitude		Effective
(m)	(ft)	Performance Time
5,500	18,000	15 min
6,700	22,000	10 min
7,600	25,000	3 to 5 min
8,500	28,000	2.5 to 3 min
9,100	30,000	1 to 2 min
10,700	35,000	30 sec to 1 min
12,200	40,000	15 to 20 sec
13,100	43,000	9 to 12 sec
15,200	50,000	9 to 12 sec

Research has indicated that pilots experiencing hypoxia are subject to mental blocks and a slowing of response time, as well as a failing of sensory function, working memory, and motor skills leading up to the time at which corrective action is no longer able to be taken (Fowler, Banner, & Pogue, 1993; Fowler, Elcombe, Kelso, & Porlier, 1987; Fowler & Nahthoo, 1997; Fowler & Prlic, 1995; Fowler, Prlic, & Brabant, 1994; Fowler, White, Wright, & Ackles, 1982; Phillips et al., 2009; Phillips et al., 2012). Regarding the characterization of the time of effective performance, it has been suggested that a pilot's capabilities are adequate enough to take corrective actions up to the point of incapacitation (i.e., the limits set forth in the TUC table). This assumption is reflected in procedures that require hypoxic pilots to recognize their own symptoms and initiate emergency procedures. However, it may well be the case that corrective action becomes impossible prior to incapacitation as cognitive performance begins to decline. Little effort has been made to assess the quality of performance in the time prior to incapacitation. The TUC table has been well-established for over 50 years, but it does not address these more subtle breakdowns in performance associated with hypoxic exposure.

Previous investigations have shown hypoxia-induced performance decrements on flight-related tasks, such as the inability to maintain a constant speed, heading, or altitude while performing a flight simulation (Gold & Kulak, 1972; Sausen, Wallick, Slobodnick, Chimiak, Bower, Stiney, and Clark, 2001). Participants in these studies demonstrated notable cognitive deficits prior to the loss of consciousness, but cognitive performance was not measured at time intervals sufficient to model the onset or rate of cognitive decline. An examination using smaller time intervals and outcome measures that are maximally sensitive to the effects of hypoxia would be required in order to model the onset of impairment and rate of cognitive decline in conjunction with decreasing blood oxygen saturation.

Hypotheses/objectives:

The aim of the current work was to complement the existing TUC table by examining the rate of cognitive decline at three different altitudes (20,000, 22,000, and 25,000 feet) in a more fine-grained, minute by minute analysis of performance. As such, deficits evidenced in task performance could be thought of as analogous to the decline in efficiency that is experienced by pilots in a hypoxic environment, where even minor disruptions to timely action potentially jeopardize mission success and safety. Performance was measured at one-minute intervals using Simple Reaction Time (SRT) and Choice Reaction Time (CRT) tasks under hypoxic conditions to assess the rate of cognitive deterioration throughout the exposure. These reaction time tasks permit the measure of decrements in behavioral alertness (indexed by shifts in speed) caused by the introduction of hypoxia. It was hypothesized that hypoxia exposure at or above 20,000 ft (equivalent to $\leq$ 10.5% oxygen at sea level) would result in measurable and significant detriments to task performance prior to the established TUC estimates.

Method

Participants

The protocol was approved by the Institutional Review Board at Naval Medical Research Unit Dayton (NAMRU-D). Twenty-one members of the military, contractor, and civilian community employed at Wright-Patterson Air Force Base served as participants in this study. They ranged in age from 22 to 46 years, with a mean age of 31.29 years. Potential participants were excluded if they had any pre-existing medical conditions that would disqualify them from safely being exposed to reduced oxygen levels, including a previous or current diagnosis of anemia, asthma, heart/circulatory disease, high blood pressure, sickle cell trait, or any pulmonary

or seizure disorder. Individuals were also disqualified if they had been diagnosed with pneumonia during the previous year, were habitual tobacco smokers, had lived at altitudes above 5,000 ft in the previous three months, consumed more than three alcoholic beverages per day (on average), or were taking any prescription medication (besides oral contraceptives). Likewise, those who were found to have low levels of hematocrit or hemoglobin (indicating low blood oxygen carrying capacity) were not considered. Participants who reported or tested positively for pregnancy were disqualified from the study, as the risks of hypoxia to a human fetus are currently unknown. Also, those taking over-the-counter medications, supplements, and vitamins were asked to abstain from consumption for 72 hours prior to participation in the study. Of the total number, three participants were excluded from the study based on these criteria.

Each participant included in the study was exposed to one of three normobaric hypoxia profiles: 20,000 ft, 22,000 ft, or 25,000 ft. Potential candidates were asked to engage in a single altitude exposure, but were also given the option to participate in the other altitude profiles, given that a full week had passed between exposures. Of the total number of altitude exposures during the course of the present study, seven sessions were recorded at the 20,000 and 22,000 ft exposure, while eight were recorded in the 25,000 ft exposure.

Apparatus

Reduced Oxygen Breathing Device-2 (ROBD). The ROBD-2 (Environics®) is a computerized gas-blending instrument that is used to simulate varying altitudes in a normobaric environment. The system uses Thermal Mass Flow Controllers to combine breathing air and nitrogen to produce altitude-equivalent O_2 contents (4.4 - 21% oxygen) for altitudes from sea-level to 34,000 ft. The device is also capable of delivering 100% O_2.

ADInstruments model ML206 Gas Analyzer. The ADInstruments model ML206 uses an infrared CO_2 sensor and optical O_2 detector connected to a vacuum sampling pump attached to a port in the flight mask. The analyzer samples the gas mixture in the mask to monitor equipment function and participants' breathing.

Software. The LabVIEW software suite was used to control the ROBD and record participants' physiological and self-reported symptoms. Additionally, the PowerLab computer system interfaced with the gas analyzer to measure levels of carbon dioxide (CO_2) and oxygen (O_2) in participants' expired breath. Stimulus presentation and response recording were orchestrated by proprietary software developed at NAMRU-D.

Flight helmet and mask. A standard Navy issue aviator's mask was used to deliver gases from the ROBD. The mask was attached to a standard flight helmet.

Nonin® model 8000 R Ear Cup Sensor. The Nonin® model 8000 R in-helmet ear cup reflectance sensor is an oximeter that measures arterial oxygen saturation (SpO_2) from the temporal artery.

Datex-Ohmeda 3900 P Pulse Oximeter. The Datex-Ohmeda 3900 P pulse oximeter measured SpO_2 at the index finger on the non-dominant hand.

CNAP® 500 Continuous Blood Pressure Monitor. The CNAP® Monitor 500 is a standalone, noninvasive unit that continuously measured blood pressure during exposure using a standard cuff on the dominant arm and finger cuffs on the non-dominant middle and ring fingers.

Propaq® Encore Medical Monitor. This monitor was used to index blood pressure and heart rate frequency data during screening. Participants were fitted with a standard blood pressure cuff on the dominant arm.

i-Stat®1 Analyzer. The i-Stat®1 Analyzer assessed hematocrit and hemoglobin levels using a small sample of drawn blood to determine medical eligibility.

Tasks

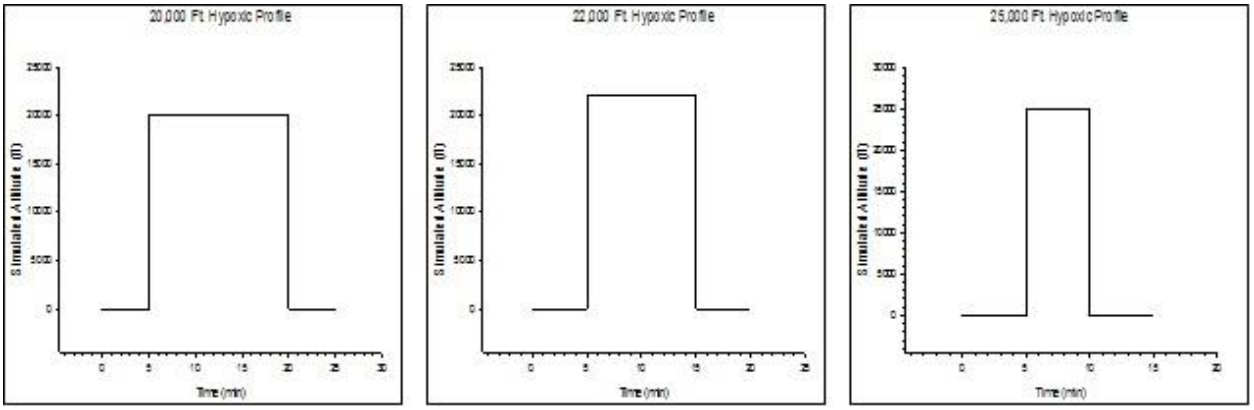
Simple Reaction Time/Choice Reaction Time Task (SRT/CRT). The SRT/CRT combined task is designed to measure the speed of response to a visual target where the response to the stimulus is either predictable (SRT) or unpredictable (CRT). The SRT and CRT tasks were presented in random, sequential groups, each lasting up to 30 sec. Following the first series of presentations, the participant performed the alternate task for up to an additional 30 seconds to form a minute long task block. For the SRT trials, participants were required to hold down the "5" key on a keyboard numeric pad until an up arrow appeared, at which time the "5" key was released and the "8" key was pressed. The task instructions for the CRT were similar to those given for the SRT, but the target arrow could point up, down, left, or right. Participants were required to depress the key on the numeric key pad corresponding to the direction of the arrow (i.e., 8 for up, 2 for down, 4 for left, and 6 for right). The arrow targets in both types of task were presented at random intervals ranging from 2,000 to 5,000 msec.

Design

Each of the three altitude profiles employed a single-blind, cross-over design with participants completing a series of practice trials, the experimental hypoxia trials, and sea-level equivalent control trials. The altitude profile to which the participant was assigned determined the temporal length of the sequence of SRT/CRT trials – those exposed to the 20,000 ft profile participated in the reaction time trials for 15 min during each visit, while those assigned to the 22,000 and 25,000 ft profiles participated for 10 and 5 min, respectively. Regardless of altitude,

the experimental trials were preceded and followed by 5 minutes of sea-level O_2 exposure. The time course of all three altitude profiles can be seen in Figure 1.

Figure 1. Hypoxic Exposure Profiles at 20,000 ft., 22,000 ft., and 25,000 ft.



Procedure

During the first of three visits to the laboratory, participants completed an informed consent form after receiving an explanation of the study and potential risks associated with a normobaric hypoxia exposure. Following this, participants completed a medical screening questionnaire which solicited information regarding any factors that could impact inclusion in the study. After the questionnaire, all female participants provided a urine sample for pregnancy testing. Participants' blood pressure was tested to screen for hypertension and a blood sample was taken to be tested for hematocrit and hemoglobin levels to ensure their blood was capable of carrying the normal amount of O_2.

After the screening and consent processes, eligible participants were sized for a flight helmet, flight mask, and blood pressure cuffs. Participants then donned the experimental equipment, which was tested for basic levels of comfort and signal quality from the

physiological sensors. During this time, participants were trained on the SRT/CRT tasks and engaged in five one-minute practice blocks.

Participants could choose to combine the consent/screening process with the first exposure or do the sessions separately. If the participant completed the informed consent and practice session separately from the exposure, the participant returned 24 hours later and completed a questionnaire which confirmed compliance with pre-established alcohol, caffeine, supplement, and medication usage standards given during consent and female participants were again administered a pregnancy test. Otherwise, these steps were omitted and subjects donned all aforementioned equipment and monitoring devices.

Upon donning the needed monitors and equipment, participants were exposed to either a mixture of sea-level O_2 or one of the reduced concentration O_2 mixtures, depending on the random order of assignment. Participants performed the SRT/CRT trials throughout the ensuing exposure, ending when the appropriate amount of time had elapsed or for one of the following reasons: 1) if the participant exhibited symptoms of presyncope (non-responsiveness), 2) an SpO_2 level below 60% on either oximetry sensor was measured, 3) a 30% change from baseline blood pressure was observed, or 4) the participant requested to be removed from the hypoxia stimulus. Subsequent to SRT/CRT block during the exposure, subjects were queried by the investigators regarding any experienced symptoms and their severity, the most common of which are listed in Table 2 below.

Table 2

Common Symptoms Associated with Hypoxia.

Common Symptoms	
Tingling	Shortness of Breath
Hot Flashes	Blurred Vision
Cold Flashes	Nausea
Dizziness	Apprehension
Tunnel Vision	Pressure in Eyes
Trouble Concentrating	Fatigue
Light Dimming	Lack of Coordination
Euphoria	Headache

Upon reporting for the next day, participants completed the same tasks as the previous day, but were exposed to the experimental condition (hypoxia or placebo) they had not yet experienced.

Results

Control Issues

Preliminary inspection of the data indicated that dropout among participants was relatively common during the experimental trials. To complete the analysis, a simple linear regression was used to replace missing data cells for cases in which the participant was unable to finish the prescribed protocol. For the three altitudes, 20,000 ft, 22,000 ft, and 25,000 ft, the missing data accounted for 18%, 18%, and 6.5% of the total number of cases, respectively.

The issue of deterioration in performance was addressed in terms of the relative quality of responses. An examination of reaction times in this manner represented the most basic determination of deviations from baseline, which was expressed as a difference score between an individual's hypoxia exposure trial and the temporally correspondent placebo trial. Thus, the final index for analysis was represented by the following equation:

$$\boldsymbol{RT}_{Hypoxia} - \boldsymbol{RT}_{Placebo} = \Delta \boldsymbol{RT}$$

Performance Efficiency

Means of median response time difference scores between the hypoxia and placebo trials are displayed for each of the three altitudes, 20,000, 22,000, and 25,000 ft, in Figures 2, 3, and 4, respectively. Individual samples t tests were employed to evaluate each of the difference scores in the figures against a hypothesis of no (zero) change with an alpha level set at .05.

As can be seen in Figure 2, a significant difference was found between the SRT placebo and hypoxia trials for those in the 20,000 ft exposure starting in Minute 2, $t(6) = 3.83$, $p = .009$. No significant differences were found between the experimental trials with respect to the CRT task, $p > .05$.

An inspection of the data collected from those in the 22,000 ft condition indicated an increment in response time between the placebo and hypoxia trials in the SRT task, but a relative stability in the CRT task, which can be seen in Figure 2. These impressions were confirmed, revealing a significant difference in the SRT task during Minute 5, $t(6) = 3.36$, $p = .015$, but showing no significant changes in reaction time in the CRT task, $p > .05$.

Median reaction time difference data from those in the 25,000 ft condition is plotted in Figure 2. A similar rise in reaction times is evident in both the SRT and CRT tasks throughout the exposure, with the difference between the placebo and hypoxia trials becoming significant during Minute 4, $t(7) = 3.68$, $p = .008$, and $t(7) = 2.70$, $p = .031$, for both task types.

Figure 2. Median response time differences between the hypoxia and placebo trials in the SRT and CRT tasks

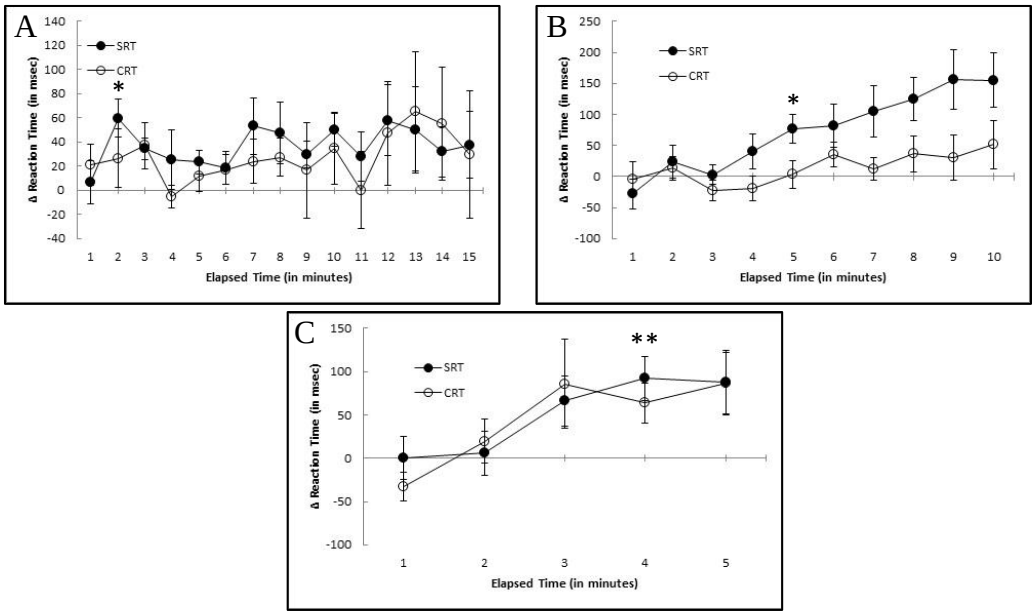


Figure 2. (A) Median response time differences between the hypoxia and placebo trials in the SRT and CRT tasks for 20,000ft altitude. Error bars are standard errors. (B) Median response time differences between the hypoxia and placebo trials in the SRT and CRT tasks for 22,000ft altitude. Error bars are standard errors. (C) Median response time differences between the hypoxia and placebo trials in the SRT and CRT tasks for 25,000ft altitude. Error bars are standard errors. Asterisks indicate significant differences from placebo (* for SRT, ** for SRT and CRT).

Third Quartile Analysis.

Concordant with a view proposed by Sanders (1983), a considerable amount of research regarding stress state variables has shown that there is a close tie between external stressors and reaction time performance. It was suggested that a stressor (hypoxia, in this case) would affect reaction time in such a manner that the magnitude of slow responses would increase, seen at the higher end of the response distribution, while its effects would remain absent at the middle portion and lower end, leaving the overall distribution of response times largely unchanged. Thus, a traditional examination of the variance surrounding the mean or median of a distribution

would have little power to detect a true change brought forth by this type of environmental stressor. In other words, hypoxia may have increased the number of lapses but this would not necessarily be captured by traditional analysis methods relying on measures of central tendency. Therefore, to further examine the effects of hypoxia on performance, the third quartile of the response distribution was analyzed for differences between the placebo and hypoxia trials in both the SRT and CRT task types.

Difference scores between the placebo and hypoxia trials observed in the third quartile of median response times during the 20,000 ft exposure are plotted as a function of elapsed time in Figure 3.

An analysis of the difference scores between the placebo and hypoxia trials among those in the 20,000 ft group revealed significant changes during Minute 3 of the SRT task, $t(6) = 6.46$, $p = .001$, and Minute 10 of the CRT task, $t(6) = 2.52$, $p = .046$, consistent with similar findings examining the third quartile or slowest 10% of reaction time distributions when exposed to hypoxic stress as compared to a median analysis of the same data distribution.

As in the previous analysis, those within the 22,000 ft condition demonstrated a differing pattern of results than that seen in the median analysis. As can be seen in Figure 3, significant differences were found in between trials in Minute 5 of the SRT task, $t(6) = 4.05$, $p = .007$, and Minute 6 of the CRT task, $t(6) = 3.04$, $p = .023$.

Along these lines, significant differences were found in the 25,000 ft condition during Minute 3 in the SRT task, $t(7) = 2.49$, $p = .042$, and Minute 2 in the CRT task, $t(7) = 5.15$, $p = .001$, seen in Figure 3. Both times represented a marked change from the median analysis, and fell at or below the minimum times outlined in the TUC table.

Figure 3. Response time differences between the hypoxia and placebo trials

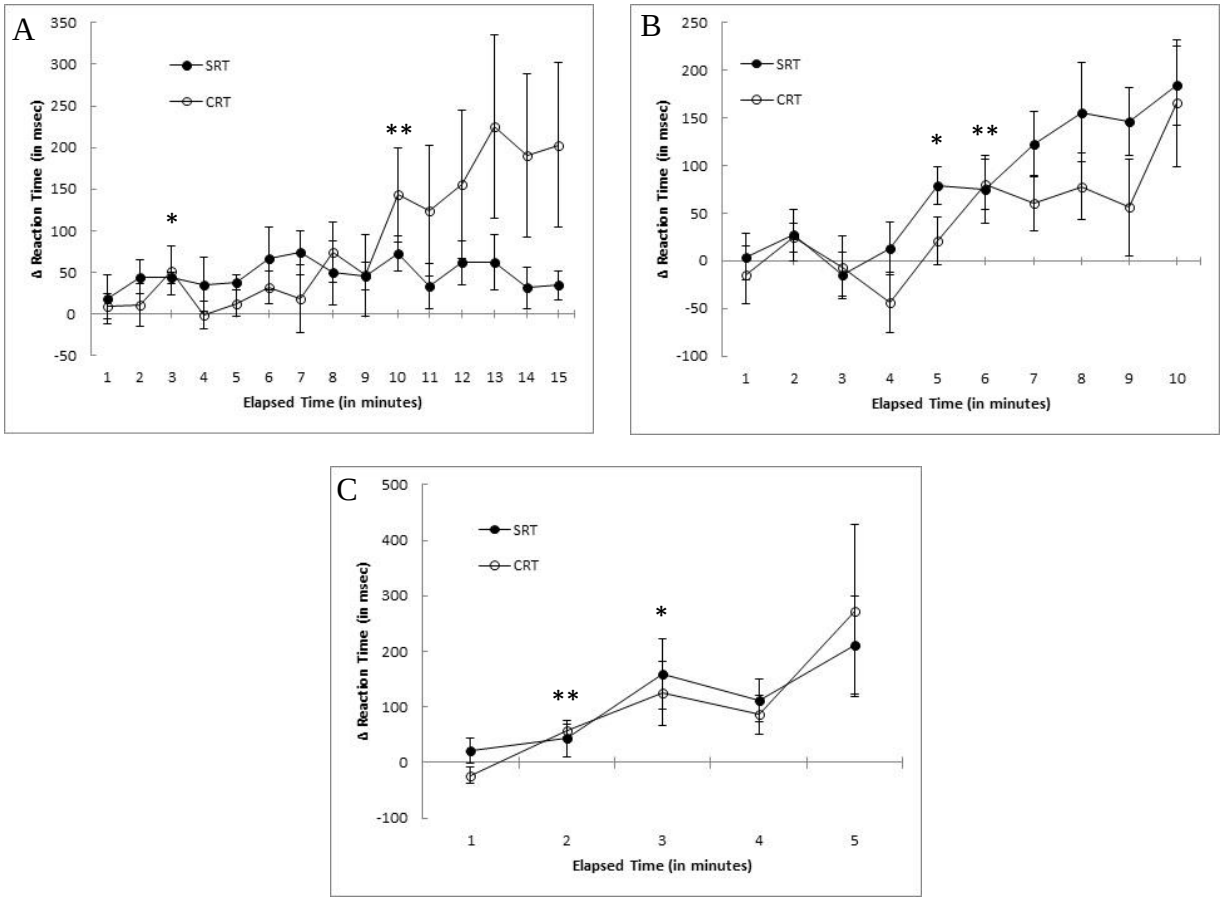


Figure 3. (A) Response time differences in the third quartile between the hypoxia and placebo trials in the SRT and CRT tasks for 20,000ft altitude. Error bars are standard errors. (B) Response time differences in the third quartile between the hypoxia and placebo trials in the SRT and CRT tasks for 22,000 t altitude. Error bars are standard errors. (C) Response time differences in the third quartile between the hypoxia and placebo trials in the SRT and CRT tasks for 25,000ft altitude. Error bars are standard errors. Asterisks indicate significant differences from placebo (* for SRT, ** for CRT).

Discussion

A central feature of the classification of hypoxia with regard to the TUC table is the assumption of the relative stability of performance prior to reaching the times outlined therein. However, a careful review of the current literature could lead one to challenge that assumption,

as individuals vary greatly in their response to hypoxic stress. For that reason, the goal of the present study was to examine the temporal envelope of the effects of hypoxia in a more fine-grained manner to establish a veridical onset time for performance deficits before the time ranges specified within the TUC table. Toward that end, one-minute intervals were used in which the time course of performance was charted.

When examining the subjects' median response times, it was found that hypoxic exposure did not broadly diminish the subjects' speed of reaction beyond that of the times outlined in the TUC table. Following the procedure recommended by Sanders (1982) and Dinges & Powell (1988), however, produced more telling results. The skewedness of the distribution was taken into account, and the third quartile values were examined for differences between the hypoxia and placebo trials. When examining what could be considered lapses, the slowest 25% of responses, it became apparent that the effects of hypoxia on neurobehavioral performance involve a great amount of variability in the subjects' capacity to compensate for the physiological insult as the hypoxic exposure time increases. Consistent with expectation, deficits were soon apparent in participants' responses, as reaction times began to evidence declining performance much earlier into hypoxic exposure than those times found in the median analysis, often in advance of those times suggested by the TUC table. These data lend support to the hypothesis that, for the majority of altitudes examined, hypoxia disturbs performance at a measurable level prior to the times set forth in the TUC table and are consistent with findings reported by Phillips and his associates (2009).

The distinction in the results found among the median reaction times and the third quartile reaction times evokes a relatively recent concept that is primarily associated with sleep deprivation and fatigue research – the state instability hypothesis. The state instability hypothesis

suggests that individuals are able to maintain a static level of performance, even when enduring a physiological stressor such as hypoxia, through the allocation of progressively increasing amounts of effort, necessary to offset any negative effects (Dinges & Powell, 1988). When this effort is enough to overcome the deleterious effects of the stressor, performance will appear relatively stable for a short period. Participants can temporarily increase their attention to compensate in the face of increasing physiological demand, but cannot sustain it. For example, when the need for sleep is high, the level of attention will increase to compensate, which produces highly variable performance and behavior (Zhou et al. 2011). Attention escalates and deescalates but not in a predictable or stable way. Over time, the ability to apportion cognitive resources to combat the decline in performance is depleted, and the frequency and severity of attentional lapses becomes more evident.

The analyses reported here document a decrement in reaction time performance prior to those times specified by the TUC table in the cases of those subjects exposed to altitudes of 20,000 ft and 22,000 ft. Initial indications of performance disruption began during minute three of the 20,000 ft exposure, approximately 10 minutes prior to the time specified in the TUC table, and minute five of the 22,000 ft exposure, roughly five minutes before the time specified in the TUC table. Contrary to expectation, however, the effects of hypoxic exposure on reaction time at 25,000 ft were not found to be significantly slower any earlier than those that had initially been outlined by the TUC table. It seems likely that any significant results in the earlier minutes were obscured by the high level of variability surrounding the observed mean as well as the lack of data points obtained before physiological or cognitive symptoms mandated a return to sea-level. One possible explanation is that participants demonstrated considerable individual differences in their ability to regulate the negative physiological and performance effects for a given length of

time, as evidenced by the magnitude of variability found within the first three minutes of the task. Conversely, in the fourth minute, a great reduction in variability is seen, indicative of an inability to compensate across the majority of subjects.

Based on the results presented here, it appears that the Time of Useful Consciousness table itself may be brought into question. Along these lines, the statistical practice of predicting individual behaviors based on an aggregation of data collected from a sample or group from which the individual is derived, known as ecological inference, can be questioned in physiological examinations such as these. Without the ability to draw on either the population mean or specific, individual-level data, this practice is often necessary to draw conclusions concerning the individual and a sample population. However, this type of application often results in inexact or even erroneous assumptions regarding the particular behaviors of the individual, when examined separately from the group mean. Also known as the ecological fallacy, this phenomenon occurs when undue attention is focused on group characteristics while minimizing the importance of individual contributions to the collective statistic.

In the case of those within this study, though drawn from a similar population and with many confounding extramural behaviors controlled for, individual tolerances to hypoxia and its effects on the reaction time task varied greatly among the subjects. In these instances, the pattern of results generated was not easily interpreted. The individual differences observed here suggest that using means for an important safety standard may not be the optimal solution. Simply aggregating the individual-level data into a group mean diminished the overall consequence of hypoxia, resulting in data insufficient to challenge the Time of Useful Consciousness table. When examined on an idiographic level, however, the conclusions to be reached are much different. The discrete results of the reaction time task render it likely that revisions to the current

TUC model are needed. As there are several contributing factors to an individual's susceptibility to hypoxia, such as physical fitness, the presence of cardiovascular or respiratory diseases, and increased metabolic demand, a more specialized approach based on subjective training throughout the individual's career seems necessary to focus the range of times within the TUC.

Regardless of future direction regarding the Time of Useful Consciousness table, the preponderance of results found in the current study demonstrate that aspects of cognitive functioning become compromised significantly earlier than predicted through the use of this tool. By focusing on the point of cognitive incapacitation, the TUC does not capture the nuances of performance degradation experienced before loss of consciousness. Furthermore, TUC is based on sample averages and may significantly overestimate the amount of time that an individual can remain at a specific altitude before total incapacitation. Given the potential consequences on flight safety, it is imperative to develop a complement to TUC that will account for operational deterioration. In addition, mitigation approaches beyond the simple recognition and reaction to hypoxic symptomology must be explored.

Disclaimers

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List of Tables

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7,600	25,000	3 to 5 min
8,500	28,000	2.5 to 3 min
9,100	30,000	1 to 2 min
10,700	35,000	30 sec to 1 min
12,200	40,000	15 to 20 sec
13,100	43,000	9 to 12 sec
15,200	50,000	9 to 12 sec

Table 2. *Common Symptoms Associated with Hypoxia.*

Common Symptoms	
Tingling	Shortness of Breath
Hot Flashes	Blurred Vision
Cold Flashes	Nausea
Dizziness	Apprehension
Tunnel Vision	Pressure in Eyes
Trouble Concentrating	Fatigue
Light Dimming	Lack of Coordination
Euphoria	Headache

List of Figures