Personal Hypoxia Symptoms Vary Widely Within Individuals

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INTRODUCTION: Exposure to high ambient altitudes above 10,000 ft (3048 m) over sea level during aviation can present the risk of hypobaric hypoxia. Hypoxia can impair sensory and cognitive functions, degrading performance and leading to mishaps. Military aircrew undergo regular hypoxia familiarization training to recognize their symptoms and understand the consequences of hypoxia. However, over the years, aviators have come to believe that individuals have a "personal hypoxia signature." The idea is that intraindividual variability in symptom experience during repeated exposure is low. In other words, individuals will experience the same symptoms during hypoxia from day to day, year to year.

METHODS: We critically reviewed the existing literature on this hypothesis. Most studies that claim to support the notion of a signature only examine group-level data, which do not inform individual-level consistency. Other studies use inappropriate statistical methods, while still others do not control for accuracy of recall over the period of years. To combat these shortcomings, we present a dataset of 91 individuals who completed nearly identical mask-off, normobaric hypoxia exposures days apart.

RESULTS: We found that for every symptom on the Hypoxia Symptom Questionnaire, at least half of the subjects reported the symptom inconsistently across repeated exposure. This means that, at best, 50% of subjects did not report the same symptom across exposures.

DISCUSSION: These data provide compelling evidence against the existence of hypoxia signatures. We urge that hypoxia familiarization training incorporate these findings and encourage individuals to expect a wide range of hypoxia symptoms upon repeated exposure.

KEYWORDS: hypoxia signature, aviation training, subjective symptoms, acute hypoxia.

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The partial pressure of oxygen is reduced at high altitudes, and exposure to this environment can result in a condition known as hypoxic hypoxia (hereafter referred to as "hypoxia"). Hypoxia can be debilitating and remains a primary threat in aviation. Sensory perception and cognition are impaired under hypoxia,[11] potentially leading to decrements in pilot performance and even incapacitation. A recent report highlights the impact of hypoxia on mishaps in tactical aviation communities.[7] Countermeasures to hypoxia include aircraft life-support systems, as well as familiarization training that instructs aviators to recognize symptoms of hypoxia and execute emergency procedures. This training is critical to help prevent in-flight hypoxia emergencies through recognition of the onset of hypoxic symptoms.

Hypoxia training began early in the history of aviation and continues to develop to leverage technological advancements and maximize its efficacy. Familiarization training in the U.S. Air Force and Navy has been standard since the 1940s and involves a controlled hypoxia exposure under instructor supervision. Initially, hypobaric chambers were used to induce hypoxia. More recently, cost and safety concerns led to the development of normobaric alternatives with similar efficacy, such as the Reduced Oxygen Breathing Device (ROBD; Environics®, Tolland, CT)[1] and Reduced Oxygen Breathing

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Environment, which became standard in naval aviator training. Efforts to simulate in-cockpit mask-on breathing more closely in tactical aircraft have led the Naval Aviation Survival Training Program to replace the ROBD with a new generation of tankless, on-demand, normobaric breathing devices, known as the Flight Breathing Awareness Trainer (Lynntech Inc., Rochester, IN), which is used in current hypoxia familiarization training.

Similar to advances in hypoxia delivery devices, protocols during familiarization training have also developed over time. In a standard U.S. Air Force protocol, students accompanied by an instructor ascend to varying simulated altitudes in a hypobaric chamber and learn to recognize corresponding impairments in their ability to perceive colors, complete basic cognitive tasks, and communicate. A current U.S. Navy protocol incorporates simulated flight in virtual reality during the exposure. The frequency of this hypoxia training is variable between the services and based on airframe. For example, naval aircrew undergo annual didactic hypoxia training and biennial Dynamic Hypoxia Training for Class 1 (ejection seat) aircraft or quadrennially for Class 2 (non-ejection seat parachute equipped) and Class 4 (pressurized, non-parachute equipped) aircraft.

Familiarization training also involves executing emergency procedures once the trainee notices physical or cognitive symptoms associated with hypoxia, such as “pulling the green ring” to trigger the flow of supplemental oxygen and initiating descent to a safer altitude. Satisfying this learning objective is especially critical as an aviator’s sensitivity to their own internal state remains one of the only tools to detect the onset of hypoxia during an in-flight emergency. Enabling this objective is a supposition that intraindividual variability in symptom experience is low. In other words, individuals each have a unique set of hypoxia symptoms or a “signature” that persists over time, across conditions, and with repeated exposures. In fact, one of the most popular Aerospace Medicine textbooks[15] states explicitly as it relates to hypoxia training: “Subjective experience is idiosyncratic and generally regarded as reproducible, although anecdotal evidence suggests that an individual’s symptoms may evolve and change with age.”

In this report, we critically review the literature and describe evidence for and against the existence of the “hypoxia signature” hypothesis. By applying common standards of statistical rigor to these studies, we show that across a variety of experimental conditions intraindividual variability in hypoxia symptom reporting remains high. If aviators think that they have a unique and stable set of hypoxia-related symptoms, they may fail to recognize alternative symptoms during an in-flight hypoxia event. Considering this, we recommend that current hypoxia familiarization training protocols incorporate this finding and encourage students to stay vigilant for a wider range of hypoxia symptoms.

There is a small extant literature on the reliability of hypoxia symptoms over time. This work has focused almost entirely on aircrew recognition of past and present symptoms during hypoxia familiarization training and/or experiences during flight. Two prior studies compared symptoms experienced by aircrew during a current training exposure and then compared those symptoms to recalled symptoms from 4–5 yr ago during their prior training exposure.[9,17] Both studies relied on recall of the symptoms with no method for assessing the accuracy of that recall. Having subjects recall prior symptoms and then going through an exposure to identify symptoms may have biased individuals to report symptoms that they recalled. Moreover, Woodrow and colleagues limited their analyses to group-level comparisons, which only suggests that on average across a large group, symptoms were consistent.[17] This tells us nothing about whether individual trainees reported consistent symptoms now compared to 5 yr ago. However, Smith did examine individual-level consistency and found that 65% of subjects reported the same five dominant symptoms across two familiarization trainings, and that hours of flights experience did not change that relationship.[14] Finally, one study creatively compared in-flight hypoxia symptoms to those experienced during ROBD training in aircrew; however, they used an inappropriate statistical test (i.e., Chi-squared) rendering their conclusions uninterpretable.[6] One of the assumptions of a Chi-squared is that each person can only contribute a single data point, and, therefore, this test should not be used with repeated-measures designs.[8] Clearly, in this study, subjects contributed multiple data points (i.e., in-flight and ROBD symptom reports). Taken together, these prior studies provide little defensible evidence for a hypoxia signature.

More recently, a few additional studies have examined this same question of how symptom reporting potentially changes (or does not change) over time. Leinonen et al. compared the time it took to recognize symptoms during prior training to current training. Indeed, they found that subjects were significantly faster to recognize the onset of symptoms during refresher, compared to initial training.[10] While they did not examine whether the same symptoms were recognized, their study nonetheless provided evidence in supporting the effectiveness of hypoxia familiarization training. There have been 2 additional studies examining the same dataset of 341 trainees and comparing current and recalled symptoms.[5,16] Tu and colleagues performed group-level statistical analyses and found no difference in symptom reporting between the current and recalled experiences.[16] However, they provided no empirical evidence that symptom reporting was consistent at the individual level. Chiang et al., on the other hand, recognized this shortcoming and did an individual-level analysis using a McNemar test.[5] They reported no significant difference in frequency of recalled in-flight symptoms and current chamber training symptoms. Unfortunately, no frequency data were provided, and no specific test statistics were included, other than a blanket “all Ps > 0.05” statement.

METHODS

Several prior studies afford an opportunity to examine the consistency of hypoxia symptoms in a tightly controlled experimental setting. Specifically, three prior studies all using normobaric, mask-off hypoxia exposure involved healthy subjects completing identical or near identical exposures days apart.[2–4] All three study protocols were approved by the Naval Medical Research Unit—Dayton's Institutional Review Board in compliance with all applicable federal regulations governing the protection of human subjects. Here, we combined data from these three studies to provide more statistical power in subsequent analyses. For all 3 datasets, we assessed whether a subject reported each of the 15 symptoms on the Hypoxia Symptom Questionnaire (HSQ).[13] We only examined the presence versus absence of each symptom in the two exposures, hence the data were nominal and include no information about symptom severity.

While details can be found elsewhere, we provide a brief description of each study in the below analysis. First, Blacker and McHail examined the time course of recovery following a 10-min exposure to 9.7% O_2 (20,000-ft equivalent).[4] The 2 exposures themselves did not differ at all and were an average of 28.2 d apart (SD = 40.7; included COVID-19 lockdown) for 27 subjects. Subjects reported their symptoms after exposure using free recall. Symptoms were then categorized into those included in the HSQ. Second, Blacker and McHail tested 33 subjects on two 15-min exposures with 9.7% O_2 (20,000-ft equivalent) an average of 8.78 d apart (SD = 16.17).[3] The only difference between these two exposures was that one included auditory stimuli being presented and the other presented visual stimuli. Subjects reported symptoms using the HSQ. Finally, Blacker used two 15-min hypoxia exposures that differed only in the simulated altitude used by comparing 9.7% O_2 (20,000-ft equivalent) and 11.6% O_2 (15,000-ft equivalent).[2] A total of 31 subjects completed the 2 visits an average of 8.13 d apart (SD = 5.16). Subjects reported symptoms using the HSQ.

Together, these datasets yielded 91 subjects with 2 normobaric hypoxia exposures each. To examine the consistency of symptom presence versus absence in the two exposures, we used a McNemar test.[12] A McNemar test is like a Wilcoxon signed-rank test, but is used on nominal instead of ordinal data.[8] This test is used when there is interest in how subjects' scores or evaluations change upon repeated administration. In other words, it tallies the number of people who changed their response (i.e., inconsistent symptom reporting) and the number who did not change their response (i.e., consistent symptom reporting), then compares the two. The dependent variable in question must be categorical with only two categories, and the two groups must be mutually exclusive (i.e., you cannot simultaneously report and not report the same symptom across both exposures). We therefore used a McNemar test on each individual symptom from the HSQ.

RESULTS

Table I reports several key metrics, including: the frequency at which each symptom was reported in at least one exposure; the frequency at which each symptom was reported in both exposures; the frequency at which each symptom was only reported in one out of the two exposures; and the McNemar test *P*-value. For example, of the 91 subjects included, fatigue was the most commonly reported symptom, with 58 individuals (63.74%) citing fatigue on at least 1 occasion. For those 58 individuals, 46.55% (*N* = 27) reported fatigue in both exposures, whereas 53.45% (*N* = 31) reported fatigue in 1 exposure and not in the other. This can be interpreted as approximately half of the individuals reporting this symptom consistently whereas the other half reported it inconsistently. Similar comparisons can be made by examining each symptom in Table I. The highest proportion of reporting a symptom in both exposures was breathlessness, which was a perfect 50/50 split between consistent and inconsistent reporting.

Table I. Individual Symptom Frequencies and Statistics.

SYMPTOM	FREQUENCY OF REPORTING SYMPTOM IN AT LEAST ONE EXPOSURE (%)	FREQUENCY OF REPORTING SYMPTOM IN BOTH EXPOSURES (%)	FREQUENCY OF REPORTING SYMPTOM IN ONE BUT NOT THE OTHER EXPOSURE (%)	McNEMAR TEST: *P*-VALUE
Fatigue	58 (63.74%)	27 (46.55%)	31 (53.45%)	[a]0.012*
Dizziness	54 (59.34%)	19 (35.19%)	35 (64.81%)	[a]0.018*
Breathlessness	52 (57.14%)	26 (50%)	26 (50%)	[a]0.327
Blurred Vision	41 (45.05%)	20 (48.78%)	21 (51.22%)	1.000
Tunnel Vision	41 (45.05%)	18 (43.90%)	23 (56.10%)	0.210
Light Dimming	35 (38.46%)	16 (45.71%)	19 (54.29%)	0.167
Loss of Coordination	34 (37.36%)	14 (41.18%)	20 (58.82%)	0.012*
Hot Flashes	34 (37.36%)	10 (29.41%)	24 (70.59%)	0.064
Tingling	33 (36.26%)	15 (45.45%)	18 (54.55%)	0.238
Headache	24 (26.37%)	7 (29.17%)	17 (70.83%)	0.332
Apprehension	22 (24.18%)	7 (31.82%)	15 (68.18%)	0.607
Nausea	16 (17.58%)	4 (25%)	12 (75%)	1.000
Euphoria	14 (15.38%)	4 (28.57%)	10 (71.43%)	0.021*
Cold Flashes	9 (9.89%)	0 (0%)	9 (100%)	0.039*
Loss of Consciousness	8 (8.79%)	1 (12.5%)	7 (87.5%)	1.000

Note: Frequency of symptom observation is out of a total of 91 subjects. Frequency of reporting symptom in both exposures or in only one exposure is out of the number of people who reported it at all.

*$P < 0.05$. *P*-values are all exact *P*-values using the binomial distribution unless otherwise denoted.

[a] = Asymptotic *P*-value.

Results of the McNemar test showed that fatigue, dizziness, loss of coordination, euphoria, and cold flashes had significantly different proportions of symptom presence between the two exposures; all *P*-values were less than 0.05. All other symptoms did not have a statistically significant difference in these proportions, all *P*-values were greater than or equal to 0.064. Table I contains exact and asymptotic (where applicable) *P*-values for each symptom.

DISCUSSION

The hypoxia signature presumes individuals exhibit a comparable set of symptoms across repeated hypoxia exposures, thereby enabling effective self-diagnosis on account of one's personal history of symptom manifestation. While group-level analyses of repeated hypoxia events support the notion that certain symptoms recur across exposures, there is a lack of within-subjects studies investigating individual-level experiences using appropriate statistical methodologies and rigor. The current study addressed this gap by comparing symptom reports of 91 subjects who underwent 2 near-identical normobaric hypoxia exposures using a within-subjects design and data-appropriate analyses.

This study examined reports of 15 hypoxia symptoms across 2 visits. Numerically, for all but one symptom, subjects were more likely to report experiencing the symptom in one exposure but not the other. That is, except for breathlessness, subjects did not experience the same symptoms across exposures. For five of the symptoms, a statistically significantly greater proportion of subjects reported experiencing the symptom in only one rather than both exposures. Our data suggest that some symptoms are more likely to occur than others, and that experiences of the same symptom across multiple exposures can happen—in some cases quite often. However, in no cases was a symptom reported as more likely to recur than not. We contend that these data refute the notion that individuals should expect comparable symptoms across repeated hypoxia exposures. Therefore, this study failed to find support for the hypoxia signature hypothesis.

Group-level analyses of reported symptoms, inaccuracies in textbooks, and anecdotal experiences may help explain the popularity of the hypoxia signature phenomenon. However, the very idea demands individual-level examination, rendering aggregated analyses inadequate. Further, while our data suggest some individuals will report experiencing the same symptom across repeated exposures, by no means should this be considered the law of the land – or a training course learning objective, for that matter. Indeed, we would argue that incorporating the message of variability in symptoms is critical to improving the effectiveness of hypoxia familiarization training.

Human physiology is complex and the ways and means by which our bodies respond to environmental threats vary according to a great diversity of factors. In a highly controlled repeated exposure study using near-identical hypoxic conditions, the variable that changes most is the human condition at the time of exposure. Fitness, fatigue, hydration, diet, distraction, dress, and stress are all potential contributors to hypoxia experiences. As these vary, so too might one's response to hypoxic conditions. Moreover, in our dataset examined here, we found wide intraindividual variability in symptom reporting with identical hypoxia delivery methods (i.e., mask-off, normobaric exposure). If we then consider symptom reporting across modalities (i.e., normobaric mask-off to hypobaric mask-on), we anticipate an even larger variability in symptom reporting within an individual. In fact, this variability across modalities may represent a means for improving training efforts by purposefully inducing hypoxia in multiple ways to highlight the inconsistency in subjective experience that can occur. While hypoxia does produce general patterns of symptom experiences, it is overly simplistic and grossly misleading to build an expectation that an individual will experience the same set of symptoms with each hypoxia exposure.

Here we detail both from the literature and an experimental dataset that evidence for a hypoxia signature is weak. While we attest that our data here are compelling, additional prospective studies are needed to further support this evidence. Future prospective studies will also need to incorporate more rigorous experimental designs and ensure that statistical analyses are appropriate and support the conclusions drawn. However, that is not to say that hypoxia familiarization training is not without its merits. For example, one study recently found that trainees were faster to identify subjective symptoms of hypoxia during refresher compared to initial training.[10] This is critical when seconds can mean the difference between a fatal mishap and a near miss. Until pilot physiological monitoring capabilities advance and become viable for in-cockpit warning systems, one of the only lines of defense against hypoxia and other respiratory threats is personal recognition of symptoms. Therefore, the narrative in which hypoxia familiarization training is contextualized needs to be carefully considered. Finally, more research is needed to support the development of future training approaches that consider the vast inter- and intraindividual differences that occur during hypoxia.

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