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Hypoxic Hypoxia at Moderate Altitudes: State of the Science

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14. ABSTRACT

A systematic literature review of research on acute hypoxic hypoxia within the range of 8,000 to 15,000 feet pressure altitude was conducted. The goal was to evaluate the state of the science regarding mild hypoxic impairment of mental functions, sensory deficits, and other pertinent findings that may affect aviation-related duties. Defence Technical Information Center and Dialog searchers were performed in conjunction with a research librarian. The minimum altitude where hypoxic deficits manifest remains unclear. Cognitive testing is often not reproducible under similar research conditions; measurements of visual decrements produce more consistent results. Cognitive deficits seem to be particularly difficult to quantify, possibly due to individual variability and lack of sensitivity and/or specificity of the cognitive test utilized. The manifestation of acute mild hypoxia at moderate altitude may not be solely a function of partial pressure of oxygen, but rather the balance of respiratory gases, possible disruption of oxygen-dependent neurotransmitter synthetic pathways, and the inherent hypoxia sensitivity of various neuron populations.

15. SUBJECT TERMS

mental function, sensory deficit, aviation, cognitive testing, vision, partial pressure of oxygen

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Introduction

The inherent danger of high altitude has been documented since the late 19th century. In 1875, Gaston Tissandier and his colleagues, Croce-Spinelli and Sivel, attempted a balloon ascent to 28,215 feet (ft) (8600 meters [m]). Only Tissandier survived this ascent. Despite having onboard oxygen (O_2) provided by Paul Bert (known as the "Father of Aviation Medicine"), this event marks the first two documented fatalities of hypobaric hypoxia. Hypobaric hypoxia is defined as the reduction of alveolar oxygen partial pressure (P_AO_2) resulting from the reduction in total atmospheric pressure that occurs with increasing altitude. Hypoxic hypoxia is the result of reduction in oxygen partial pressure in the arterial blood (P_aO_2), of which acute hypobaric hypoxia is one cause (Pandolf & Burr, 2001). In 1984, Ernsting stated, "The most important single hazard of flight at high altitude is hypoxia." The onset of hypoxia can be insidious and may easily result in an aircraft mishap if not quickly recognized and immediately corrected. It is well established that breathing ambient air at altitudes between 15,000 and 20,000 ft (4592 to 6096 m) produces gross physiological disturbances. Above 20,000 ft, mental and physical performance rapidly deteriorate leading to convulsions, unconsciousness, and death. The onset and severity of hypoxia depends on several factors. These factors include altitude attained, time at altitude, rate of ascent, physical activity, ambient temperature, acclimatization, and individual variability. For the purposes of this discussion, "moderate altitude" refers to the 8,000 to 15,000 ft range.

In comparison to altitudes above 15,000 ft, the onset and severity of the signs and symptoms of hypoxia at moderate altitude are relatively less well-characterized and difficult to objectively quantify. Previous studies have shown that breathing ambient air between 8,000 and 12,000 ft may result in hyperventilation, particularly during increased physical activity (Ernsting, 1984). Hyperventilation increases P_AO_2, and subsequently, P_aO_2. This increased rate and depth of breathing causes a reduction in partial pressure of arterial carbon dioxide (P_aCO_2). The resulting hypocapnia causes respiratory alkalosis and cerebral vasoconstriction, exacerbating cerebral hypoxia. It is important to remember that, at moderate altitude, physiological compensation may be adequate in most healthy individuals. Therefore, the manifestation of hypoxia may vary significantly from one individual to another, as will the scope and severity of physiological decrements. The severity of hypoxic signs and symptoms within this range of altitudes depends on individual respiratory response and compensatory capacity. Individual variability makes it difficult to establish one particular threshold altitude at which hypoxia signs and symptoms become measurable.

A literature review conducted by Tune (1964) concluded that perceptual motor performance becomes significantly degraded at 10,000 ft (3048 m). This altitude is now generally accepted as the upper boundary of the "physiological zone." Symptoms of hypoxia have been reported on several occasions at altitudes as low as 8000 ft (2439 m), and at even lower altitudes when combined with strenuous physical activity (Smith, 2005). The results of previous cognitive studies have been ambiguous, while other studies have not been able to replicate similar impairments at equivalent ranges of simulated altitudes. In this report, we present a systematic literature review of studies conducted at altitudes or simulated altitudes in the range of 8000 to 15,000 ft. The review evaluates the state of the science regarding mild hypoxic impairment of mental functions, sensory deficits, and other pertinent research findings that may affect aviation-

related duties at moderate altitudes. We specifically focus on studies of cognition, psychomotor performance, and visual degradation since the brain and retina are extremely O_2-dependent. Finally, we examine the role of cerebral dysfunction in the manifestation of cognitive deficits resulting from acute mild hypoxia.

Background

Oxygen is a key component in aerobic metabolism, specifically in oxidative phosphorylation. Aerobic metabolism refers to the series of metabolic pathways by which cells produce energy in the form of adenosine triphosphate (ATP). In this process, molecular O_2 is reduced to water by electrons provided by the tricarboxylic acid cycle (TCA cycle). As the TCA cycle generates electron-carrying molecules for use in oxidative phosphorylation, carbon dioxide (CO_2) is also produced, and subsequently released from the cells as a waste product. The reduction of O_2 occurs with the concomitant production of ATP. ATP is used for a multitude of biochemical processes required to sustain life. Without adequate available ATP, cell death would occur rapidly. Hence, there is a strict dependence on constant adequate O_2 supply in order for ATP synthesis to occur. A severe deprivation of O_2, i.e., hypoxia, leads to a severe deprivation of ATP, and ultimately, rapid deterioration of most physiological processes.

The manifestation of acute hypoxic hypoxia results in compensatory changes primarily in three physiological systems: the cardiovascular system, the respiratory system, and the central nervous system (CNS). The following is a short summary of general physiological compensatory mechanisms in response to acute hypoxia.

Cardiovascular compensation in acute hypoxia

In general, hypoxia causes vasodilation in most peripheral blood vessels. This is accompanied by regional redistribution of cardiac output, with increased blood flow to the heart and brain, while blood is shunted away from less vital organs. Heart rate begins to rise in resting individuals breathing ambient air at approximately 6000 to 8000 ft, and at 25,000 ft, heart rate is approximately doubled (Pandolf & Burr, 2001). In resting individuals, there is also a rate-driven increase in cardiac output, that is, stroke volume is largely unaffected. Systolic blood pressure increases; however, this is accompanied by a reduction in peripheral vascular resistance, and thus mean arterial pressure remains fairly constant. Coronary blood flow increases with the increase in cardiac output, but this is also accompanied with a reduction in cardiac reserve. Under these conditions, a steep fall in P_aO_2 can result in myocardial depression, which may, in certain individuals, elicit compensatory vasoconstriction and/or arrhythmias resulting in cardiac arrest.

Respiratory compensation in acute hypoxia

Ascent to altitude occurs with a non-linear decrease in ambient atmospheric pressure (P_B). With the reduction in P_B, the partial pressures of the atmospheric gases decrease proportionately. The reduction of the inspired partial pressure of oxygen (P_IO_2) results in the reduction of P_AO_2, therefore, as altitude increases, P_AO_2 decreases. Furthermore, alveolar O_2 is also diluted by CO_2, which is continuously released from pulmonary blood into the alveoli, and water that vaporizes

into inhaled air from respiratory surfaces. The table illustrates partial pressure of carbon dioxide (P_ACO_2) and P_AO_2 at different altitudes when breathing air and when breathing 100% O_2:

Table.

Alveolar gas partial pressures and arterial oxygen saturation at various altitudes.

Breathing Ambient Air						**Breathing 100% O_2**		
Altitude (ft/m)	**Barometric Pressure (mmHg)**	**PO_2 in Air (mmHg)**	**P_ACO_2 (mmHg)**	**P_AO_2 (mmHg)**	**Arterial Oxygen Saturation (%)**	**P_ACO_2 (mmHg)**	**P_AO_2 (mmHg)**	**Arterial Oxygen Saturation (%)**
0	760	159	40	104	97	40	673	100
10,000/3048	523	110	36	67	90	40	436	100
20,000/6096	349	73	24	40	73	40	262	100
30,000/9144	226	47	24	18	24	40	139	99
40,000/12,192	141	29				36	58	84
50,000/15,240	87	18				24	16	15

Note: millimeters of mercury (mmHg). Adapted from Textbook of Medical Physiology (p. 528), by J. E. Hall, 2011, Philadelphia, PA: Saunders Elsevier. Copyright 2011 by Saunders Elsevier. Adapted with permission.

In terms of alveolar gases, an equation can be derived for P_B by considering that, at any given time, alveoli contain four gases. Therefore, P_B in the alveoli of the lungs is defined mathematically (ignoring the insignificant contribution of other gases) by Equation 1:

$$(1) \qquad P_B = P_AN_2 + P_ACO_2 + P_AO_2 + P_AH_2O,$$

where P_AN_2 is the alveolar partial pressure of nitrogen, and P_AH_2O is the alveolar partial pressure of water vapor at 37 $^{\circ}$C. Assuming body temperature remains constant, P_AH_2O remains constant (47 mmHg). Nitrogen is a physiologically inert gas. It is neither produced nor consumed by the body. At sea level, nitrogen diffuses from the alveoli into oxygenated blood. On ascent, nitrogen diffuses out of the tissues and into the alveoli. Upon reaching the final altitude, nitrogen diffusion reaches equilibrium and a new steady state is achieved. The difference between P_IO_2 and P_AO_2 arises from P_ACO_2 in the alveoli. P_ACO_2 depends on the amount of CO_2 production and the rate of alveolar ventilation. This ratio of CO_2 production to alveolar ventilation is independent of P_B. If the metabolic rate of an individual remains constant, this ratio will also remain constant on ascent up to approximately 10,000 ft for most healthy individuals (Pandolf & Burr, 2001). As P_AO_2 falls below 100 mmHg, arterial chemoreceptors increase their rate of discharge. This stimulates an increase in ventilation, which results in hyperventilation. Hyperventilation is defined as ventilation greater than what is required to eliminate metabolic CO_2 production. As hyperventilation removes CO_2 from the alveoli, the P_AO_2 rises. The steady-state relationship between P_AO_2 and P_ACO_2 is given by Equation 2:

$$(2) \qquad P_AO_2 = P_IO_2 - P_ACO_2 (F_IO_2 + [1 – F_IO_2]/R),$$

where F_IO_2 is the fraction of O_2 in inspired air (0.21; the concentration of O_2 in ambient air is 21%), and R is the respiratory exchange ratio which represents rate of CO_2 output to the rate of O_2 uptake. If R = 1, then

$$(3) \qquad P_AO_2 = P_IO_2 - P_ACO_2$$

Thus, if P_IO_2 is constant, then as P_AO_2 increases, P_ACO_2 decreases.

In the above situation, hyperventilation increases P_AO_2 at the expense of an excess loss of CO_2, which leads to hypocapnia. Hypocapnia results in a respiratory alkalosis, a condition in which the normal physiological acid-base balance is disturbed. The most profound effects of this disturbance in flight, is its effect on cerebral circulation, discussed below. The increased ventilatory rate experienced during acute hypoxia rises to a maximum between 5 and 10 minutes (min), and then over the next 20 min partially declines back toward the normoxic level (Pandolf & Burr, 2001). This hypoxia-induced ventilatory depression occurs both at constant and variable PCO_2. Research has concentrated on the possibility that this hypoxic ventilatory depression is mediated by γ-aminobutyric acid (GABA), a central neurotransmitter released by inhibitory interneurons within the brain and spinal cord during hypoxia (Nilsson & Lutz, 1993).

In the pulmonary circulation, hypoxemia causes vasoconstriction in pulmonary vessels. This occurs under hypoxic conditions as a compensatory mechanism in an attempt to maintain ventilation to perfusion ratio. If blood oxygen saturation (S_aO_2) falls below 80% (Pandolf & Burr, 2001), however, general vasoconstriction occurs within the pulmonary vessels. This, along with the increased cardiac output associated with an ascent to altitude, results in increased pulmonary artery pressure.

At an altitude of 10,000 ft, the values for P_B, P_AO_2, and P_aO_2 are approximately 523 mmHg, 74 mmHg, and 69 mmHg, respectively (Fox, 2006). At this P_AO_2, S_aO_2 is approximately 87 to 90%. The significance of these values can be illustrated graphically by considering the oxyhemoglobin dissociation curve (figure). As altitude increases above 10,000 ft, P_AO_2 decreases, resulting in rapid desaturation of hemoglobin.

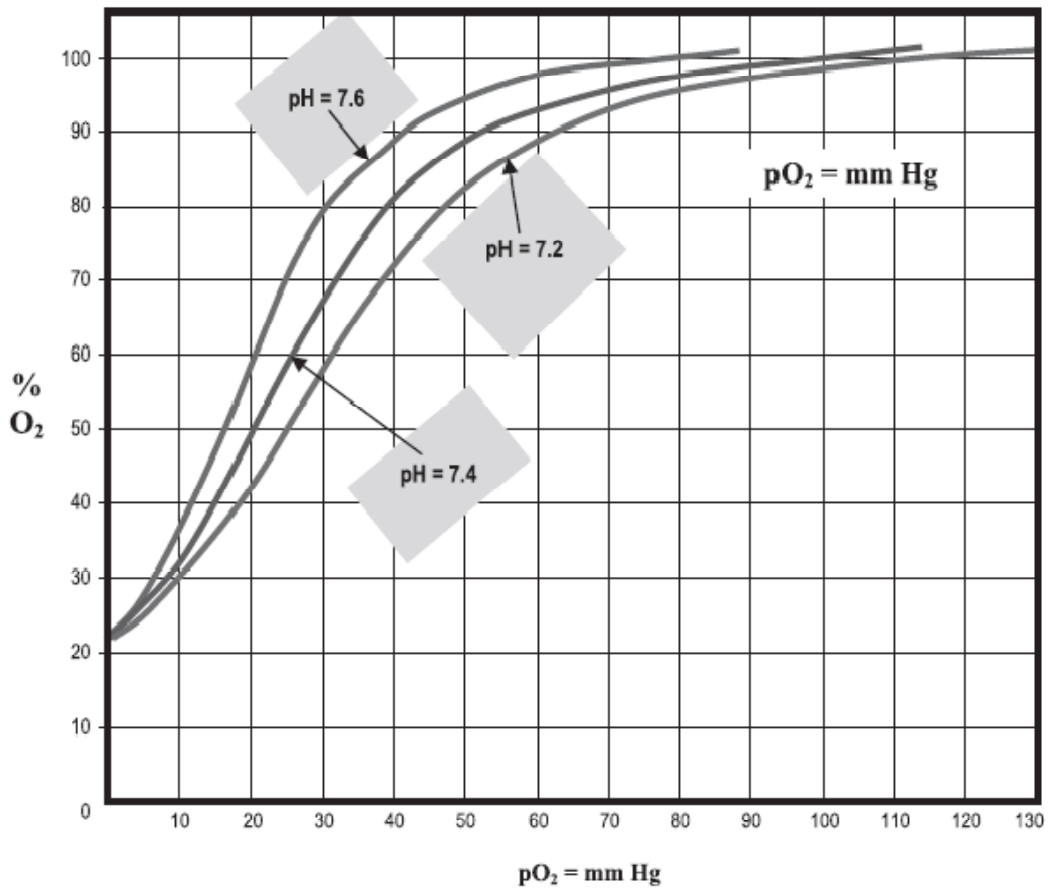

Figure. Oxyhemoglobin dissociation curve. From Applied Aviation Physiology (p. 65), by N. E. Villaire and R. W. Hansrote, 2006, Casper, WY: Endeavor Books-Mountain State Lithographing. Copyright 2005 by Endeavor Books-Mountain States Lithographing. Reprinted with permission.

The figure above depicts the curve graphed at different pH values. Clearly, a pH lower than 7.4 (physiological pH) shifts the curve to the right, and conversely, pH values higher than 7.4 shift the curve to the left. A shift of the curve to the right indicates greater O_2 unloading to the tissues; a shift to the left indicates less O_2 unloading, but slightly more O_2 loading in the lungs. Factors other than pH may shift the oxyhemoglobin curve to the left or right. Factors that shift the curve to the right include, increased PCO_2, an increase in body temperature, and increased concentrations of 2,3 bisphosphoglycerate (2,3-BPG) in the red blood cells. Increasing PCO_2 ultimately results in a decrease in plasma pH. The affinity of hemoglobin for O_2 decreases as pH decreases, causing more O_2 unloading and formation of deoxyhemoglobin. Under hypoxic conditions, compensatory hyperventilation results in respiratory alkalosis, that is, a higher than normal pH. Therefore, hypocapnia causes the oxyhemoglobin curve to shift to the left. Non-pilot aircrew, such as loadmasters, are typically more physically active than pilots during flight. Depending on the level of physical activity, increased metabolic production of CO_2 and skeletal muscle lactic acid, and local increase of muscle temperature can all contribute to a right shift in the curve, indicating more O_2 unloading, leading to more rapid desaturation of hemoglobin.

Conditions such as anemia or high altitude, cause an increase of 2,3-BPG production. Red blood cells themselves cannot use O_2 for aerobic metabolism. They must rely strictly on anaerobic glycolysis for their own supply of ATP. Glycolysis in red blood cells produces the unique by-product 2,3-BPG. When oxyhemoglobin releases O_2, production of 2,3-BPG increases. When 2,3-BPG combines with the increasing concentrations of deoxyhemoglobin (as O_2 is unloading), deoxyhemoglobin becomes stabilized, leading to more O_2 unloading. Therefore, an increase in 2,3-BPG results in more rapid hemoglobin desaturation.

Central nervous system disturbance in acute hypoxia

The CNS is exquisitely sensitive to changes in P_aO_2. When P_aO_2 is 50 mmHg or greater, compensatory hyperventilation results in hypocapnia, which causes cerebral vasoconstriction, and consequently, a decrease in cerebral blood flow. This decrease in cerebral blood flow can exacerbate hypoxia in some areas of the brain. A decrease in P_aO_2 to approximately 35 mmHg and below results in cerebral vasodilation, which can increase cerebral blood flow between 50 to 100% (Pandolf & Burr, 2001).

The neurological effects of acute hypoxia can range from impairment of psychomotor and cognitive function and visual disturbances to loss of consciousness. With respect to neurological effects of acute hypoxia, there is great variability between individuals. Some of this variability seems to be related to the differences in respiratory responses among individuals. The severity of the neurological decrements depends on the degree of hypoxia and the degree of hypocapnia. As mentioned above, at very low cerebral P_aO_2, the effect of hypocapnia is abolished and there is a net increase in cerebral blood flow. This increase in blood flow has been implicated in the development of high altitude cerebral edema in mountain climbers.

Military significance

The current military operating environments necessitate flights above 10,000 ft. In this environment, the crews of unpressurized aircraft are at risk of developing hypoxia during the mission. In general, aircrews typically associate hypoxia with altitudes significantly greater than 10,000 ft or with flights of long duration at 10,000 to 15,000 ft. Within this range of altitude, human physiological compensatory mechanisms may range from very effective in certain individuals to ineffective in others. Factors such as increased physical activity and ambient temperature can effectively lower the threshold altitude at which symptoms of hypoxia may appear. Given the insidious nature of hypoxia, the manifestation of mild hypoxia at moderate altitude can be very subtle and can go completely unrecognized.

The North Atlantic Treaty Organization (NATO) and Partners for Peace (PfP) allied forces have likewise recognized the potential aircrew hazards, performance decrements, and mission risks for operations at moderate altitudes in excess of 10,000 pressure altitude. Within the structure of the NATO Research and Technology Organization (RTO), the Human Factors and Medicine (HFM) Technical Panels provide a scientific base for decisions and standardization regarding human protection and military performance optimization in operational environments through information exchange, collaborative scientific experimentation, and shared subject matter expertise (North Atlantic Treaty Organization [NATO], 2006).

In January 2010, Research Task Group (RTG) HFM-190, "Oxygen requirements in unpressurized aircraft operating below 18,000 feet" was established as a vehicle to comprehensively address such concerns among participating nations (NATO, in press). Issues of human physiologic protection, regulatory standardization, aircrew training fidelity, and optimal equipment selection have all been cited as areas to be addressed under the panel's justification. The genesis of the current review coincided with the inception of this RTG.

Objectives

This review was conceived with three primary objectives.

a. Determine what is presently known about cognitive and visual decrements resulting from mild hypoxia occurring at moderate altitudes.

b. Assess the existing literature with respect to the physiological parameters studied, and the methods used in the execution of the current research.

c. Facilitate evidence-based decisions regarding use of supplemental O_2, regulatory controls, and informed training and mission planning for Commanders and aircrew.

Methods

We conducted a systematic literature search regarding the state of the science for mild hypoxic impairment of mental functions, sensory deficits, and any other pertinent research findings that may affect aviation-related duties. All searches were conducted in conjunction with a USAARL research librarian. The primary search engines employed were Defense Technical Information Center (DTIC) and Dialog, which searches the National Technical Information Service (NTIS), Medline, Embase, and PsychInfo. The search string was as follows: "hypoxia" and "moderate altitude" or "8,000 ft" or "9,000 ft" or "10,000 ft" or "11,000 ft" or "12,000 ft" or "13,000 ft" or "14,000 ft" or "15,000 ft" and "cognition" or "cognitive" or "vision" or "performance" or "impairment." Exclusionary criteria included publications related specifically to any type of mountain sickness, chronic hypoxia, hypoxic exposures at altitudes greater than 15,000 ft or lasting longer than 12 hours (hr), and cardiopulmonary pathophysiology. Molecular or cellular-level studies that were focused on elucidation of cellular-level events were generally excluded as well unless a particular study exhibited direct relevance to CNS dysfunction under hypoxic conditions.

The DTIC search yielded 248 articles of which 223 were excluded. The Dialog search yielded 32 articles, 5 technical reports, 1 master's thesis, 2 abstracts, and 2 manuals. Excluded from the Dialog search were 17 articles, 2 technical reports, and 2 manuals. Additionally, 52 articles, 1 master's thesis, and 16 abstracts were obtained for review from references of original search criteria. Of these 52 articles, 14 were subsequently excluded. The total publications included were 78 articles, 3 technical reports, 2 master's theses, and 18 abstracts.

Results

The following results are organized into three main sections. The first section presents results of selected cognitive and psychomotor studies. The next section presents results of visual studies. The last section presents a short review of the literature regarding CNS dysfunction resulting from mild hypoxia.

Cognitive and psychomotor

Cognitive and psychomotor deficits resulting from mild hypoxia appear to be most difficult to quantify and reproduce consistently. Several research groups report cognitive impairment, while others are unable to reproduce similar results. For example, Denison, Ledwith, and Poulton (1966) noted an increased reaction time on the Manikin test in exercising subjects at 8000 ft. Denison et al. attributed the increased reaction time to task novelty. Using the same experimental design as Denison et al., Fowler, Paul, Porlier, Elcombe, and Taylor (1985) could not demonstrate learning difficulties up to 12,000 ft. Rice et al. (2005) used the CogScreen®-HE to approximate the altitude at which cognitive deficit occurs. At a simulated altitude of 15,000 ft, they found that volunteers averaged 12 or more errors on the vigilance exam, but found no significant decrements at 12,000 and 10,000 ft. In a similar experiment using CogScreen®-HE, Hewett, Curry, Rath, and Collins (2009) could not reproduce the same results. These subjects demonstrated no significant cognitive deficits. Comparing the experimental designs of Rice et al. and Hewett et al., the notable differences were the final altitude and time at altitude, 15,000 ft for 60 min, and 14,000 ft for 45 min, respectively.

Several studies indicate that in measuring cognitive performance, visual perception plays an important role in the process. Fowler, Taylor, and Porlier (1987) reported a threshold estimate of 9750 ft for perceptual motor performance decrements due to hypoxia and cited disruption of vision as a factor influencing this decrement. In 1993, Fowler, Banner, and Pogue conducted an additive factors method experiment to determine whether preprocessing and identification stages of information processing are implicated in the slowing of reaction time (RT) by hypoxia. Their results indicate that visual slowing probably plays an important role in the disruption of these tasks while hypoxic, particularly under conditions of suboptimal lighting.

At moderate altitudes, it is not uncommon to find mixed reports of both increases and decreases in some performance parameters. For example, Schlaepfer, Bartsch, and Fisch (1992) found an increase in visual perception with mild hypoxia. Findings such as this one could possibly be due to hyperventilation and the resulting increase in P_AO_2 and hypocapnia. Several lines of research indicate that one must consider the balance of respiratory gases when evaluating visual performance under hypoxic conditions. Hypocapnia is known to increase visual sensitivity (Wald, Harper, Goodman, & Krieger, 1942) as well as to accelerate dark adaptation (Connolly & Hosking, 2006). The importance of the balance between O_2 and CO_2 in the manifestation of the signs and symptoms of hypoxia has also been demonstrated by Luna, French, Neville, Mitcha, and Storm (1994). A time-indexed, computerized Manikin test was conducted which measured several physiologic parameters, such as hemoglobin saturation (HbO_2), end-tidal P_AO_2, and P_ACO_2. The results indicated that the best overall correlation in assessing task performance was by using a hybrid relationship between HbO_2 and P_ACO_2. This

implies that P_AO_2 in itself may not provide the best correlation with task performance. The importance of the contribution of PCO_2 fluctuation has also been reported by Karl, McMillan, Ward, Kissen, and Souder (1978). In a study with Rhesus monkeys, Karl et al. found that breathing supplemental 5% CO_2 at all levels of hypoxia induced in the study, maintained brain tissue PCO_2 at control levels and retarded the fall of brain tissue PO_2, and can reduce hypoxia-induced (8% O_2) performance decrement.

When attempting to assess aircrew performance, perhaps it may be more useful to measure performance based on flight-relevant tasks. Nesthus, Rush, and Wreggit (1997) utilized flight-relevant tasks in simulated flight performance by using a Multiple Attribute Task Battery to test cognition in a cross-country flight scenario. They found that significantly more procedural errors were committed by the hypoxia group during simulated cruise flight at 10,000 ft, both during the descent and approach phases from 10,000 ft, and during descent from 12,500 ft. In 2005, Smith conducted a retrospective survey of Australian Army helicopter aircrew who had operated at altitudes up to 10,000 ft. In this study, 53 surveys were returned, representing 25 loadmasters, 23 pilots, and 5 aircrewman technicians. The helicopter aircrew reported symptoms consistent with hypoxia at altitudes within the "physiological zone." Loadmasters reported more effects than pilots. This most likely reflects the increased physical activity, and consequently, a greater metabolic demand for O_2 than required by pilots. Overall, aircrew experienced potentially operationally significant symptoms at a mean altitude of 8426 ft.

Vision

Nervous tissue is highly O_2 dependent. In comparison with any other body system, the brain and the retina have the highest O_2 uptake per unit mass (Billings, 1973). This fact makes visual performance and sensitivity ideally suited for hypoxia studies. In 1939, McFarland and Evans reported a decrease in visual light sensitivity at 7400 ft. Mild hypoxia is also known to compromise threshold sensitivity during dark adaptation. Numerous subsequent studies and in-flight observations confirm retinal sensitivity to hypoxia. Several studies also confirm that, when assessing visual sensitivity and dark adaptation, one must consider the physiological balance of respiratory gases as well. Alpern and Hendley (1952) demonstrated that hypocapnia enhances visual sensitivity and contrast discrimination. Wald et al. (1942) found that hypocapnia accelerates dark adaptation. The mechanism by which hypocapnia affects visual sensitivity is unknown, however respiratory alkalosis seems to be a requisite physiological condition. Wald et al. found that adding 2% CO_2 to breathing gas abolished the effect of hypocapnia. Other more recent studies indicate that both PO_2 and PCO_2 affect dark adaptation and visual sensitivity. Connolly and Hosking (2006) reported that early scotopic sensitivity was delayed by hypoxia and hastened by hypocapnia and hyperoxia. Their results also indicate that rod photoreceptors are functionally hypoxic when breathing air at one atmosphere. In 2008, Connolly, Barbur, Hosking, and Moorehead demonstrated that contrast sensitivity is degraded beyond the fovea in good viewing conditions at 10,000 ft. The outer retina has been shown to be more susceptible to hypoxia. Their results also indicate that changes in visual sensitivity persist for about 20 to 25 min after hypoxic exposure.

In light of current military operations, there has been considerable investigation on the effects of mild hypoxia on visual performance while using night vision goggles (NVG) (Leber, Roscoe,

& Southward, 1986). Supplemental O_2 significantly improved naked-eye but not NVG-augmented night resolution acuity up to a simulated altitude of 13,000 ft. Davis et al. (1995) found that visual acuity with NVGs was degraded slightly after 30 min of exposure to 14,107 ft, although less than what would be expected with unaided night vision under these conditions. Balldin et al. (2007) compared cognitive and visual performance at near ground level pressure altitude and at 10,000 ft over a 12-hr exposure to approximate the operational envelope and mission time flown by the special operations community. This study found that 12-hr exposure at 10,000 ft produced no significant negative impact on cognitive function, but minor negative effects on NVG performance under operational lighting (starlight) conditions.

CNS dysfunction

In contrast to severe hypoxia, brain levels of ATP are well-maintained during mild hypoxia (Gibson, Pulsinelli, Blass, & Duffy, 1981). Why then are cognitive and psychomotor impairments observed in mildly hypoxic individuals? One possible explanation could be cerebral vasoconstriction due to hypocapnia resulting from compensatory hyperventilation. This raises the possibility that some areas of the brain may be more than just mildly hypoxic even at moderate altitudes. Another question: What is the minimum altitude at which these decrements become apparent? Studies by Nelson (1982) indicate that the decisive altitude for changes in higher cognitive functioning lies between 13,123 and 16,404 ft. Pavlicek Schirlo, Nebel, Regard, Koller, and Brugger (2005) investigated the effects of hypoxia on subjects exposed to altitudes of 3500 to 4500 m (9842 to 14,764 ft, respectively) for 2 hr. Their results showed no significant changes in higher cognitive and emotional function tests at 14,764 ft. They concluded that selected cognitive and affective frontal lobe functions were preserved despite significant O_2 desaturation and drop in diastolic blood pressure, which indicates hypoxic impairment of the vasomotor center. This finding suggests that short-term adaptation mechanisms may lead to preservation of these functions. Though most neurons stop generating action potentials under hypoxic conditions, some populations of neurons are more resistant to hypoxia than others (Peña & Ramirez, 2005).

Gibson et al. (1981) proposed that the signs and symptoms of mild to moderate hypoxia result from altered turnover of several neurotransmitters. Turnover is defined as the overall rate at which whole amine store in a given tissue is replaced (Cooper, Floyd, & Roth, 1986). The rate of turnover is not necessarily equal to biosynthetic rate, but it can be used as an estimate of the functional state of a variety of catecholaminergic neurons. Hypoxia induces changes in concentrations of norepinephrine (NE). Acetylcholine (ACh) and serotonin (5-HT) concentrations are affected as well. For example, ACh synthesis is reduced as the rate of carbohydrate oxidation is reduced. ACh is known to be involved in the regulation of processes such as learning and memory. It should be noted that anticholinergic drugs, such as scopolamine, can produce deficits in memory. Tyrosine hydroxylase (TH), which catalyzes the rate-limiting step in the synthesis of catecholamines, is directly dependent on O_2. Rostrup et al. (2007) reported that TH activity may be severely limited by O_2 availability even at moderate hypoxic conditions.

Discussion

At pressure altitudes above 18,000 ft, CNS decrements are unequivocal, measurable, and are clearly attributed to acute hypoxia. This does not seem to be the case at altitudes between 8000 and 15,000 ft. Within this range of pressure altitude, individuals are in a compensatory mode, and some individuals compensate for the reduction in atmospheric pressure more rapidly than others. The predominant compensatory mechanisms include hyperventilation, which as previously mentioned, results in hypocapnia, leading to cerebral vasoconstriction. The compensatory mechanisms themselves create a more complex physiological environment, which includes an imbalance in respiratory gases and an increase in plasma pH. Thus, the degree of hypoxia and severity of the symptoms become quite variable. Environmental factors, such as temperature and physical activity further complicate a dynamic physiological picture. These factors possibly contribute to the variability of results obtained in studies of acute hypoxic hypoxia.

Cognitive and psychomotor

The results of this literature search suggest that cognitive and psychomotor testing during mild acute hypoxia may produce varying results. In a questionnaire-based study conducted by Smith (2008), cognitive and psychomotor impairment dominated the symptoms reported after acute hypoxia training, as well as the symptoms remembered from previous hypoxia training. Yet, cognitive testing is often not reproducible and several studies produced conflicting results. The difficulty in obtaining reproducible results in cognitive testing may be related to several factors. One factor is the degree of physiological variability from one individual to another, that is, the ability of an individual to compensate adequately under hypoxic conditions at a given altitude. Other sources of ambiguity may be related to instrumentation used in hypoxia testing and a lack of agreement on standardized metrics. Furthermore, some of the tests themselves lack sensitivity and/or specificity to the decrements under scrutiny. With this in mind, it may be of benefit if future studies investigating the effects of mild hypoxic hypoxia focused on standardization of agreed-upon common aviation-specific tasks. Such studies could be conducted in simulator-based hypoxic environment. When examining cognitive and psychomotor function, it is critical that tests of those functions with proven sensitivity and specificity are selected.

Vision

Studies of the visual consequences of acute hypoxia have produced more consistent results than cognitive and psychomotor testing. This is not entirely unexpected considering the extraordinary sensitivity of the retina to lack of O_2. Recent research indicates that both cone and rod functions demonstrate a decrease in sensitivity during acute hypoxia (Connolly & Hosking, 2006). Furthermore, recovery of rod sensitivity has been shown to be delayed by several minutes under hypoxic conditions, suggesting hypoxia delays photochemical regeneration processes at the photoreceptor level. The finding that 100% O_2 delivered at sea level increases and hastens rod sensitivity may have significant tactical value. If rod recovery time is enhanced with O_2, this may reduce the transition time between lighted and dark conditions (e.g. muzzle flash effects and transitions between NVG and unaided vision). Connolly and Hosking's study

also demonstrated that early scotopic sensitivity is hastened by hypocapnia. This finding has important implications, particularly for acute hypoxia research conducted at moderate altitude. Within this altitude range, the compensatory onset of hyperventilation and subsequent hypocapnia with increasing altitude can potentially confound experimental results in hypoxia research efforts, both in visual and cognitive studies. Studies conducted by Fowler et al. (1985, 1987) demonstrated the effects of slowing of visual processing when measuring cognitive performance. Hypocapnia, respiratory gas balance, and plasma pH should all be taken into consideration when conducting acute hypoxia experiments at moderate altitude.

CNS dysfunction

The specific underlying mechanisms responsible for the observed neurological decrements during hypoxia are not completely understood. Rostrup and colleagues' findings (2008) that TH activity may be severely impaired under mildly hypoxic conditions, and a U.S. Army study on the beneficial effects of tyrosine (Banderet et al., 1985) supplementation, lend credibility to Gibson and colleagues' (1981) argument of altered turnover of key neurotransmitters. Recent neurophysiological studies indicate that various neuronal circuits within the brain express different responses to hypoxia. Physiological responses to hypoxia depend on the type of hypoxia (for example, acute versus chronic or intermittent versus continuous). Peña and Ramirez (2005) argue that neuronal responses to hypoxia are regulated in a heterogeneous fashion. The time course of physiological regulatory processes is quite different in acute hypoxia compared to chronic hypoxia. It has also been demonstrated that there are significant differences between types of neurons, and even between those located within the same brain region (Haddad & Jiang, 1993). For example, hypoxia causes hippocampal neurons to stop action potential generation, whereas some certain brain stem neurons involved in generation of respiratory rhythm are able to maintain cardiorespiratory functions during hypoxic episodes (Peña, Parkis, Tryba, & Ramirez, 2004). In their review article, Peña and Ramirez conclude that in order to understand how the nervous system responds to hypoxia, more studies integrating cellular and systems level approaches are needed.

Hypoxia recognition training

Most Hypoxia Recognition Training (HRT) is conducted either in a hypobaric chamber or under normobaric conditions using mixed gases to simulate an altitude of 25,000 ft. At this altitude, the symptoms of hypoxia are quite severe and develop rapidly. This is generally not the case when operating between 8000 and 15,000 ft. Aircrews that operate within the above altitude range will not experience the same symptoms with the same severity as during a 25,000 ft hypoxia demonstration. A 25,000 ft training scenario may not be realistic for this type of aircrew, and may lead to lack of recognition of insidious hypoxia in flight at moderate altitude.

Current HRT methods include hypobaric chamber training, normobaric devices using mixed gases, and Combined Altitude Depleted Oxygen (CADO), which is a hybrid method utilizing a hypobaric chamber and an O_2-depleted gas mixture. The most well-known, traditional method of HRT is hypobaric or low-pressure training. In this method, air inside the chamber is evacuated via a vacuum pump, reducing the atmospheric pressure inside the chamber, thereby effectively creating a high-altitude environment. The reduction of ambient atmospheric pressure

results in a reduction of the P_AO_2 in the lungs of the subjects, which induces hypoxia. The typical altitude at which the hypoxia demonstration is given is 25,000 ft. While certainly very effective in producing hypoxia and demonstrating other physiological effects of a high-altitude environment, hypobaric chamber training poses the risk of decompression sickness. Consequently, there has been much interest in safer alternatives for HRT.

Over the past 10 years, normobaric methods have gained popularity for use in training aircrew. These systems generally employ hypoxic gas mixtures to induce hypoxia. One such method currently in use by the US military services is the Reduced Oxygen Breathing Device (ROBD), a closed-loop rebreather device that uses compressed air that is subsequently mixed with nitrogen, which dilutes the air, thereby reducing the concentration of O_2 in the inspired air. This allows the ROBD operator to simulate the PO_2 of the desired altitude. In US Navy studies, hypoxia induced by the ROBD has been found physiologically equivalent to that induced by the hypobaric chamber (Vacchiano, Vagedes, & Gonzalez, 2004). Non-rebreathing systems have also been studied and successfully used to demonstrate symptoms of hypoxia to aircrew.

In 2001, the Royal Australian Air Force developed CADO (Cable & Westerman, 2010). This hybrid method of HRT incorporates a hypobaric chamber ascent to 10,000 ft and a hypoxic exposure to a physiological altitude of 25,000 ft. Hypoxia is induced by breathing a depleted O_2 gas mixture. Canadian forces have also adopted this method of HRT. This method has the advantage of allowing the student to experience the pressure effects of ascent to altitude and a 25,000-ft hypoxia demonstration in a safer environment than a standard altitude chamber profile. Regardless of the method, most hypoxia demonstrations are traditionally conducted at a simulated altitude of 25,000 ft.

In an attempt to develop future aviation physiology training strategies for aircrew, Cable (2003) analyzed incidents of hypoxia reported to the Directorate of Flying Safety of the Australian Defence Force (DFS-ADF) during the period of 1990-2001. The results of this analysis indicated that majority of hypoxia symptoms occurred between 10,000 and 19,000 ft. He concluded that the current hypobaric chamber training methods should be reviewed for relevance to the most at-risk aircrew population, and recommended that methods simulating subtle incapacitation should be explored. In his analysis, Cable reported that 75.8% of the hypoxic episodes were recognized by the aircrew themselves. Clearly, this demonstrates the importance and effectiveness of HRT. The 25,000-ft hypobaric chamber profile and/or the normobaric mixed-gas equivalent training are effective methods of inducing hypoxia for recognition of one's personal symptoms of hypoxia. However, by themselves, these methods may not be the most realistic for aircrew commonly flying between 8000 and 15,000 ft. The onset of acute hypoxia at 25,000 ft is more rapid and the signs and symptoms are of greater severity than those appearing at moderate altitudes. Consequently, the first hypoxic episode at moderate altitude may go unrecognized because aircrew may be expecting signs and symptoms similar to 25,000 ft. HRT should be more applicable to aircrew operating at moderate altitudes.

Many physiologists are not convinced that hypobaric and normobaric hypoxic environments are physiologically equivalent. Recent research has demonstrated that the signs and symptoms associated with hypobaric hypoxia and normobaric hypoxia may not always be identical. Savourey, Launay, Besnard, Guinet, and Travers (2003) reported that, compared to normobaric

hypoxia, hypobaric hypoxia leads to greater hypoxemia, hypocapnia, alkalosis, and a lower S_aO_2 when subjected to an equivalent ambient PO_2. The Equivalent Air Altitude model states that different combinations of ambient atmospheric pressure (P_B) and inspired fraction of O_2 (F_IO_2) that produce the same P_IO_2 result in identical physiological responses. Recent evidence shows that different combinations of P_B and P_IO_2 may produce different responses to the same P_IO_2 (Conkin & Wessel, 2008). This finding would invalidate the Equivalent Air Altitude model as the ideal description of isohypoxia. Isohypoxia is defined as the same distribution of hypoxic signs and symptoms under any circumstances of equivalent hypoxic dose. Most recently, Self, Mandella, Prinzo, Forster, and Shaffstall (2010) evaluated the physiological equivalence of normobaric versus hypobaric hypoxia. In this study, 20 subjects were exposed to 5-min, 25,000-ft equivalent environments in an altitude chamber and then in a ground-level portable reduced O_2 training enclosure. They found that the mean number of hypoxia symptoms between hypobaric and normobaric environments after 1 min were significant, but not at 3 and 4 min. Alveolar gas composition and arterial hemoglobin O_2 desaturation patterns differed as well between a ground-level and hypobaric exposure. Based on these results, combined with similar patterns in symptom frequencies, they concluded that ground-level hypoxia training may be a sufficient alternative for altitude chamber training. Although normobaric and hypobaric hypoxia training at 25,000 ft seems to produce equivalent symptoms, there are clearly some physiological differences that warrant further investigation.

Conclusions

A specific altitude and duration at which cognitive deficits manifest remains unclear. However, trends suggest considerable evidence of impairment of varying degrees between 12,000 and 15,000 ft. All other variables being equal, physical activity accelerates the onset of signs and symptoms at a given pressure altitude.

The literature regarding hypoxic visual decrements is more consistent. The outer retina is more susceptible to hypoxia than the inner retina. When attempting to study the effects of hypoxia on vision, hyperventilation may confound experimental results, for example, the resulting respiratory alkalosis may enhance visual sensitivity and contrast discrimination, and accelerate dark adaptation. The effects of hypoxia persist well after descent to lower altitude. Visual degradation has been shown to occur at about 4000 to 5000 ft under scotopic conditions and at 10,000 ft under photopic conditions.

Nervous tissue is known to be highly O_2 dependent and susceptible to hypoxia. Neurological dysfunction is well-established above 15,000 ft. The possible causes of mild hypoxic dysfunction include poor individual physiologic compensation, disruption of several O_2-dependent neurotransmitter synthetic pathways, and respiratory gas imbalance related to the degree of hyperventilation. Decrements may be subtle and variable from 8000 ft to 15,000 ft.

Recommendations

Given the totality of the literature reviewed, and the current state of the science, the authors recommend the following:

We have identified several areas where the current state of the science is lacking (see Results section). It is the opinion of the authors that near future research should engage the following topics: (1) augment validated neuropsychological metrics (surrogate investigational end points) with actual flight task metrics (desired end points of interest) under moderate hypoxic conditions, (2) determine efficacy of potential neuropsychological performance-enhancing agents (e.g. tyrosine supplementation) for both acute and chronic hypoxia, and (3) investigation of a mixed gas formulation with varying concentrations of CO_2 to investigate the contribution of hypocapnic effects on hypoxic performance at moderate altitudes.

The ability to compensate to hypoxic challenge varies not only between individuals, but also within the same individual, depending on one's physiological condition at the onset of hypoxia. However, in healthy individuals, all of these systems operate within a normal range of human variant. Yet we have different regulatory guidance regarding the use of supplemental O_2 between different nations, and even within the branches of the military. Selected examples of such guidance can be found in Appendix B.

There are significant differences between the U. S. Army regulations versus those of the U.S. Navy and the U.S. Air Force (as well as the Federal Aviation Administration and our allied services). One might argue that each branch of service has different mission requirements. Although this is true, all aircrew are human and all are susceptible to hypoxia, regardless of the mission. Furthermore, the armed forces fly many of the same platforms and mission profiles. Taking this into account, it may be worthwhile to investigate the possibility of suitable universal regulations regarding supplemental O_2 use in-flight.

Since there is no magic line at which everyone becomes hypoxic, we recommend that the potential for in-flight hypoxia at moderate altitude be addressed during mission planning. A case has also been made that HRT should be relevant and representative of true mission conditions. We recommend that hypobaric/normobaric training at a simulated altitude of 25,000 ft be augmented with a method that can produce subtle hypoxic impairment. The development of such a method should be explored.

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Appendix A.

List of articles.

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Acevedo & Ekkekakis (2001)	N/A	Literature review	N/A	Further investigation into the psychophysical and the affective responses to exercise in adverse environmental conditions can be facilitated through the utilization of a proposed transactional psychobiological model.
Artino et al. (2009)	N/A	Retrospective survey (N)	156 ROBD: 50 121 ROBD: 30	Findings suggest breathing- gas flow rate contributes to air hunger; may impact training fidelity
Banderet et al. (1985)	4200 and 4700 m	H	27	Tyrosine enhanced performance and reduced subjective symptoms; mood states were also improved
Balldin et al. (2007)	10,000 ft	H	30	No significant negative impact on cognitive function; but minor negative effects on NVG performance under operational lighting (starlight) conditions
Bahrke and Shukitt-Hale (1993)	N/A	Review paper	N/A	N/A
Billings et al. (1964)	7000, 10,000, and 13,000 ft	In-flight/mixed gas	20	Ventilation and respiratory exchange ratios increased as tracheal O_2 tension was reduced; alterations were due to mild hypoxia

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Brinchmann-Hansen and Myhre (1990)	8000, 10,000, 12,500, and 15,000 ft	H	10	Vasodilating effect of hypobaric hypoxia was nonlinear from sea level to 15,000 ft; variability of hypoxic vascular response within different parts of individual retinas and between different retinas
Brinchmann-Hansen and Myhre (1989)	8000, 15,000, and 18,000 ft	H	30	Study established a critical level of hypoxia where complete recovery of macular sensitivity is not achieved
Burkett and Perrin (1976)	15,000 and 20,000 ft	H	8	Hypoxia does not cause significant deterioration of hearing for pure tones
Butler (2008)	N/A	Conference presentation	N/A	Tissue O_2 delivery can be impaired at 8000 ft cabin altitude during aeromedical evacuation
Cable (2003)	N/A	Retrospective study	N/A	Hypoxia incidents most commonly occur at altitudes less than 19,000 ft
Chevion et al. (2007)	Not specified	H	11	Study demonstrated that hypoxia-reoxygenation injury, tested in animal and tissue studies, is applicable to acute exposure to hypoxia at a systemic level
Chiles et al. (1971)	14,000 ft	H	9	Altitude clearly a more powerful variable on pilot performance than temperature
Christensen et al. (1977)	21 and 8% O_2 113 parts per million (ppm) CO/17% O_2 114 ppm CO	N	10	Statistically significant change in vigilance performance found between control and low O_2; performance under CO and combination of CO and low O_2 was not different from control

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Conkin and Wessel (2008)	N/A	Review paper	N/A	Results of literature review provide evidence for an independent effect of barometric pressure on hypoxia and AMS, and thereby invalidate Equivalent Air Altitude model as an ideal model of isohypoxia.
Connolly and Hosking (2006)	10,000 and 15, 000 ft	H	5	Early scotopic sensitivity delayed by hypoxia and hastened by hypocapnia and hyperoxia; rod photoreceptors functionally hypoxic when breathing air at one atmosphere
Connolly and Hosking (2007b)	14.1 and 100% O_2	N	12	Contrast sensitivity degraded beyond the fovea in good viewing conditions at 10,000 ft; changes in visual sensitivity persist for about 20 to 25 min after hypoxic exposure
Connolly et al. (2008)	14.1% O_2	N	12	In the mesopic range, mild hypoxia impairs chromatic sensitivity progressively with reducing luminance
Connolly and Hosking (2009)	14.1 and 100% O_2	N	12	Outer retina may be susceptible to hypoxia under twilight viewing
Connolly and Hosking (2007a)	21% O_2	N	12	Results support a close relationship between the respiratory partial pressure of CO_2 and flicker sensitivity
Crow and Kelman (1971)	2000, 8000, and 12,000 ft	H	86	Short-term memory seems to be impaired at 12,000 ft

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Crow and Kelman (1973)	2000 and 12,000 ft	H	49	No evidence of impairment in psychological performance at 12,000 ft
Davis et al. (1995)	4300 m	H	17	Visual acuity with ANVIS is degraded slightly after 30 min of exposure to 4300 m, but less than expected with unaided night vision under these conditions
Delgado-Esteban et al. (2002)	95%N_2/5% CO_2	N	Cerebral cortical neurons	Tetrahydrobiopterin (BH_4) deficiency increases neuronal vulnerability to hypoxia-induced mitochondrial damage
Denison et al. (1966)	5000 to 8000 ft	H/N	Experiment 1: 8 Experiment 2: 28	Mild hypoxia affects performance of a novel task
DeVilbiss (1998)	5000, 10,000, 15,000, 18,000, and 20,000 ft	H	15	NVG performance at 10,000 ft altitude was degraded without supplemental O_2 as compared to both 100% and normal supplemental settings
Dhar et al. (2006)	3000 ft (ground level)	N	10	Mild hypoxia possible accentuated the ischemic effects of +Gz acceleration in the retina; possible implication in relaxed rapid onset rate +Gz tolerance
Du et al. (1999)	2800, 3600, and 4400 m	H	18	Performance of short-term memory decreased after exposure to acute mild and moderate hypoxia for 1 hr
Ernsting (1973)	N/A	Review paper	N/A	N/A
Ernsting (1978)	N/A	Review paper	N/A	N/A
Ernsting (1984)	N/A	Symposium	N/A	N/A
Fowler et al. (1985)	11 to 16% O_2	N	Experiment 1: 32 Experiment 2: 20	No learning impairment up to 12,000 ft

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Fowler et al. (1987)	9.5 to 14.5% O_2	N	6	Threshold estimate of 9750 ft for performance decrements due to hypoxia; disruption of vision influences this decrement
Fowler et al. (1993)	8 to 13% O_2	N	14	Visual slowing probably played an important role in the disruption of perceptual-motor tasks by hypoxia
Fraser et al. (1987)	5000, 8000, 10,000, and 12,000 ft	H	39	Effects of mild hypoxia on the postural control system examined by measuring the postural sway; total sway increased at all altitudes above ground level controls, but no change seen at 12,000 ft
Fulco and Cymerman (1987)	N/A	Book chapter	N/A	N/A
Gibson (1981)	N/A	Seminar	N/A	N/A
Gibson (1978)	Sea level hyperventilation	N	9	Hypocapnic hyperventilation to a P_ACO_2 of 15 Torr caused a marked decrement in motor performance; no effect on intellectual performance as measured by the manikin and verbal transformation tasks
Gold and Kulak (1972)	12,300 and 15,000 ft	N	7	Supplemental O_2 is needed at or above 12,000 ft for any crewmember involved in a complex task

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Green and Morgan (1985)	2440, 3050, and 3660 m	H	150	A significant difference was found between the group tested at 3660m and the remaining groups for error rate but not for speed of work; No effect of altitude on the way in which the task was learned could be demonstrated
Hackworth et al. (2003)	N/A	Survey	67	General agreement that pilots should receive introductory hypoxia training, recurrent hypoxia training, and altitude chamber training
Haddad and Jiang (1993)	N/A	Review paper	N/A	N/A
Hall (1953)	25,000 ft/variable gas mixtures of O_2/CO_2	H	10	Hypoxic and CO_2 stimuli to breathing act independently at altitude; adding CO_2 to O_2 breathed by men at altitude seems to appreciably increase the elimination of nitrogen
Hampson (2007)	N/A	N/A	N/A	Report on Royal Australian Air Force hypoxia training methods.
Hayashi and Fukuda (2000)	N/A	Review paper	N/A	N/A
Hewett et al. (2009)	8000 to 14,000 ft	N	50	No significant cognitive deficits
Hornbein (2001)	N/A	Review paper	N/A	N/A
Hudson et al. (2010)	N/A	Survey	32	CV-22 Osprey flights at higher altitudes were six times more likely to experience low-O_2 caution than flights at lower altitudes; no single parameter caused low-O_2 cautions with the CV-22 OBOGS system.

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Karakucuk et al. (2004)	3000 m	H	16	Moderate altitude adversely affected the total number of errors on FM-100 Hue color vision testing in a photopic environment; Deterioriation was significant in the blue-yellow range
Karl et al. (1978)	21, 12, 10, and 8% O_2; 5% CO_2	N	8 Rhesus monkeys	With addition of 5% CO_2 to the inspired atmospheres, cerebral PO_2 relatively elevated, but declined as hypoxia intensified; Cerebral PCO_2 and avoidance task performance sustained at near baseline values with inspired 5% CO_2.
Kellogg (1977)	N/A	Review paper	N/A	N/A
Kelman and Crow (1969)	2000 and 8000 ft	H	22	Failed to confirm the decrement in psychomotor performance found by others using an orientation test at 8000 feet
Knudtzon et al. (1991)	15,000 ft	H	5	Reduced ambient pressure per se has no influence on the carotid baroreflex control of heart rate
Kobrick (1975)	13,000, 15,000, and 17,000 ft	H	9	Response times to flash stimuli were impaired in direct relation to hypoxic exposure severity
Kobrick (1976)	N/A	Polynomial regression analysis	43	The main effect of hypoxic exposure was elevation of the response time impairment in direct relation to severity

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Leber (1985)	Sea level, 7000, 10,000, and 13,000 ft	N	6	Supplemental oxygen significantly improved naked-eye but not NVG-augmented night resolution acuity up to an altitude of 13,000 feet above sea level (ASL)
Leber et al. (1986)	7000, 10,000, and 13,000 ft	N	4	Supplemental O_2 did significantly improve naked-eye but not NVG-augmented night resolution acuity up to a simulated altitude of 13,000 ft
Lewis and Haymaker (1948)	N/A	Retrospective	75 autopsy cases	N/A
Li et al. (2000)	2800, 3600, and 4400 m	H	18	No measurable impairment of visual reaction time and psychomotor performance up to 2800 m; adverse effects on psychomotor performance at 3600 m and above
Loeppky and Roach (1996)	15,100 ft	H/N	6	Ventilation and chemosensitivity are about the same after 30 min of altitude and equivalent hypoxia; however when the drop in inspired O_2 is not synchronous with the drop in ambient pressure, like at altitude, ventilation values may be altered
Loeppky et al. (1990)	14,828 ft	N	6	Tissue oxygenation and cardiopulmonary function were not notably effected by head-down tilt during hypoxia
Luna et al. (1994)	12,000, 15,000, 18,000, and 21,000 ft	H	8	Alveolar PO_2 in itself may not provide the best correlation with task performance

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Mahoney et al. (2007)	N/A	N/A	19	Cold exposure degrades cognitive performance and supplementation with tyrosine alleviates working memory decrements
McFarland and Evans (1939)	7400, 11,000, and 15,000 ft	N	20	Decrease in light sensitivity at 7400 ft
McFarland and Halperin (1940)	10,000 and 18,000 ft	N	11	Hypoxia results in a large decrease of visual acuity at low illuminations; It is important pilots use O_2 during night flights than during daylight flights
Nelson (1982)	Sea level, 3810 and 5000 m	H	20	Critical altitude for psychological changes lies between 4000 to 5000 m, as virtually no significant variations were noted at 3810 m
Nesthus et al. (1997)	8000, 10,000, and 12,5000 ft	In-flight/mixed gases	20	Significantly more procedural errors committed by the hypoxia group during simulated cruise flight at 10,000 ft, both during the descent and approach phases from 10,000 ft, and during descent from 12,500 ft
Nesthus et al. (1997)	5000, 8000, and 12,500 ft	N	18	Smoker group exhibited higher error rate on Multi-Attribute Task Battery
Nordahl et al. (2002)	Profile 1: 8000, 14,000, 18,000, and 25,000 ft Profile 2: 14,000 ft	H	12	Changes in postural control at altitudes up to 18,000 ft probably due to hypoxia; venous gas emboli may form during acute exposure to 14,000 ft

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Obminski et al. (1997)	5,000 m	H	53	No single consistent change in salivary cortisol level occurred among the different subjects in response to the level and duration of hypobaric hypoxia studied
Paul and Fraser (1994)	5000, 8000, 10,000, and 15,000 ft	H	144	Results indicated the ability to learn new tasks not impaired by mild hypoxia up to 12,000 ft
Pavlicek et al. (2005)	3000 m and 4500 m	H	21	No significant changes in higher cognitive and emotional function tests; Selected cognitive and affective frontal lobe functions preserved despite significant O_2 desaturation and drop in diastolic blood pressure
Peña and Ramirez (2005)	N/A	Review paper	N/A	N/A
Rahn, Otis, & Fenn (1947)	12,000, 16,000 (6% CO_2), 18,000, 20,000, and 22,000 ft	H	8	Hand steadiness showed a barely significant change at 12,000 feet, worse with increasing altitude; Addition of 6% CO_2 to the inspired air at 16,000 feet increased the alveolar PCO_2 to 10 mm and the PO_2 4 mm
Replogle et al. (1971)	12,000 and 22,000 ft	N	6	Adaptive tracking tasks significantly sensitive to hypoxic stress
Rice et al. (2005)	15,000 ft	N	60	Volunteers averaged 12 or more errors on the vigilance exam

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Rickards and Newman (2002)	3,775,500 and 11,000 ft	N	14	No significant changes in the blood pressure response to orthostasis with hypoxia; Heart rate (HR) changes suggest the ability to modulate HR under orthostatic stress is reduced with exposure to low-level normobaric hypoxia
Rostrup et al. (2008)	N/A	N/A	Cell cultures	TH activity may be severely limited by O_2 availability at moderate hypoxic conditions
Saul et al. (2002)	10,000 to 24,000 ft	In-flight/mixed gases	1	Voluntary hyperventilation may result in overventilation and severe hypocapnia; Subject breathing into a mixing chamber was able to maintain an S_aO_2 of 90% at 20,000 ft
Sausen et al. (2001)	6.20/93.80, 7.00/93.00, and 7.85%/92.15% O_2/N_2	N	12	Data consistent with those expected from hypoxic states; Supported the validity of the reduced O_2 breathing paradigm for hypoxia training
Savourey et al. (2003)	4500 m	H/N	18	Compared to normobaric hypoxia, hypobaric hypoxia led to greater hypoxemia, hypocapnia, blood alkalosis, and lower O_2 arterial saturation

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Scano et al. (1966)	11% O_2	N	30	Perception and recognition of visual information of indicators and instruments are, in most subjects, considerably hindered by the combined action of nystagmus and hypoxia
Schlaepfer et al. (1992)	3450 m	H/N	10	Mild hypoxia increased visual perception above normal
Smith (2005)	10,000 ft	Retrospective survey	53	Aircrew experienced potentially operationally significant symptoms at a mean altitude of 8426 ft
Smith (2006)	Sea level, 2000, and 7000, 9000 ft	H	6	Physical activity below 10,000 ft can produce hypoxemia
Strand & Owe (2008)	8000 and 16,000 ft	H	131	SpO_2 fell within first 5 to 8 min after acute exposure to 16,000 ft; critically low SpO_2 demonstrated after 8 to 9 min
Takagi and Watanabe (1999)	6000 m	H	16	With inter-stimulus intervals of 2 seconds, acute hypoxia served to reveal the functional properties of the early and late components of contingent negative variation (CNV); CNV may be regarded as good indices of higher cerebral function under hypoxic conditions
Temme et al (2010)	8000, 12,000, and 14,000 ft	N	72	Variability of pulse-oximetry data cautions usual practice of using Reduced Oxygen Breathing Device (ROBD) altitude as experiment's independent variable

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Terry (2001)	10,000 and 14,000 ft	H	10	Cognitive performance was better at 10,000 ft as compared to ground level and 14,000 ft a rest; post-exercise scores were significantly greater than pre-exercise scores regardless of altitude
Tsarouchas et al. (2008)	15,000 ft	H	10	Evoked brain responses allowed for early detection of subtle electrophysiological modulations coupled to cognitive-behavioral alterations, assessment of 'functional' hypobaric hypoxic sensitivity thresholds, and reveal the susceptibilities of complex visuocognitive processes even to moderate hypoxic insults
Tutt et al. (2006)	5,000, 8,000, 12,000 ft	H	92	Study indicated statistically insignificant influence of low-grade hypoxia on NVG vision at exposure conditions of this study
van der Post et al. (2002)	Manipulation of SPO_2 to 90 and 80%	N	12	Cognitive performance was decreased by an SPO_2 of 80% and increased by an SPO_2 of 90%
Vacchiano et al. (2004)	25,000 ft	H/N	70	Objective and subjective effects of decreasing tissue oxygenation were the same regardless of whether this decrease was produced at sea level or at altitude

Author(s) (Year)	Altitude (ft or m)/O_2 Concentration	Method (hypobaric [H]/normobaric [N])	Sample	Major Results
Vaernes et al. (1984)	3048 m	H	7	No relationship between impaired performance and duration of exposure found; mild hypoxia yielded varying degrees of impairment of cognitive functions
Vingrys and Garner (1987)	12,000 ft	H	2	Found a generalized loss of color vision affecting both red-green and blue-yellow discrimination at an altitude of 12,000 ft
Wagner et al. (2010)	5000, 8000, and 10,000 ft	N	13	Balance performance on Computerized Dynamic Posturography (CDP) showed degradation of performance under hypoxic conditions.
Wangsa-Wirawan and Linsenmeier (2003)	N/A	Review paper	N/A	N/A
Watson et al. (2000)	1200, 2400, and 3700 m	N	4	Auditory sensitivity for frequencies up to 16 kilohertz is unaffected by hypoxia
Wientjes et al. (1999)	N/A	N/A	11	Tyrosine supplementation can be effective in preventing cognitive degradation in highly demanding military operational environments
Wu et al. (1998)	3600, 4400, and 5000 m	H	16	Error rate on continuous calculation test and reaction time on addition-subtraction test increased significantly after 1 hr exposure to 3600 m
Yusfin et al. (1953)	5000 to 7000 m	H	25	Oxygen inhalation at high altitudes restores color discrimination to all three receptors, almost to the initial level

Appendix B.

Regulatory examples governing hypoxia in unpressurized aircraft.

U.S. Army Flight Regulations (Army Regulation [AR] 95-1) (2008):

a. Unpressurized aircraft. Oxygen will be used by aircraft crews and occupants for flights, as shown below:

(1) Aircraft crews.

(a) On flights above 10,000 feet pressure altitude for more than 1 hour.

(b) On flights above 12,000 feet pressure altitude for more than 30 minutes.

(2) Aircraft crews and all other occupants.

(a) On flights above 14,000 feet pressure altitude for any period of time.

(b) For flights above 18,000 feet pressure altitude, oxygen prebreathing will be accomplished by aircrewmembers. Prebreathing may utilize either 100 percent gaseous aviator's oxygen from a high pressure source, or an onboard oxygen generating system (OBOGS) that supplies at least 90 percent oxygen. Prebreathing will be for not less than 30 minutes at ground level and will continue while en route to altitude. In those extraordinary cases where mission requirements dictate rapid ascent, commanders may authorize shorter prebreathing times on a case-by-case basis, with the realization that such practice increases the risk for developing altitude decompression illness. Return to NORMAL OXYGEN (pressure demand regulator, gaseous oxygen-equipped aircraft) is authorized on descent below 18,000 feet pressure altitude, provided continued flight will not exceed this altitude. (p. 43)

U.S. Navy (OPNAVINST 3710.7U) (2009):

8.2.4.1 Unpressurized Aircraft

In unpressurized aircraft with oxygen systems, the pilot at the controls and aircrew participating in physical activity (loadmasters) shall use supplemental oxygen continuously when cabin altitude exceeds 10,000 feet. When oxygen is not available to other occupants, flight between 10,000 and 13,000 feet shall not exceed 3 hours duration, and flight above 13,000 feet is prohibited. In aircraft where oxygen systems are not available (such as helicopters), it must be determined that it is mission essential for flight altitude to exceed 10,000 feet. Time above 10,000 feet shall not exceed 1 hour and altitude shall not exceed 12,000 feet. (pp. 8-10)

U.S. Air Force (Instruction 11-202V3_ACCSUP_I) (2010):

6.4. Oxygen Requirements. (N/A for UAS ground control stations) The PIC shall ensure sufficient oxygen for the planned mission (including contingencies) is available to all occupants

before takeoff. Normally, aircrew will use supplemental oxygen anytime the cabin altitude exceeds 10,000 ft MSL.

6.4.1. Unpressurized Operations. When mission essential, aircrew trained IAW AFI 11-403, Aerospace Physiological Training Program, may operate aircraft unpressurized above 10,000 ft. MSL without supplemental oxygen IAW MAJCOM guidance and the following restrictions:
6.4.1.1. Total flight time (without supplemental oxygen) above 10,000 ft. MSL shall not exceed 1 hour if any portion of the flight above 10,000 ft. MSL is in IMC, at night, or when using NVGs, employing weapons, conducting airdrop or air-refueling, or performing high-g maneuvers.

6.4.1.2. Maximum of 30 minutes (without supplemental oxygen) between 12,500 and 14,000 ft. MSL.

6.4.1.3. Supplemental oxygen must be used by all persons while above 14,000 ft. MSL.

6.4.1.4. Any occupant, not trained IAW AFI 11-403, limits the cabin altitude to:

6.4.1.4.1. 10,000 ft. to 13,000 ft. MSL for three hours without supplemental oxygen.

6.4.1.4.2. 13,000 ft. MSL without supplemental oxygen.

6.4.1.5. FL 250 shall not be exceeded even if occupants have oxygen. (pp. 41-42)

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