CME

Effects of Acute, Profound Hypoxia on Healthy Humans: Implications for Safety of Tests Evaluating Pulse Oximetry or Tissue Oximetry Performance

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Extended periods of oxygen deprivation can produce acidosis, inflammation, energy failure, cell stress, or cell death. However, brief profound hypoxia (here defined as Sao_2 50%–70% for approximately 10 minutes) is not associated with cardiovascular compromise and is tolerated by healthy humans without apparent ill effects. In contrast, chronic hypoxia induces a suite of adaptations and stresses that can result in either increased tolerance of hypoxia or disease, as in adaptation to altitude or in the syndrome of chronic mountain sickness. In healthy humans, brief profound hypoxia produces increased minute ventilation and increased cardiac output, but little or no alteration in blood chemistry. Central nervous system effects of acute profound hypoxia include transiently decreased cognitive performance, based on alterations in attention brought about by interruptions of frontal/central cerebral connectivity. However, provided there is no decrease in cardiac output or ischemia, brief profound hypoxemia in healthy humans is well tolerated without evidence of acidosis or lasting cognitive impairment. (Anesth Analg 2017;124:146–53)

In this article, we review the effects of acute profound hypoxia on human physiology and central nervous system function. As clinicians and scientists who have worked for many years on oxygen sensing, tissue protection against hypoxic injury, and adaptation to high-altitude environments, we are struck by the widespread lack of knowledge concerning the tolerability of acute, profound hypoxemia in humans. To bring these opinions into focus, we will examine historical development of the appreciation of the effects of oxygen deprivation. We will review how molecular oxygen at the mitochondria enables highly efficient ATP production and how, over long periods and with severe hypoxia, anaerobic metabolism has limited capacity to provide adequate energy production unless metabolic rate is drastically curtailed. Some of the adaptations that enable diverse types of organisms to tolerate oxygen deprivation will be covered and the problems of chronic hypoxia in humans will be reviewed. We will conclude by examining the evidence that acute profound hypoxia causes lasting harm in humans. The available evidence is overwhelming and points to the conclusion that, unless hypoxia is truly chronic, or the circulation fails (ie, hypoxia combined with ischemia), that any effects of even profound hypoxia are reversible and without persistent effects in otherwise healthy individuals.

HISTORIC APPRECIATION OF THE PROBLEMS OF HYPOXIA IN HUMANS AND ANIMALS

The "discovery" of oxygen and the recognition of the effects of oxygen deprivation have a complex and interesting history. Six different scientists are credited with the discovery of molecular oxygen.[1] Perhaps the first clear recognition that one of the components of air (1/5th by volume, in fact) was essential for life, consumed during breathing and by fire, was by John Mayow, working in Robert Boyle's Oxford laboratory in 1668. Boyle's publications clearly identified a component of air as required for life and recognized that tolerance of air deprivation varied; neonatal humans or domestic animals evinced far greater tolerance of asphyxia or air deprivation than adults of the same species.[2] The recognition that high altitude involves reduction in air density can be traced to 1644 when Torricelli described the first mercury barometer and penned the seminal statement, "We live submerged at the bottom of an ocean of the element air." Blaise Pascal recognized that air pressure fell with increasing altitude, and Otto von Guericke demonstrated the enormous force of atmospheric pressure. When Robert Boyle learned about Guericke's experiments, he and Robert Hooke constructed the first air pump, allowing small animals to be exposed to reduced ambient pressures. The physiological effects were predictable.

With the invention of ballooning, humans could suddenly experience very low pressures and high altitudes, sometimes with lethal effects. When the French balloon Zenith ascended >8000 m, 2 of the 3 persons on board died, and the third probably was only partially conscious.[3] Bert[4] was the first person to clearly state that the deleterious effects of high altitude were caused by the low partial pressure of oxygen. In the subsequent century, thousands of

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researchers became focused on altitude effects on humans and other animals. West[5] has written a comprehensive recent review on the history of these early altitude studies. One of the major contributions of altitude studies has been that they have provided deeper understanding of the limitations on gas exchange and gas transport in the lung and tissues. The physiology defined and clarified in altitude studies applies not only to healthy humans adapting to high-altitude hypoxia but also to the understanding of how adaptation fails in chronic diseases involving impairments of gas exchange and gas transport.

CELLULAR EFFECTS OF SEVERE HYPOXIA: THRESHOLDS OF ANAEROBIC METABOLISM AS A SIGN OF FAILURE OF ADAPTATION

Our understanding of the cellular and molecular effects of oxygen deprivation has expanded dramatically in recent decades. The fundamental cellular and molecular stresses of hypoxia are based on the fact that oxygen deprivation reduces the availability of an electron receptor at the terminus of the electron transport chain in the mitochondria. The gradient of electrons and protons generated across the mitochondrial membrane provides the chemical potential energy captured for ATP production (oxidative phosphorylation). Catalyzed by cytochrome oxidase, the electrons combine with protons and molecular oxygen to form water, as in the following equation:

$$4e^- + 4H^+ + O_2 \xrightarrow{cytochrome\ oxidase} 2H_2O.$$

In fact, it is thought that the inception of anaerobic metabolism and lactic acid accumulation occur when the partial pressure of oxygen (Po_2) at the mitochondria falls to near 0 mm Hg, corresponding to a tissue Po_2 of approximately 10 to 20 mm Hg.[6] The use of oxygen as the electron acceptor in energy metabolism has made possible the high metabolic rates that enable endothermy and its many manifestations: the evolution and adaptive radiation of mammals, avian and mammalian flight, sustained aerobic exercise, complex nervous systems, and many others. It is not an exaggeration to state that the adaptive radiation of organisms capable of using oxidative phosphorylation for energy production has had a major influence on higher life on our planet. At the molecular level, the basis for this is simple: oxidative phosphorylation generates 16 times as much ATP per mole of glucose as does anaerobic metabolism.[7] Therefore, to maintain energy charge (ATP/ADP) when oxygen availability is limited, anaerobic metabolism must increase manyfold. In hypoxia-intolerant animals, anaerobic metabolism generates lactic acid or other acidic byproducts and also results in rapid substrate depletion, limiting survival. In hypoxia/anoxia-tolerant organisms, an entirely different strategy is utilized—that of reducing metabolism to avoid running out of substrate and limiting the generation of acidic metabolic end products.[8–10] The conclusion from a large number of studies is that acidosis is an indication of the failure of oxygen supply at the tissue level; therefore, the presence of acidosis is a sign that oxygen deprivation has reached a critical level and threatens long-term energy production and cellular homeostasis.

EXCEPTIONAL TOLERANCE OF HYPOXIA: LESSONS FROM COMPARATIVE PHYSIOLOGY AND ADAPTATION OF HUMANS TO EXTREME ENVIRONMENTS

Strategies Used by Hypoxia and Anoxia-Tolerant Organisms

Comparative physiologists have provided extremely important insights into how organisms adapt to life with limited oxygen availability. A summary of these adaptations has been reviewed by Jonz et al[11] and earlier by Bickler and Buck.[12] Adaptations to severe hypoxia almost always involve decreased metabolism and increased reliance on anaerobic energy production. Hypothermia, hibernation, anaerobiosis, use of other substrates, and nonoxygen molecules as electron acceptors are all involved in the adaptations for life with limited oxygen availability. A detailed review of these fascinating adaptations are beyond the scope of this article; however, to provide some context to understanding the less impressive but still significant adaptive capacities of humans to hypoxia, we will provide some background.

Successful anaerobes produce all ATPs needed for essential life processes by anaerobic processes such as glycolysis. Because of the fundamental metabolic fact that anaerobic energy production is relatively inefficient, ATP consumption must be decreased manyfold to maintain cellular and organismal integrity. In some anoxia-tolerant organisms, this strategy results in a 10,000-fold increase in tolerance of oxygen deprivation compared with mammals. Viewed in basic energetic terms, to function in low-oxygen conditions, organisms must either utilize adaptations for extracting oxygen from a low-oxygen ambient environment, or they must produce enough ATPs for their needs using anaerobic metabolism. For long-term survival using anaerobic metabolism, drastic reductions in metabolism are also required. The types of adaptations involved in these strategies span the range of biological organization from the molecular to the evolutionary and ecological. Notable adaptations include various types of energy-saving dormancy and hibernation states.[12] The Western painted turtle (*Chrysemys picta*) and crucian carp (*Carassius carassius*) represent perhaps 2 of the most extreme examples of complete anoxia tolerance, with the ability to tolerate arterial oxygen partial pressures (Pao_2) of near 0 for months at a time without detectable negative consequences.[13]

Profound hypothermia is the only state in humans that can approach the degrees of reduction in ATP utilization seen in some of the examples above, but human tissues have poor tolerance of low temperatures compared with many other vertebrates. Despite the advantages of reduction in metabolic rate brought about by profound hypothermia, the intrinsic hypothermia intolerance of human tissues has produced a mixed record of benefits and injuries resulting from the clinical use of profound hypothermia.[14–17]

Adaptation to hypoxia in hypoxia-sensitive tissues and organisms (such as most mammals) has been extensively studied, chiefly in efforts to identify targets to protect hypoxia and ischemia-sensitive tissues. A potentially clinically useful example of exceptional tolerance of hypoxia is the phenomenon of hypoxic or ischemic preconditioning. Preconditioning

involves a sublethal hypoxic or ischemic stress that induces a state of tolerance to subsequent more profound hypoxia or ischemia.[18,19] Preconditioning has been shown to protect a diverse range of tissues, including heart, brain, liver and kidneys, all organs that are quickly damaged by ischemia (but not necessarily hypoxia, see the section TISSUE INJURY FROM ACUTE HYPOXIA: PURE HYPOXIA VERSUS HYPOXIA PLUS ISCHEMIA). At the cellular level, there are a large number of potential signaling mechanisms that underlie preconditioning and other kinds of adaptation to oxygen lack. Oxygen-sensitive transcription factors, such as hypoxia-inducible factor 1 (HIF1-α),[20] are an important group of mechanisms that link lack of oxygen to the transcription of genes that enable metabolic adaptation to the changing demands of limited oxygen availability. Transcription factors are not the only adaptation, however; there are oxygen-sensitive ion channels, cellular redox-based changes and signals, and numerous other adaptations that have been identified.[11] This is a very active field of research, with >5000 citations in PubMed for the search terms: hypoxic/ischemic preconditioning. The involvement of the HIF system in preconditioning is well established, and the potential clinical applications of HIF-based therapies in ischemic diseases have been recently reviewed.[21]

Human Adaptation to Hypoxia

Humans have an impressive capacity to adapt to low-oxygen environments, given time. Studies on the adaptation of lowland natives to high-altitude environments and of high-altitude populations have produced numerous reports. Adaptation to high-altitude hypoxia occurs acutely (over days to weeks), as in high-altitude sojourns by lowland natives, and over generations, as selection for traits that are associated with resistance to chronic mountain sickness (CMS) in high-altitude populations in the Andes or the Himalayas. For a recent review on high-altitude adaptation in human populations, see the study by Gilbert-Kawai et al.[22] The capacity of humans to adapt to hypoxia at high altitudes over the course of several weeks can be quite dramatic; numerous measurements of saturation levels in climbers on mountaineering expeditions document saturations in the 60% range or lower, with lower values not unusual. In climbers on Mt. Everest, a Pao_2 of 19, with a calculated saturation of 34% was recorded.[23] Not infrequently, members of high-altitude medical teams report measuring saturations in team members in the 40% range, often with no obvious effects on cognitive performance. Without acclimatization, saturations <40% would probably not be tolerated for >30 minutes without experiencing impaired cognition and decreased levels of consciousness, even without cardiovascular compromise. The evidence for long-term cognitive effects of hypoxia in mountain climbers is discussed in the section TRANSIENT VERSUS PERSISTENT NEUROCOGNITIVE CHANGES AFTER PROFOUND HYPOXIA. In the aviation field, a significant amount of research has addressed responses to acute hypoxia, as in a sudden loss of cabin pressure at high altitudes. The thresholds for loss of consciousness remain somewhat undefined, however, and depend on the $Paco_2$, which determines cerebral blood flow.[24]

Another dramatic example of human adaptation and tolerance of hypoxemia is that of elite breath-hold divers. There are a number of published reports of elite breath-hold divers achieving saturations of around 50% without apparent ill effects. For example, Lindholm and Lundgren[25] reported alveolar gas composition in 9 breath-hold divers who floated face down in a 28°C pool, for 5 minutes. End-tidal Po_2 at dive termination averaged 26.9 mm Hg. Elite divers frequently train for such breath-holding feats and may rely on some form of preconditioning to enhance their capabilities.

Disease in Humans Related to Chronic Hypoxia

Chronic severe hypoxia clearly produces disease and disability. Perhaps the clearest example of a disease in humans caused by hypoxia in otherwise apparently healthy humans is chronic mountain sickness (CMS). CMS was first described by Carlos Monge-Medrano around 1925.[26] This condition occurs in lowland natives residing at altitudes >3500 m for more than approximately 3 months. The populations initially described as developing CMS were costal natives of European or South American descent who relocated to high-elevation mines in the Andes, such as the Cerro de Pasco mining region, elevation 4300 m (14,200 feet). Some of these mining camps are at elevations >15,000 feet (approximately 4600 m). CMS is associated with polycythemia, systemic and pulmonary hypertension, decreased exercise tolerance, decreased growth, hypertension, sleep disturbance, and cognitive decline.[27,28] Residents of intermediate elevations, such as Leadville, CO (10,152 feet; 3094 m), experience milder forms of CMS, and pregnancy at those elevations can lead to low-birth-weight babies.[29] It should be noted that the severity of CMS pathology is often related to preexisting

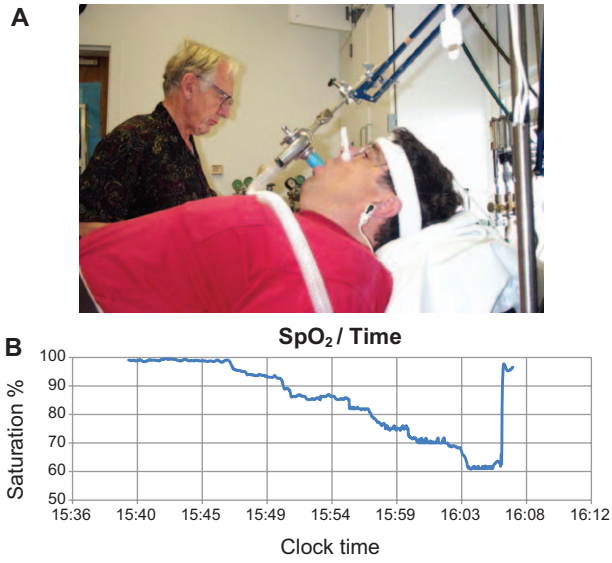

Figure. A, Photograph of Dr John Severinghaus conducting a desaturation study in the early 1990s on a volunteer subject. The control of saturation involves a gas mixing manifold (partially visible at the far right of the photograph), end-tidal gas analysis with a mass spectrometer, and a computer algorithm that calculates estimated saturation breath by breath from end-tidal oxygen, end-tidal carbon dioxide, and inputs of oxyhemoglobin affinity (P_{50}), alveolar-arterial Po_2 difference, and blood base excess. B, Typical desaturation profile in a pulse oximeter performance study. This profile involves a series of progressively lower and stable plateaus of saturation during which arterial blood samples are obtained and pulse oximeter readings are recorded. The steady-state conditions during sampling ensure that potential errors related to pulse oximeter averaging times and lung-to-finger circulation delays are minimized.

cardiovascular disease, diabetes mellitus, vascular disease, and cigarette smoking. Highland natives from the Tibetan Plateau and the Andes apparently are resistant to the development of CMS, probably related to genetic adaptions in these populations.[30] Identification of the genetic basis for altitude adaptation and resistance to the pathology of CMS has been actively investigated in recent years.[31] The expressions of the genes *SENP1* and *ANP32D* have been linked to susceptibility to the disease.[32] SENP1 catalyzes the maturation of the small ubiquitin-related modifier (SUMO) protein, which is involved in processing damaged/misfolded proteins and protecting proteins from misfolding. The *ANP32D* gene is a tumor-suppressor gene and a nuclear phosphoprotein. How either of these genes relates specifically to risk for CMS is not yet established.

Respiratory and cardiovascular diseases are the most important causes of chronic hypoxia in lowland natives. Chronic severe hypoxemia is associated with a number of diseases, including congenital heart disease, chronic obstructive pulmonary disease, severe asthma, pulmonary fibrosis, hepatopulmonary syndrome and central hypoventilation syndromes from brain tumors, amyotrophic lateral sclerosis, and others. Chronic hypoxia in these conditions causes nutrient malabsorption in the gut, weight loss, sleep disturbance, and cognitive dysfunction,[33] as well as right heart failure from pulmonary hypertension.[27] Acute respiratory distress syndrome leads to cognitive dysfunction,[34] although it is not clear whether the cognitive impact is a result of the hypoxemia per se or from the other stresses of critical illness and critical care. Long-term use of supplemental oxygen in patients with chronic obstructive pulmonary disease is associated with improvements in outcomes, including cardiovascular and cognitive benefits.[35–38]

Chronic, intermittent hypoxemia associated with sleep apnea is increasingly common in westernized societies. Sleep apnea involves brief and numerous periods of hypoxia and reoxygenation over periods of months and years. Somewhat paradoxically, these repeated bouts of hypoxia and reoxygenation are not associated with preconditioning benefits, but with negative consequences on the brain and other organs. The cognitive impact of sleep apnea and sleep disturbance has been studied extensively, but it remains unclear to what extent sleep deprivation and hypoxia/reoxygenation each contribute to the cognitive problems of of people who have sleep apnea. Animal models have enabled researchers to address this outstanding question with the imposition of repeated bouts of ambient hypoxia in animal models. In rodents, repeated bouts of hypoxia over months are associated with inflammation and cell loss in several brain regions.[39] It seems to us that this is probably also the case in humans experiencing severe sleep apnea.

TISSUE INJURY FROM ACUTE HYPOXIA: PURE HYPOXIA VERSUS HYPOXIA PLUS ISCHEMIA

We believe that there is widespread lack of knowledge concerning the potential for deleterious effects of acute hypoxia on humans. In our experience, many clinicians believe that even momentary saturations in the 70s can cause brain damage in otherwise healthy individuals, even without a coexisting decrease in blood pressure. This misconception probably has arisen because the literature on ischemic brain injuries often fails to distinguish purely hypoxic events from combined hypoxic and ischemic events. Pure hypoxia and hypoxia/ischemia because of very different stresses produce dramatically different pathogenesis and effects on brain, heart, liver, and kidneys. Specifically, numerous publications on hypoxic/ischemic brain injuries fail to adequately distinguish hypoxia (alone, no significant circulatory failure), asphyxia (suffocation, leading to hypoxia and circulatory collapse; eg, birth asphyxia from umbilical cord compression combined with inadequate lung ventilation), pure ischemia (eg, embolic stroke), or a combination of hypoxia leading to circulatory collapse and tissue ischemia. Without a doubt, even in otherwise healthy individuals, if the hypoxia is severe enough (ie, near anoxia) and prolonged enough, the circulation will eventually fail and ischemia will become a component of the subsequent pathology.

Some of the authors of this article have an extensive history of consultation for medical-legal advice concerning the possibility of brain damage resulting from hypoxia or ischemia during medical care. In our combined 90+ man-year history of this activity, the authors are not aware of any cases where brain damage resulted from an event that involved hypoxia without coexisting pathology or compromised perfusion. In fact, the leading risk factor for brain damage following a hypoxic/ischemic event (eg, loss of airway, failure to ventilate) is a cooccurring circulatory compromise, requiring the need for cardiopulmonary resuscitation with chest compressions. In situations where only hypoxia has occurred, it is hard to identify reports of persistent and clear cognitive deficits. The issue of long-term cognitive effects from brief periods of hypoxia is discussed in "Is There Any Evidence That Acute Profound Hypoxia Produces Lasting Cognitive Impairment?".

EFFECTS OF HYPOXIA ON INDIVIDUALS WITH HEART AND LUNG DISEASES

Individuals with coexisting cardiovascular or pulmonary disease are undoubtedly at greater risk for circulatory compromise caused by hypoxemia. This is for several important reasons. First, oxygen delivery to the myocardium may already be marginal in individuals with coronary artery disease, leading to myocardial stress during decreases in the arterial oxygen content. The decrease in oxygen delivery can result in depressed myocardial function, wall motion abnormalities, electrocardiogram changes similar to ischemia, and arrhythmias. The sympathetic nervous system is activated by systemic hypoxia,[40] resulting in increased heart rate, pulmonary vascular resistance, and systemic vascular resistance. These are additional stresses for the already compromised myocardium. Another risk factor for hypoxia-induced depression of the myocardium is anemia, because this will reduce oxygen delivery to the heart tissue. The compensatory increased blood flow in response to reduced oxygen availability is impaired with coronary artery disease. Similarly, coexisting pulmonary disease increases the risk of reaching critical oxygen delivery to tissues because of impaired gas exchange.

In contrast to situations where tissue ischemia occurs, hypoxia itself is very well tolerated in otherwise healthy individuals with normal cardiopulmonary function. Several research laboratories have extensive experience with studies

involving acute profound hypoxia in humans. These laboratories have been involved with the testing and development of pulse oximeters, tissue oximeters, cerebral oximeters, and cerebral blood flow measurements for >30 years (Figure). These laboratories include the UCSF Hypoxia Research Laboratory, the Clinimark laboratory in Colorado, the Human Pharmacology Laboratory at Duke University, Hartmut Goering's laboratory at Lubeck Germany, and others. At these centers, we estimate that >10,000 subjects have been enrolled in studies that involve repeated stepwise reduction in arterial saturations to levels as low as 45% for brief periods. In a typical 1-hour study, subjects may spend a total of about 15 minutes at saturations <80%. Authors of this article have personally experienced saturations of 45% during such testing without apparent ill effects on blood pressure and without losing consciousness. Heart rate increases are usual but are involved in maintaining oxygen delivery to tissues in the face of hypoxia, and even increase to rates in the 130s or higher are well tolerated by young healthy subjects.

Other research activities that involve acute, profound hypoxia in healthy subjects include measurements of hypoxic ventilatory responses. These studies are done at dozens of centers around the world. As far as we are aware, there has not been a single significant complication related to hypoxia in any of these studies. Aside from the expected physiologic responses to hypoxia in healthy individuals such as increased respiratory rate or tachycardia, the incidence of other effects such as headache, nausea, or anxiety occur at rates <1%. In addition, it is important to note that the majority of the approximately 10,000 subjects enrolled in these studies also had a 22-gauge radial arterial line for blood sampling. As far as we are aware, there have been no significant complications due to the arterial cannulations in this healthy population. Even in surgical and intensive care unit patients, the rate of serious complications with ≥20-gauge arterial lines is only about 3 per 10,000.[41]

HYPOXIA AND ISCHEMIA HAVE DRAMATICALLY DIVERGENT EFFECTS ON THE HUMAN BRAIN

The central nervous system is arguably the organ system that is the most sensitive to short- and long-term impairment from oxygen and/or blood flow deprivation. Ischemic cerebrovascular disease is 1 of the top 5 causes of death worldwide.

Ischemic brain injury is quite distinct to the transient alterations in high-level cognitive function seen with acute, brief durations of hypoxia. The most important differences are that brief periods of ischemia (as short as 4 minutes of global ischemia) can produce long-lasting, if not permanent, neurologic deficits. With ischemic brain injury, it is essential that global ischemia (typically associated with cardiac arrest) be distinguished from focal ischemia, such as that caused by embolic stroke, aneurysmal rupture, intracranial bleed from trauma, arteriovenous malformation.

There are a number of excellent reviews concerning the pathophysiology and treatment of ischemic cerebrovascular diseases. In terms of the cognitive effects of global ischemia (eg, cardiac arrest followed by successful return of spontaneous circulation), we direct the reader to reviews by Alexander et al[42] and Lu-Emerson and Khot.[43] A review by Howard et al[44] discussed neuroimaging and electroencephalographic findings after hypoxic/ischemic central nervous system insults clearly states that purely hypoxic insults, when they occur, have a different pattern of neurologic injury than combined hypoxic/ischemic insults do. Isolated hypoxic brain injury is usually caused by asphyxia (eg, being trapped in an enclosed space for an extended period) and can involve damage to deep grey matter such as the caudate, putamen, and thalamic regions; in contrast, after combined hypoxic/ischemic brain injury (eg, after global ischemia from cardiac arrest), neuroimaging (magnetic resonance imaging) often reveals high signal in the caudate and putamen but less in the thalamic regions and with altered signals in various regions of the cortex.

In rare circumstances, isolated hypoxic brain injury occurs and can present a clinical picture similar to that seen in carbon monoxide poisoning. This syndrome, known as delayed posthypoxic leukoencephalopathy, involves changes seen after an initial apparent recovery from hypoxic coma. One to 4 weeks later, a relapse is seen, with cognitive deterioration, with frontal lobe and extrapyramidal symptoms, including urinary incontinence, gait disturbance, and parkinsonian expression and rigidity.[45]

Garcia-Molina et al[46] review the neurologic findings in a group of patients with ischemic anoxia (21 cases) versus those in hypoxemic anoxia (11 cases). Memory problems were common in both groups, with more severe effects in the group with documented evidence of ischemia. However, sudden ischemic–hypoxic injury caused by cardiac arrest does not preferentially damage memory systems; this may be an isolated finding after a purely hypoxic event. The common pattern of impairment in the subacute phase after cardiac arrest is a combination of memory, and subtle motor and variable executive deficits.[47]

TRANSIENT VERSUS PERSISTENT NEUROCOGNITIVE CHANGES AFTER PROFOUND HYPOXIA

There is no question that hypoxia exposure can, if profound enough (approximately 65% saturation or less), produce transient changes in neurocognitive function. The most outstanding question of relevance to laboratory study of hypoxia, and for high-altitude sojourners, is whether these changes are persistent and of any concern to the health and well-being of humans. The consensus is that there is no evidence that brief profound hypoxia causes any lasting neurologic deficits.

There have been numerous studies that have examined the effects of acute and chronic hypoxia on human cognitive performance (for reviews, see the study by Yan[48]). The settings of these studies have been high-altitude research expeditions, hypobaric chambers, or breathing systems involving controlled levels of hypoxemia in the laboratory. Most of the information concerns cognitive studies performed during high-altitude research expeditions and laboratory evaluation of acute hypoxia. The information about the long-term effects of hypoxia on neurocognitive function in residents of high-altitude cities or mining camps is less complete. In those population-based studies, it is difficult to find the appropriate control groups for comparison, because researchers need to account for variables such as

coexisting diseases, cigarette smoking, education level, and numerous other variables, all of which can impact cognitive performance. Reversible changes in cognitive performance have also been demonstrated in acute anemia.[49]

In terms of acute hypoxia and reoxygenation, most of the information relates to studies done to discern the potential for cognitive impacts in aviators who experience sudden loss of cockpit pressure at high altitudes. A number of different tests have documented decrements in cognitive and motor performance under conditions of acute hypoxia.[50,51]

The largest body of information concerning the neurocognitive effects of relatively longer duration, but not chronic hypoxia relates to members of high-altitude mountaineering expeditions. Altitude exposures reduce neurocognitive function as assessed by a number of metrics, predominately in the domains of attention and processing speed, which roughly reflect cortical and cortical/subcortical connectivity, respectively. A number of studies have documented impairments in attention and processing speed during exposure to high altitudes.[52–54] It is generally felt that these cognitive deficits improve with acclimatization and are reversible on descent to lower elevations. There is very limited information about the long-term effects of repeated prolonged exposures to very high altitudes. However, a study published in 2008 by Di Paola et al[55] raised concerns in the high-altitude climbing community about repeated exposure to high altitudes and led to a commentary in the *New York Times*.[56] Some of the climbers studied in the study by Di Paoula et al were engaged in high-altitude expeditions for over a decade. In the study, a region of reduced white matter density/volume was found in the left pyramidal tract near the primary (Broca area 4) and supplementary (Broca area 6) motor cortex when mountain climbers at baseline were compared with controls. Further, when neuroimaging of mountaineers was compared before and after an expedition, a region of reduced gray matter density/volume was found in the left angular gyrus (Broca area 39). We emphasize that these changes occurred after many weeks of hypoxia exposure over periods of many years, so their significance to acute and brief hypoxia such as used in pulse oximeter testing is probably quite low. However, the findings of the Di Paola et al's study suggest that extremely high-altitude exposures may cause subtle white and gray matter changes that mainly affect brain regions involved in motor activity. This report added to others[57–61] that documented brain structure changes in extreme mountaineers.

It is important to recognize that the high-altitude exposures experienced by the subjects in these studies were for long durations; ie, weeks at a time with multiple exposures per year over many years.

Acute profound hypoxia exposure in laboratory setting produces transient cognitive effects similar to reversible changes during altitude exposure and the persistent changes seen after traumatic brain injury. For example, in a recent study by Turner et al,[62] the following cognitive effects were seen during 50 minutes of breathing 10% oxygen (Sao_2 about 75%): 10% to 30% declines in neurocognitive index, composite memory, verbal memory, visual memory, processing speed, executive function, psychomotor speed, reaction time, complex attention, and cognitive flexibility. The unifying feature of all these changes is that hypoxia produces a distraction such that subjects have a difficult time focusing on anything other than air hunger. None of the study participants reported residual effects of the hypoxia exposures.

IS THERE ANY EVIDENCE THAT ACUTE PROFOUND HYPOXIA PRODUCE LASTING COGNITIVE IMPAIRMENT?

There is only 1 report, by Phillips et al,[63] that we can find that documents even short duration persistence of cognitive deficits following acute hypoxia. Some aspects of visual function assessed in that study were reported to be impaired for up to 24 hours after simulated exposures to altitudes equivalent to 18,000 feet (saturation cutoffs 50%, duration 30 minutes). However, there are significant flaws in the experimental design of the Phillips study, including lack of comparable measurements in a control group not exposed to hypoxia and lack of description of saturation profiles. There was also lack of appropriate statistical analysis applied to the question of whether the lasting deficits were statistically different from baseline. Another finding reported by Phillips et al is that cerebral oxygenation returns to only about 95% of baseline levels 24 hours after hypoxia. However, there was no control group not exposed to hypoxia and statistical analysis appears inadequate (eg, no variability in the mean data at various times after hypoxia was reported). Furthermore, in our laboratory, we have found that cerebral oxygenation, measured by 5 different cerebral oximeters and blood gas/cooximetry on jugular bulb blood samples rapidly returns to prehypoxia baseline when Sao_2 is acutely reduced to 70%.[64] Our data, obtained from >100 subjects with cerebral oximeters, jugular bulb catheters, arterial lines, and peripheral pulse oximeters, are clear: recovery from acute desaturation to the 60s and 70s is rapid, and if anything an overshoot of brain tissue oxygenation occurs during recovery. No cognitive effects are observed in our population of healthy subjects. Long-term cognitive changes were not found in elite breath-hold divers exposed to multiple episodes of severe hypoxemia, including hypoxemia severe enough to cause loss of consciousness.[65]

Naturally occurring hypoxia in healthy individuals is fairly common but it is generally unrecognized because the human body has a large capacity for compensation. This is what allows for such a diverse range of human activities. The human body has the capacity to safely go from sea level to atmospheres below the surface of the ocean during dive vacations or to the top of a mountain in Colorado for ski trips. In fact, many individuals who drive to the scenic view at the top of the 14,265 foot Mount Evans near Denver have oxygen saturations in the 65% to 85% range. Some experience shortness of breath; however, because of the wide variation in compensation mechanisms some do not. These individuals are often exposed to profound hypoxia for longer periods than in a typical pulse oximeter breathing trial.

CONCLUSIONS

Brief and profound hypoxia (Sao_2 50%–70% for 10–30 minutes) in healthy humans is well tolerated and not

accompanied by systemic acidosis or circulatory impairment. In contrast, prolonged hypoxia, such as accompanying CMS or chronic lung diseases, is associated with morbidity. In the case of brief hypoxia, evidence supports the conclusion that there is no central nervous system injury. We conclude that brief hypoxia used for control of breathing studies, pulse oximeter performance testing, or experienced by breath-hold divers is highly unlikely to lead to cognitive impairment.

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