Published in final edited form as:

Aerosp Med Hum Perform. 2016 May ; 87(5): 477–486. doi:10.3357/AMHP.4463.2016.

Central Nervous System Oxygen Toxicity and Hyperbaric Oxygen Seizures

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Abstract

INTRODUCTION—The use of hyperbaric oxygen (O_2) as a therapeutic agent carries with it the risk of central nervous system (CNS) O_2 toxicity.

METHODS—To further the understanding of this risk and the nature of its molecular mechanism, a review was conducted on the literature from various fields.

RESULTS—Numerous physiological changes are produced by increased partial pressures of oxygen (PO_2), which may ultimately result in CNS O_2 toxicity. The human body has several equilibrated safeguards that minimize effects of reactive species on neural networks, believed to play a primary role in CNS O_2 toxicity. Increased partial pressure of oxygen (PO_2) appears to saturate protective enzymes and unfavorably shift protective reactions in the direction of neural network overstimulation. Certain regions of the CNS appear more susceptible than others to these effects. Failure to decrease the elevated PO_2 can result in a tonic-clonic seizure and death. Randomized, controlled studies in human populations would require a multicenter trial over a long period of time with numerous endpoints used to identify O_2 toxicity.

CONCLUSIONS—The mounting scientific evidence and apparent increase in the number of hyperbaric O_2 treatments demonstrate a need for further study in the near future.

Keywords

hyperbaric oxygen seizures; hyperbaric oxygen therapy; CNS oxygen toxicity

Modern therapeutic use of hyperbaric oxygen (HBO_2) in clinical medicine began in the 1950s.^{64,83} Boerema, a Dutch surgeon, in conjunction with the Royal Dutch Navy, was the first physician to “drench” the tissue of a patient with increased partial pressure of oxygen (PO_2) with the use of a hyperbaric chamber.¹⁶ Through his work and subsequent experiments, HBO_2 has been shown to have positive effects in treating wounds,^{67,104} and as a treatment for carbon monoxide (CO) toxicity.^{85,89} In 1977, Blue Cross/Blue Shield accepted a report from the Undersea Medical Society (now Undersea and Hyperbaric Medical Society) on hyperbaric oxygenation, which resulted in a list of disorders for which hyperbaric treatment should be considered. Many of today’s indications for hyperbaric oxygen therapy (HBO_2T) stem from this list. Current indications for HBO_2T covered by

Medicare are shown in to Table I.^{79,84,94} More research is needed to conclude for which indications HBO₂T is most beneficial and to what extent.³²

HBO₂T is a therapeutic modality that exposes the body to 100% inspired oxygen (O₂) at ambient pressures greater than one atmosphere.^{79,107} Therapeutic administration of supplemental O₂ generally refers to increasing the fractional inspired O₂ (F_IO₂). Without the use of a hyperbaric chamber, F_IO₂ equals the partial pressure of inspired O₂ (P_IO₂). This limits the range of P_IO₂ from 0.21 ATA [F_IO₂ = 21% at one atmosphere of absolute pressure (ATA)] to 1.0 ATA (F_IO₂ = 100% at 1 ATA); 1 ATA equals one atmosphere of pressure at sea level. Hyperbaric chambers increase ambient pressure, allowing the P_IO₂ to exceed 1 ATA. The majority of clinical uses for HBO₂T derive their benefit from the increased P_O₂ that HBO₂T provides.¹⁷ The increased P_O₂ delivered throughout the body causes reactive oxidative species (ROS) that promote wound healing and postischemic tissue survival.¹⁰⁵ Hydrostatic effects of HBO₂T that affect bubble size are beneficial for illnesses such as decompression sickness.⁸³ HBO₂T has been gaining increased attention in the popular press^{87,113} and among scientific researchers.⁷⁰

The toxic nature of O₂ is often underappreciated. There are side effects of the hydrostatic and oxidative changes that HBO₂T creates, including HBO₂ seizures.^{18,92} Determining mechanisms of HBO₂ toxicity and its ability to cause seizures has been an effort of researchers in the hopes of maximizing the potential benefits of HBO₂T while minimizing its risks.

Both patients and hyperbaric medical attendants are routinely exposed to the hyperbaric environment (although attendants do not routinely breathe HBO₂) and are therefore exposed to an increased risk of O₂ toxicity. There are special populations outside of medicine who are also routinely exposed to HBO₂, including military, commercial and recreational divers, and subterranean workers.^{37,49,118} The risk of O₂ toxicity is increased when the ratio of O₂ to inert gas is raised in the hopes of minimizing deleterious gas effects. Combat divers use pure O₂ via a rebreather apparatus for clandestine purposes (to avoid bubbles).^{37,82} High P_O₂ greatly increases the risk of O₂ toxicity even at shallow depths but it also purges nitrogen from a diver's body. Following missions, divers can be extracted and flown well above sea level with little concern for decompression sickness, making it ideal for clandestine and lengthy underwater operations.^{43,82} Concerns over CNS O₂ toxicity remain a limiting factor in standard operating procedures for closed-circuit diving operations and HBO₂T alike.^{37,83} Some deleterious effects of gases under pressure and the populations at risk are listed in Table II.

O₂ toxicity in humans can be categorized into two major types: low pressure or chronic O₂ toxicity, such as pulmonary toxicity, nonspecific cellular toxicity, organ damage and erythrocyte hemolysis; and high pressure or acute O₂ toxicity, most commonly associated with CNS O₂ toxicity.^{29,106} Chronic toxicity tends to occur when the P_O₂ exceeds 0.5 ATA for extended periods of time. People may be most familiar with retinal manifestations of O₂ toxicity resulting in blindness of premature neonates. Prolonged exposure to elevated P_O₂, whether increased concentrations of oxygen inspired at atmospheric pressure or low concentrations of inspired oxygen at high ambient pressures, places humans at risk for

pulmonary oxygen toxicity.^{44,45} It is characterized by decrease in pulmonary function, chest tightness, exertional dyspnea, and cough. Moderate to severe cases can involve pulmonary edema, hemorrhage, or death.^{42,44}

The risk of CNS O₂ toxicity is a function of both Po₂ and exposure time, directly proportional to both: the greater the Po₂, the greater the risk of HBO₂ seizure.⁶¹ While the onset of seizures is usually in the vicinity of 2–3 ATA, the pressure at onset may be significantly lowered by coexisting conditions such as immersion, exercise, and respiratory acidosis due to moderate CO₂ retention.⁶⁹ 1.9 ATA is a noticeable threshold for increased risk.^{69,77} Even at lower Po₂ HBO₂ seizures can occur particularly when combined with inert gases or carbon monoxide (CO).^{9,52} The most dramatic manifestation of CNS O₂ toxicity is an HBO₂-induced seizure. Additional effects of CNS O₂ toxicity may also occur, including autonomic, motor, and cardiorespiratory signs and symptoms,⁴⁰ such as bradycardia, hyperventilation, dyspnea, and altered cardiorespiratory neural reflexes.⁴³

CNS O₂ toxicity often presents acutely with little or no warning. Common signs and symptoms of CNS O₂ toxicity are easily remembered using the mnemonic VENTID-C^{3,11,83}:

Visual symptoms: tunnel vision, blurred vision, or decreased peripheral vision

Ear symptoms: tinnitus, roaring, pulsing sounds, or perceived sounds not from an external stimulus

Nausea: often with vomiting and headache

Twitching/Tingling: of extremities, facial muscles

Irritability: or any change in mental status such as confusion, agitation, anxiety, or undue fatigue

Dizziness: or clumsiness, loss of coordination

Convulsions: and death

Unfortunately many of these symptoms are not exclusive to O₂ toxicity, and CNS O₂ toxicity does not usually proceed through any predictable sequence of the above signs. Convulsions, the most serious effect of O₂ toxicity due to its fatal potential if left untreated, may occur without warning or other accompanying signs.^{43,64} O₂-induced seizures are characterized as generalized tonic-clonic seizures, though focal seizures may be the only neurological manifestation at times.^{64,99} During the seizure, the individual loses consciousness and convulses, usually progressing through both a tonic phase, in which all of the muscles are stimulated at once and lock the body into a state of rigidity, and a clonic phase, during which various muscles may cause violent thrashing motions.^{42,63} Brain activity is depressed during the postictal period, during which the individual is usually unconscious and subdued. This is usually followed by a period in which the individual is semiconscious and very restless, usually sleeping on and off for as little as 15 min or as long as an hour or more. Afterward he or she often becomes suddenly alert and complains of no more than fatigue, muscular soreness, and possibly a headache. After an O₂ toxicity convulsion the individual usually remembers clearly the events up to the moment when

consciousness was lost, but remembers nothing of the convulsion itself and little of the postictal phase.⁶⁴

Convulsions unrelated to O₂ toxicity may also occur in HBO₂ environments and would present identically to a HBO₂-induced seizure. It is critical to differentiate seizures resulting from hyperbaric oxygen from other etiologies, such as hypoglycemia. A convulsion due to O₂ toxicity has little lasting effects, assuming the O₂ pressure is immediately decreased; however, a hypoglycemic seizure unrecognized and untreated can be fatal. Unlike other tonic-clonic seizures, such as those seen in epilepsy, the danger of hypoxia during breathholding in the tonic phase of a HBO₂-induced convulsion is minimized by the high Po₂ in the brain and tissues; the source of the toxicity helps minimize hypoxia in the tissue during the seizure. A greater danger is posed by decreasing pressure in a chamber too quickly, which could potentially lead to a gas embolism. Since it would be difficult to differentiate between a postictal individual and an unconscious victim suffering from a cerebral arterial gas embolism, those experiencing O₂-induced seizures in a hyperbaric chamber under pressure are generally kept at that same pressure until their convulsions cease. The Po₂ in such cases is diminished solely by altering the breathing gas mixture. Patients suffering from O₂-induced seizures generally have full recoveries within 24 h with no lasting effects, and it is unclear whether there is increased susceptibility to future incidents of O₂ toxicity.¹¹

The primary treatment for an O₂-induced seizure is to lower the inspired Po₂. This is accomplished by decreasing ambient pressure, switching to a breathing mixture with a lower percentage of O₂, or both. Decreasing inspired Po₂ may not immediately reverse the effects of CNS O₂ toxicity and is not without risk. It is believed that the biochemical processes responsible for the toxicity remain in place for a period after the Po₂ has been decreased in the ambient or inspired atmosphere. The individual experiencing the toxicity is not considered clear from danger until several minutes have passed after the Po₂ has been decreased.^{34,83}

In practice, the risk of acute O₂ toxicity is often mitigated by interspersing short periods of air amid the pure O₂ therapy at increased pressure commonly referred to as “air breaks.”¹¹ It is a logical measure and some species such as insects have evolved discontinuous breathing in order to minimize risks of O₂ toxicity even at 1 ATA.⁵⁶ However, there is limited clinical data to support this practice.²⁸ Some data supports the use of intermittent air breaks of 5–10 min to prolong HBO₂ exposure prior to the onset of seizures.²⁴ Yet, animal models demonstrate the possibility that the rapid decreases in Po₂ may actually instigate seizure activity¹⁴ while appearing to be beneficial in preventing pulmonary oxygen toxicity.⁵⁵ While intermittent exposures may decrease symptoms of CNS toxicity, measured molecular activities maintain prebreak levels, adding further confusion to the mechanism and success of air breaks during HBO₂T.⁶⁴ Therefore, understanding the mechanisms leading to HBO₂ CNS toxicity can help to mitigate toxicity.

A search of current work on this subject including PubMed searches using the words “hyperbaric seizure” and “hyperbaric convulsion” yielded hundreds of peer-reviewed publications pertaining to HBO₂ seizures. Several reviews and case series exist that

emphasize the incidence of hyperbaric oxygen seizures. To the author's knowledge there are no peer-reviewed review articles focusing on HBO₂ seizures. A recent review on CNS oxygen toxicity was written in 2004.¹¹ This review emphasizes primary research into the underlying mechanism by which increased Po₂ causes HBO₂ seizures in humans. While this review is not exhaustive, its goal is to summarize the majority of the existing knowledge on this topic by adequately sampling current research.

Mechanisms

Methods and models used to investigate the mechanisms of HBO₂ toxicity on the nervous system must attempt to isolate two interdependent variables: 1) effects due to the increased ambient pressure on the CNS; and 2) effects due to the increased Po₂. Small mammals serve as a good animal model for studying the cellular mechanisms of oxidative stress in the mammalian central nervous system.² Therefore, many research studies have used mice, rats or other small rodents as models for research.^{68,117}

The normobaric hyperoxic brain slice model is a common research model. It is a less desirable model to study the effects of oxygen toxicity on neuronal activity since most in vitro preparations of CNS tissue and cells use a 95% O₂ control level during preparation. Humans inspiring normobaric air have relatively low Po₂ in their brain, 35 mmHg or less, depending on the region.¹⁹ Murine brains have even lower ranges of Po₂ in their brain, from 5 to 25 mmHg.¹²⁶ Direct investigation using hyperbaric oxygen is preferred.

The use of in vitro electrophysiological methods to investigate the cellular mechanisms of O₂ toxicity within a hyperbaric chamber has been limited by the challenges of working with or in a sealed pressure chamber and the mechanical disturbances experienced during tissue compression. Chamber design improvements have minimized these obstacles, allowing easier experimentation on animal models in ambient pressures around 5 ATA. Refinements in chamber design and using an ambient atmosphere of 100% helium have allowed intracellular experiments in rat brain slices. Electrophysiological studies on rat neurons have shown that increases in the Po₂ in cerebral tissue lead to increased ROS production, followed by increased cortical EEG activity, and finally resulting in the onset of an O₂-induced seizure activity.^{37,108}

Effects on the CNS attributed to increased hydrostatic pressure, such as high-pressure nervous syndrome,³⁷ tend to occur at very high pressures, ranging from 15 to 70 ATA. This results from compression of cerebral spinal fluid, circulation, and extracellular and intracellular fluid compartments of the CNS. Cellular mechanisms most likely involve synaptic and membrane dynamic responses to severe and fast changes in pressure.^{33,37} Therefore there is little evidence to suggest that hydrostatic pressure plays a significant role in HBO₂ seizures, particularly at pressures involved with HBO₂T less than 3 ATA.³³

A relationship exists between high pressures and glycine receptors which indicates possible roles pressure plays on HBO₂ seizures. High pressures have no effect on the maximum response of the glycine receptor to glycine; however, the half maximal effective concentration of glycine to its receptor and pressure become directly proportional at

pressures above 100 ATA.¹⁰¹ While this seems less likely to be correlated with seizures occurring at 2–3 ATA, typical of HBO₂T, it appears to be associated with high pressure neurological syndrome at much greater depths.^{37,101} The fact that glycine receptors are linked to myoclonic activity in mammals raises suspicion that conformational alterations at pressures less than 100 ATA may still participate in hyperbaric seizures to some degree at lower pressures.⁷⁶

O₂ under hyperbaric conditions behaves like a drug whose effects on metabolism exceed O₂'s common role as a simple oxidizer.⁶⁴ The molecular effects of increased Po₂ during HBO₂T affects neural networks in the CNS, resulting in overall network excitability.³⁷ Much of the research into the molecular mechanisms of CNS O₂ toxicity has focused on the neuroexcitatory and neuroinhibitory effects of neuroactive agents that results from elevated Po₂. In general, mechanisms responsible for hyperbaric oxygen seizures can be categorized to include: ROS, inhibitory neurotransmitters, excitatory neurotransmitters, extracellular effects resulting in neurotransmitter dysregulation, and the imbalance of neuroprotective mechanisms.

Oxidative stress plays a key role in the mechanism of O₂ toxicity. CNS O₂ toxicity is an acute exposure to an oxidative environment disrupting neurological function. HBO₂T greatly increases oxygen tension in the brain. Molecular O₂ is a natural oxidative reagent in cellular biochemical pathways producing various free radicals. The mammalian CNS response to hyperoxia ranges from moderate, reversible changes in neural activity to violent seizures that may lead to irreversible motor deficits and death. In vitro experiments on rat brains exposed to HBO₂ demonstrate that the Po₂ is directly proportional to ROS formation in the tissue.¹⁰⁸ The initial physiological response to hyperoxia is increased formation of superoxide and nitric oxide (NO) among other ROS.¹⁰⁵ Prolonged exposure of neural tissue to HBO₂ stresses antioxidant protective mechanisms. Oxidation of cellular components occurs due to the increased production of free radicals such as superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite. Oxidation of cellular metabolic reactants has therapeutic benefits,^{104,105} but also has negative effects. ROS can cause membrane weakening and metabolic dysregulation if normobaric O₂ is not restored. It directly affects the various ionic conductances that regulate cell excitability. ROS are also reported to target neurotransmitter systems, altering chemical synaptic transmission.^{34,37} The network of ROS and antioxidants remains unclear and requires further research.¹²³

The body scavenges oxidizing substances through enzymatic antioxidants such as superoxide dismutase for superoxide anions, catalase for hydrogen peroxide and nonenzymatic antioxidants such as reduced glutathione and vitamin E.¹⁰⁵ Glutathione is regenerated by reaction with nicotinamide adenine dinucleotide phosphate (NADPH). Therefore, sufficient levels of both glutathione and NADPH may be critical to defending against the increased level of oxidants.³⁴

Nonenzymatic antioxidants should logically protect against HBO₂ seizures. Vitamin E deficiency increases the risk of HBO₂ seizures¹⁵; however, vitamin E failed to prevent HBO₂ seizures.¹²³ Another example is superoxide dismutase. Superoxide catalyzes superoxide anions to O₂. Therefore, increased levels or activity of superoxide dismutase should decrease

levels of ROS; hence, in theory, HBO₂ seizures should be attenuated.^{57,93} However, in transgenic mice bred to overexpress human extracellular superoxide dismutase in the brain, inhibition of superoxide dismutase increased resistance to HBO₂ seizures contrary to expectations. By inhibiting superoxide dismutase, the catalysis of superoxide into O₂ (an in vivo antioxidant mechanism) is blocked, allowing superoxide levels to rise unopposed during HBO₂ exposure. A fourfold decrease in seizures was measured in these mice pretreated with diethyldithiocarbonate, an inhibitor of human extracellular superoxide dismutase.⁸⁸ The mechanism of this counterintuitive result appears to be the interaction between superoxide and other HBO₂-induced reactants.

Gamma-aminobutyric acid (GABA) has long been correlated with HBO₂ seizures.^{120,121} Though GABA has been found to be lowered in mammalian neuronal synapses during HBO₂ seizures when exposed to HBO₂ in short intervals,⁵⁸ there is evidence to suggest that the increased steady-state levels of GABA over longer intervals may be responsible for O₂-induced seizures.⁴⁶ In experiments involving transgenic mice with a HBO₂-sensitivity phenotype, data suggests that the excitatory amino acids, such as aspartate and glutamate, play as important or more important roles in HBO₂ seizures than GABA.⁸¹

Glutamate, an excitatory amino acid, is a potent, fast-acting neurotoxin in neuronal cultures. It has been shown to create morphological changes in mature cortical neurons within minutes of HBO₂ exposure with neuronal degeneration occurring over the course of hours. In vitro experiments demonstrated that one-hundredth the intracellular concentration of glutamate during hyperbaric exposures critically damages cortical neurons.²⁷ Decreased glutamate metabolism during HBO₂ exposure sensitizes neural networks to HBO₂ seizures.⁷² Conflicting evidence exists as to the degree of change in excitatory amino acids prior to and during HBO₂ seizures. Recent evidence suggests that O₂-induced seizures may result from an imbalance of excitatory and inhibitory synaptic neurotransmitters, glutamate and GABA, respectively. The imbalance results in a greater relative decrease in presynaptic release of GABA than of glutamate,³⁸ which suggests that the relative increase of excitatory neurotransmitters with respect to inhibitory neurotransmitters may be a basic mechanism of HBO₂ seizures.

Extracellular mediators of physiological functions such as NO also play a role in HBO₂ seizures. NO has been implicated in neurotoxicities resulting from excess glutamate stimulation in cultures of rat cortex, striatum, and hippocampus.³⁶ NO activity appears to increase the ratio of excitatory to inhibitory neurotransmitters which increases the probability of O₂ seizures.³⁸ Neurons containing nitric oxide synthase (NOS), widespread throughout the cortex, react to HBO₂ by increasing NO production.^{1,82} In HBO₂ environments, NO acutely decreases cerebral blood flow but then increases regional cerebral blood flow after prolonged HBO₂ exposure preceding neuronal excitation.^{39,51} NO has been associated with changes in cerebral blood flow and HBO₂ seizures.⁹⁸ Cerebral blood flow is indirectly proportional to the time of onset of HBO₂ seizures in animal models. Effects of NO with respect to HBO₂ seizures is diagrammed in Fig. 1.^{68,125} When interstitial NO, aspartate, glutamate, and GABA were measured in vivo in anesthetized rats under HBO₂ conditions with respect to blood flow and EEG activity of the striatum, increases in NO metabolites and blood preceded spikes in EEG activity and seizures. Thus, it was concluded

that HBO₂-stimulated neuronal NO production promoted an imbalance between excitatory (glutamate) and inhibitory (GABA) synaptic activity. This in turn contributes to O₂-induced seizures in rats.³⁸

The molecular mechanisms involved in HBO₂ seizures are complex. An imbalance of the redundant molecular protective mechanisms that humans have evolved to counter deleterious effects of increased Po₂, as depicted in Fig. 2, appears to lead to HBO₂ seizures. Elevated Po₂ causes concomitant saturation of the redundant antioxidant systems evolved to protect humans. Though individual reactions are well-described, the network of interactions between the various reactions are not well-described.¹²³ Increased Po₂ saturates enzymes and maximizes rates of reactions designed to protect against reactive species. For example increased Po₂ saturates superoxide dismutase, increasing superoxide. Superoxide anions can react with NO to yield nitrate (NO₃), a neurologically inert substance; however, the rate of this reaction does not appear sufficient to eliminate risks of CNS O₂ toxicity at sufficiently high Po₂ over time.

A long-standing question regarding hyperbaric oxygen seizures is whether certain regions of the CNS are more susceptible to HBO₂.¹¹² Neuroanatomic studies have shown that centrally located regions of the brain are most affected by exposure to HBO₂, including: the globus pallidus, substantia nigra, superior olivary nucleus, ventral cochlear nucleus, limbic structures, amygdala, and the spinal cord gray matter, diagrammed in Fig. 3.^{109,111} It is worth noting that the globus pallidus and substantia nigra are brain regions also susceptible to CO toxicity. Single-cell electrophysiology experiments have shown that hippocampus and brain stem neurons are disproportionately sensitive to increased Po₂ in surrounding tissues when exposed to HBO₂.^{50,65} The anatomical localization of neuroactive agents and their effects may also explain anatomical distribution of increased O₂ sensitization.^{37,90}

For example, at HBO₂ levels of 3–5 ATA, regional cerebral blood flow in the substantia nigra decreased for 30 min but gradually returned to normal levels preceding EEG spikes.³³ Acute exposure to HBO₂ results in an increased firing rate of specific neurons, particularly carbon dioxide (CO₂)/proton-chemosensitive neurons, which are coupled via gap junctions and baroreceptors, in the cerebral and cerebella cortex that demonstrate a high sensitivity to HBO₂, chemical oxidants, and neurotransmitters.^{33,40,80}

Certain conditions heighten one's risk to CNS toxicity and HBO₂ seizures. Hypercapnia elevates the risk of O₂ toxicity.^{100,119} Hypercapnic-induced intracellular acidosis makes cells more susceptible to ROS. CO₂ causes cerebral vasodilation, increases cerebral blood flow, and heightens CNS exposure to elevated Po₂. Neurons in the solitary complex are particularly susceptible to increased Pco₂ and Po₂, resulting in an increased rate of excitatory firing. Increased Pco₂ in HBO₂ environments may occur by: 1) a decrease in CO₂-carrying capacity of venous hemoglobin since venous hemoglobin may be saturated with O₂; 2) alveolar hypoventilation and CO₂ retention; and 3) CO₂-contamination due to inadequate scrubbing of recirculated breathing gas.^{37,100} Exercise also increases the risk of CNS O₂ toxicity, likely related to increased cerebral blood flow and metabolic rate.^{2,66} CO toxicity significantly increases the risk of HBO₂ seizures.^{52,97}

Current preventative measures to counter O₂ toxicity include minimizing exposure times to increased Po₂, decreasing the inspired Po₂, or inserting periods of air breaks.¹¹ There is evidence in animal models to suggest that repeated HBO₂ exposures increases risk of seizures.^{6,48,75} Data support brain derived neurotrophic factor, 7-nitroindazol (7-NI), and NO as potential mechanisms for sensitization to repeated HBO₂ seizures.^{20,25,26,60} Yet there appears to be some randomization to susceptibility. An individual may repeat the same exposure conditions and suffer from CNS O₂ toxicity for no apparent reason.¹¹

Since the mechanism of CNS O₂ toxicity remains uncertain, there is a paucity of prophylactic measures to prevent it. Certain factors are known to mitigate an individual's susceptibility to CNS O₂ toxicity. Numerous prophylactic treatments for HBO₂-induced seizures have been shown to be effective through in vivo experiments involving rats and mice.

NO is an important mediator of CNS O₂ toxicity.¹² Inhibition of NOS with nitroarginine showed similar prevention of CNS toxicity and O₂-induced seizures in both transgenic and nontransgenic mice.^{23,88,115} The potency of NOS inhibitors in preventing CNS O₂ toxicity is indirectly proportional to the disassociation constant of the inhibitor and NOS.³⁶ Intraperitoneal administration of GABA proved effective in protecting rats from O₂-induced seizures. Since GABA does not cross the blood brain barrier, the mechanism of its protection is speculated to be an osmotic effect drawing a metabolite of GABA out of the brain.⁴⁶ Pretreatment of rats exposed to HBO₂ conditions with 7-NI slowed the rate of decline in GABA levels, decreased the glutamate/GABA excitotoxicity index, and minimized EEG spikes associated with O₂ toxicity.³⁸

MK-801, an NMDA receptor antagonist, has been shown to prevent EEG spikes associated with O₂ toxicity and O₂-induced seizures.^{37,39} Other substances such as disulfiram (Antabuse)^{21,47,117} and antioxidants also appear to delay or diminish O₂ toxicity in the brain.^{34,37} Additional agents that hasten the onset or increase incidence of HBO₂ seizures include: adrenocortical hormones, epinephrine, hyperthermia, norepinephrine, thyroid hormones, vitamin E deficiency,¹⁵ brain derived neurotrophic factor,²⁵ misonidazole,⁵⁴ pseudoephedrine,⁹¹ hyperglycemia,⁴ and phosphodiesterase-5 inhibitors.⁴¹ Additional agents that delay the onset or attenuate HBO₂ seizures include: N-nitro-L-arginine (NNA),^{22,115} daurisolone (DSL),¹¹⁵ acclimitization to hypoxia, antioxidants,⁷⁴ chlorpromazine, reserpine, starvation,³¹ ganglionic blocking drugs and anti-epileptics,⁷¹ glutathione,⁶² hypothermia, hypothyroidism, insulin,⁴ CoQ10 and carnitine,⁷ acetazolamide,¹¹⁹ excitatory amino acid antagonists,³⁰ aminooxyacetic acid (AAOA),^{5,35} delta-sleep-inducing peptide (DSIP),⁷⁸ beta-carotene,¹⁰ vigabatrin,^{53,110} propionyl-L-carnitine,⁸ leukotriene and PAF inhibitors,⁷³ carbamazepine,⁹⁵ propranolol,¹¹⁷ caffeine,¹³ Dilantin,¹¹⁶ and lithium.¹⁰³ Some agents that one would expect to affect HBO₂ seizures, such as allopurinol and pyridoxine, did not.^{57,103,114}

Potential Areas of Research

A significant amount of research has been conducted on the mechanisms of CNS O₂ toxicity, but few clinical studies or trials exist as to how to prevent it. There are few attempts

in applying existing results to testing prophylactic treatments for humans. This is likely due to the potential difficulties of such studies. A search (using keywords “hyperbaric oxygen,” “hyperbaric oxygen therapy,” and “oxygen toxicity”) shows over 50 active NIH-funded clinical trials pertaining to HBO₂ and only one pertaining to CNS O₂ toxicity.⁸⁶ Potentially beneficial, “off-the-shelf” medications (FDA approved medication or nonregulated supplement) could be trialed for their efficacy in preventing or reducing the incidence of HBO₂-induced CNS toxicity, including: disulfiram (an inhibitor of alcohol dehydrogenase with some evidence of success in preventing HBO₂ seizures in animal models, approved for use in the treatment of alcohol abuse),³⁴ acamprosate (a glutamate receptor modulator approved for use in the treatment of alcohol abuse), and vitamin E (a nonenzymatic antioxidant sold as a supplement).

In a clinical setting, an HBO₂T center would have no less than 1000 treatments per year. If we assume that treatments can be taken as independent events, i.e., there is no correlation between two treatments on the same person or different individuals with the same preexisting conditions, then we can use all 1000 treatments as individual events upon which we can base our design. This is purely an assumption in order to minimize a sample size calculation. An O₂-induced seizure is the most easily quantifiable endpoint for measuring CNS oxygen toxicity, although any signs, symptoms, or composite of the two could be used.

The frequency of an oxygen-induced seizure may be approximated at 1 in 10,000 treatments, with the literature citing a wide range from 2 in 100,000 to 1 in 1000.^{97,118,124} One study estimates the probability of a CNS toxicity event as low as 1.7% over the period of a 4-h dive with $P_{O_2} = 1.4$ ATA.¹⁰²

A prospective study would seek to decrease the frequency of oxygen-induced seizures by a given factor as a result of implementing a prophylactic treatment, such as disulfiram or antioxidants. Using STATA version 9.0 for Windows (Stata Corporation, College Station, TX) the sample size needed to conduct a definitive randomized trial demonstrating a tenfold reduction in the frequency of hyperbaric oxygen-induced seizures, from 0.0001 to 0.00001, using a two-sided 0.05 level test with 80% power is 85,218, assuming equal allocation to the experimental and control arms. It could take a single hyperbaric facility over a decade to accrue enough data to execute a definitive study of this nature. This information necessitates that randomized clinical studies investigating CNS oxygen toxicity be multicenter studies with endpoints more than just seizures used to identify oxygen-toxicity.

Further, agents that mitigate O₂-induced seizures may also negatively affect the therapeutic benefits of HBO₂T, thus adding to the complexity of the study. For example, any antioxidant that can effectively eliminate ROS during HBO₂T may eliminate their role in causing HBO₂ seizures, but it would also eliminate the benefits ROS play in promoting wound healing and postischemic tissue survival.¹⁰⁵ This would require a long time, a great deal of resources, and/or multiple institutions to accomplish. It is unlikely for a research study of this magnitude to occur. Therefore, continued basic science research may be the best alternative to investigate CNS toxicity.

The advent of nanoscale devices allows for more precise delivery and investigation of mediators of O₂-induced seizures such as NO.⁹⁶ The excitatory firing rate of dorsal medullary neurons due to HBO₂ can be mimicked by the presence of pro-oxidants at normobaric conditions,³⁷ demonstrating that normobaric experimentation might be feasible to shed light on O₂'s toxic effects under pressure. Precise delivery of ROS or neurotransmitter mediators of CNS toxicity would allow for detailed experimental designs at the molecular, neuronal level in normal models at normobaric conditions. This may shed light on unanswered questions such as whether the effects of hyperoxia and the resulting ROS are presynaptic or postsynaptic in origin, currently an unanswered question. Normobaric models of the effects of HBO₂ would also open the door to the wide array of experimental tools that otherwise would not be feasible to perform in hyperbaric chambers. Finally, as data and proposed theories of O₂ toxicity increase, this area of research becomes primed for computational simulations. Current prediction models have shown that it is very difficult to build a prediction model for mild hyperoxia given the current data.¹⁰² However, computational analysis and simulations of molecular signaling interactions might enable existing and otherwise conflicting theories to coexist within a new model for CNS O₂ toxicity. This would provide a physiologically based model with greater precision and accuracy. Models of complex biological systems such as T lymphocyte activation demonstrate the feasibility of this approach.⁵⁹

Summary

The benefits of HBO₂ come with the risk of CNS O₂ toxicity. The exact mechanism of O₂ toxicity remains a mystery. Prophylactic measures and treatment for CNS O₂ toxicity remain centered on limiting exposure to high Po₂. Better understanding of molecular mechanisms causing O₂ toxicity can lead to prophylactic therapies for consideration in clinical trials. There is increasing need for research on the systemic interactions of the multiple players involved in HBO₂ seizures in order to better understand how they occur and how to prevent them.

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Fig. 1.

Schematic of extracellular interactions produced by increased P_{O_2} that result in CNS HBO_2 seizures. Increased cerebral blood flow (CBF) results in decreased time to onset of HBO_2 seizures ($tHBO_2S$). Extracellular substances such as phosphodiesterase-5 inhibitors (PDE-5i), 7-NI, N-nitro-L-arginine (NNA, a NOS inhibitor), and daurisolone (DSL, a calcium channel blocker) affect CBF. Dotted line = lessened action (-). Bold line = increased action (+). Large arrow = correlation.

Fig. 2. Schematic of some synaptic changes produced by increased Po_2 and resulting in CNS HBO_2 seizures. The human body has several equilibrated safeguards that minimize effects of ROS on neural networks. Increased Po_2 appears to saturate protective enzymes and unfavorably shift protective reactions in the direction of neural network overstimulation, resulting in HBO_2 seizures. NT = neurotransmitter; AP = action potential. Dotted line = lessened action. Bold line = increased action.

Fig. 3. Brain regions most likely involved in HBO₂-induced seizures. Certain regions of the CNS (including the solitary complex in the dorsal medulla, hippocampus, globus pallidus, substantia nigra, superior olivary nucleus, ventral cochlear nucleus, and spinal cord gray matter) appear more susceptible than others to these effects. Note the central nature of these regions, anatomically similar to CO susceptible regions.

Table I.Examples of Therapeutic Uses of HBO₂.

ELECTIVE INDICATIONS	EMERGENT INDICATIONS
Radiation injury *	Carbon monoxide poisoning
Compromised skin grafts	Decompression illness
Chronic nonhealing wounds #	Gas gangrene
Refractory osteomyelitis	Arterial gas embolism
Inhibition of clostridium perfringens	Ischemia-reperfusion injury
Suppression of autoimmune responses	Hemorrhagic anemia
Tissue salvage in burn victims	
Nerve cell regeneration	
Preparation and preservation of skin grafts	

* "Radiation injury" includes soft tissue radionecrosis, osteoradionecrosis, and hemorrhagic radiation cystitis.

Particularly diabetic ulcers

Table II.

Physiological Effects of Gases Under Pressure.*

DEPTH (PRESSURE) OF ONSET	POPULATION	TOXICITY	SOURCE
Sea level (1 ATA)	Everyone	CO	Incomplete hydrocarbon combustion
		O ₂ (pulmonary, retinal)	Long exposures to 100% O ₂
		CO ₂	Inadequate ventilation
12 fsw (1.3 ATA)	Closed-circuit diver	O ₂ (CNS)	Breathing 100% O ₂
45 fsw (2.4 ATA)	HBO ₂ T	O ₂ (CNS)	Breathing 100% O ₂
99 fsw (4 ATA)	Open-circuit diver	N ₂	Breathing compressed air
165 fsw (6 ATA)	Open-circuit diver	O ₂ (CNS)	Breathing compressed air

fsw = feet of sea water.

* This list does not include decompression sickness (DCS), which may occur at virtually any depth given the proper circumstances.