Central Nervous System Oxygen Toxicity and Hyperbaric Oxygen Seizures

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INTRODUCTION: The use of hyperbaric oxygen (O₂) as a therapeutic agent carries with it the risk of central nervous system (CNS) O₂ 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 (P\text{\textsubscript{O₂}}), which may ultimately result in CNS O₂ 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 O₂ toxicity. Increased partial pressure of oxygen (P\text{\textsubscript{O₂}}) 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 to other internal effects. Failure to decrease the elevated P\text{\textsubscript{O₂}} 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 O₂ toxicity.

CONCLUSIONS: The mounting scientific evidence and apparent increase in the number of hyperbaric O₂ treatments demonstrate a need for further study in the near future.

KEYWORDS: hyperbaric oxygen seizures, hyperbaric oxygen therapy, CNS oxygen toxicity.

such as decompression sickness. HBO₂ T has been gaining increased attention in the popular press and among scientific researchers.

The toxic nature of O₂ is often underappreciated. There are side effects of the hydrostatic and oxidative changes that HBO₂ T creates, including HBO₂ T seizures. 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 HBO₂ T while minimizing its risks.

Both patients and hyperbaric medical attendants are routinely exposed to the hyperbaric environment (although attendants do not routinely breathe HBO₂ T) 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 T, including military, commercial and recreational divers, and subterranean workers. 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). High Po₂ 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. Decompression operations and HBO₂ T alike.

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. Chronic toxicity tends to occur when the Po₂ 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 Po₂, 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. 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.

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 T seizure. 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. 1.9 ATA is a noticeable threshold for increased risk. Even at lower Po₂, HBO₂ T seizures can occur particularly when combined with inert gases or carbon monoxide (CO). 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, such as bradycardia, hyperventilation, dyspnea, and altered cardiorespiratory neural reflexes.

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:

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,

<table>
<thead>
<tr>
<th>DEPTH (PRESSURE) OF ONSET</th>
<th>POPULATION</th>
<th>TOXICITY</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level (1 ATA)</td>
<td>Everyone</td>
<td>CO</td>
<td>Incomplete hydrocarbon combustion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O₂ (pulmonary, retinal)</td>
<td>Long exposures to 100% O₂</td>
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<tr>
<td></td>
<td></td>
<td>CO₂</td>
<td>Inadequate ventilation</td>
</tr>
<tr>
<td>12 fsw (1.3 ATA)</td>
<td>Closed-circuit diver</td>
<td>O₂ (CNS)</td>
<td>Breathing 100% O₂</td>
</tr>
<tr>
<td>45 fsw (2.4 ATA)</td>
<td>HBO₂, T</td>
<td>O₂ (CNS)</td>
<td>Breathing 100% O₂</td>
</tr>
<tr>
<td>99 fsw (4 ATA)</td>
<td>Open-circuit diver</td>
<td>N₂</td>
<td>Breathing compressed air</td>
</tr>
<tr>
<td>165 fsw (6 ATA)</td>
<td>Open-circuit diver</td>
<td>O₂ (CNS)</td>
<td>Breathing compressed air</td>
</tr>
</tbody>
</table>

fsw = feet of sea water.

* This list does not include decompression sickness (DCS), which may occur at virtually any depth given the proper circumstances.
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.52,63 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 breathing 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 HBO2 treatment.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 inspiriting 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.120 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 result 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 seizures58, however, vitamin E failed to prevent HBO₂ seizures.120 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 a more 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. Decreased glutamate metabolism during HBO2 exposure sensitizes neural networks to HBO2 seizures. 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, 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. NO activity appears to increase the ratio of excitatory to inhibitory neurotransmitters which increases the probability of O2 seizures. Neurons containing nitric oxide synthase (NOS), widespread throughout the cortex, react to HBO2 by increasing NO production. In HBO2 environments, NO acutely decreases cerebral blood flow but then increases regional cerebral blood flow after prolonged HBO2 exposure preceding neuronal excitation.

Elevated Po2 causes concomitant increases in NO production. NO has been associated with changes in cerebral blood flow and HBO2 seizures. 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. 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 HBO2-induced seizures in rats.

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 is not well-described. 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. 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. 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. The anatomical localization of neuroactive agents and their effects may also explain anatomical distribution of increased O2 sensitization.

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. 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.

Certain conditions heighten one’s risk to CNS toxicity and HBO2 seizures. Hypercapnia elevates the risk of O2 toxicity. 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. Exercise also increases the risk of CNS O2 toxicity, likely related to increased cerebral blood flow and metabolic rate. CO toxicity significantly increases the risk of HBO2 seizures. Current preventative measures to counter O2 toxicity include minimizing exposure times to increased Po2, decreasing the inspired Po2, or inserting periods of air breaks. There is evidence in animal models to suggest that repeated HBO2 exposures increases risk of seizures. Data support brain derived neurotrophic factor, 7-nitroindazol (7-NI), and NO as potential
mechanisms for sensitization to repeated HBO2 seizures. 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 dissociation 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 daurisoline (DSL),115 acclimitization to hypoxia, antioxidants,74 chlormpromazine, reserpine, starvation,31 ganglionic blocking drugs and anti-epileptics,71 glutathione,62 hypothermia, hypothyroidism, insulin,4 CoQ10 and carnitine7acetazolamide,119 excitatory

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**Fig. 2.** Schematic of some synaptic changes produced by increased pO2 and resulting in CNS HBO2 seizures. The human body has several equilibrated safeguards that minimize effects of ROS on neural networks. Increased pO2 appears to saturate protective enzymes and unfavorably shift protective reactions in the direction of neural network overstimulation, resulting in HBO2 seizures. NT = neurotransmitter; AP = action potential. Dotted line = lessened action. Bold line = increased action.
some evidence of success in preventing HBO₂ seizures in ing: disulfiram (an inhibitor of alcohol dehydrogenase with abuse),34 acamprosate (a glutamate receptor modulator animal models, approved for use in the treatment of alcohol reducing the incidence of HBO₂-induced CNS toxicity, includ-

shelf “ medications (FDA approved medication or nonregulated pertaining to CNS O₂ toxicity.86 Potentially beneficial, “off-the-

nature of these regions, anatomically similar to CO susceptible regions.

cochlear nucleus, and spinal cord gray matter) appear more susceptible than others to these effects. note the central 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.

amino acid antagonists, 30 aminoxyacetic acid (AAOA), 5,35 delta-sleep-inducing peptide (DSIP), 78 beta-carotene, 10 vigaba-trin, 53,110 propionyl-L-carnitine, 9 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

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 HBO₂-T, thus adding to the complexity of the study. For example, any antioxidant that can effectively eliminate ROS during HBO₂-T may eliminate their role in causing HBO₂ seizures, but it would also eliminate the benefits ROS play in promoting wound healing and postschismic 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 prooxidants at normobaric conditions, 32 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 hypoxia given the current data. 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.

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.

REFERENCES


73. Lynch JW. Molecular structure and function of the glycine receptor chloride channel. Physiol Rev. 2004; 84(4):1051–1095.


