Central Nervous System Oxygen Toxicity and Hyperbaric Oxygen Seizures

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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.

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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 HBO_2T is most beneficial and to what extent.[32]

HBO_2T is a therapeutic modality that exposes the body to 100% inspired oxygen (O_2) at ambient pressures greater than one atmosphere.[79,107] Therapeutic administration of supplemental O_2 generally refers to increasing the fractional inspired O_2 (F_Io_2). Without the use of a hyperbaric chamber, F_Io_2 equals the partial pressure of inspired O_2 (P_Io_2). This limits the range of P_Io_2 from 0.21 ATA [$F_Io_2 = 21\%$ at one atmosphere of absolute pressure (ATA)] to 1.0 ATA ($F_Io_2 = 100\%$ at 1 ATA); 1 ATA equals one atmosphere of pressure at sea level. Hyperbaric chambers increase ambient pressure, allowing the P_Io_2 to exceed 1 ATA. The majority of clinical uses for HBO_2T derive their benefit from the increased Po_2 that HBO_2T provides.[17] The increased Po_2 delivered throughout the body causes reactive oxidative species (ROS) that promote wound healing and postischemic tissue survival.[105] Hydrostatic effects of HBO_2T that affect bubble size are beneficial for illnesses

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Table I. Examples of Therapeutic Uses of HBO_2.

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

such as decompression sickness.[83] HBO_2T has been gaining increased attention in the popular press[87,113] and among scientific researchers.[70]

The toxic nature of O_2 is often underappreciated. There are side effects of the hydrostatic and oxidative changes that HBO_2T creates, including HBO_2 seizures.[18,92] Determining mechanisms of HBO_2 toxicity and its ability to cause seizures has been an effort of researchers in the hopes of maximizing the potential benefits of HBO_2T while minimizing its risks.

Both patients and hyperbaric medical attendants are routinely exposed to the hyperbaric environment (although attendants do not routinely breathe HBO_2) and are therefore exposed to an increased risk of O_2 toxicity. There are special populations outside of medicine who are also routinely exposed to HBO_2, including military, commercial and recreational divers, and subterranean workers.[37,49,118] The risk of O_2 toxicity is increased when the ratio of O_2 to inert gas is raised in the hopes of minimizing deleterious gas effects. Combat divers use pure O_2 via a rebreather apparatus for clandestine purposes (to avoid bubbles).[37,82] High Po_2 greatly increases the risk of O_2 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 O_2 toxicity remain a limiting factor in standard operating procedures for closed-circuit diving operations and HBO_2T alike.[37,83] Some deleterious effects of gases under pressure and the populations at risk are listed in **Table II**.

O_2 toxicity in humans can be categorized into two major types: low pressure or chronic O_2 toxicity, such as pulmonary toxicity, nonspecific cellular toxicity, organ damage and erythrocyte hemolysis; and high pressure or acute O_2 toxicity, most commonly associated with CNS O_2 toxicity.[29,106] Chronic toxicity tends to occur when the Po_2 exceeds 0.5 ATA for extended periods of time. People may be most familiar with retinal manifestations of O_2 toxicity resulting in blindness of premature neonates. Prolonged exposure to elevated Po_2, 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 O_2 toxicity is a function of both Po_2 and exposure time, directly proportional to both: the greater the Po_2, the greater the risk of HBO_2 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 CO_2 retention.[69] 1.9 ATA is a noticeable threshold for increased risk.[69,77] Even at lower Po_2 HBO_2 seizures can occur particularly when combined with inert gases or carbon monoxide (CO).[9,52] The most dramatic manifestation of CNS O_2 toxicity is an HBO_2-induced seizure. Additional effects of CNS O_2 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 O_2 toxicity often presents acutely with little or no warning. Common signs and symptoms of CNS O_2 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 O_2 toxicity, and CNS O_2 toxicity does not usually proceed through any predictable sequence of the above signs. Convulsions,

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_2T	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.

the most serious effect of O_2 toxicity due to its fatal potential if left untreated, may occur without warning or other accompanying signs.[43,64] O_2-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 O_2 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 O_2 toxicity may also occur in HBO_2 environments and would present identically to a HBO_2-induced seizure. It is critical to differentiate seizures resulting from hyperbaric oxygen from other etiologies, such as hypoglycemia. A convulsion due to O_2 toxicity has little lasting effects, assuming the O_2 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 HBO_2-induced convulsion is minimized by the high Po_2 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 O_2-induced seizures in a hyperbaric chamber under pressure are generally kept at that same pressure until their convulsions cease. The Po_2 in such cases is diminished solely by altering the breathing gas mixture. Patients suffering from O_2-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 O_2 toxicity.[11]

The primary treatment for an O_2-induced seizure is to lower the inspired Po_2. This is accomplished by decreasing ambient pressure, switching to a breathing mixture with a lower percentage of O_2, or both. Decreasing inspired Po_2 may not immediately reverse the effects of CNS O_2 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 Po_2 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 Po_2 has been decreased.[34,83]

In practice, the risk of acute O_2 toxicity is often mitigated by interspersing short periods of air amid the pure O_2 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 O_2 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 HBO_2 exposure prior to the onset of seizures.[24] Yet, animal models demonstrate the possibility that the rapid decreases in Po_2 may actually instigate seizure activity[14] 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 HBO_2T.[64] Therefore, understanding the mechanisms leading to HBO_2 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 HBO_2 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 HBO_2 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 Po_2 causes HBO_2 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 HBO_2 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 Po_2. 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% O_2 control level during preparation. Humans inspiring normobaric air have relatively low Po_2 in their brain, 35 mmHg or less, depending on the region.[19] Murine brains have even lower ranges of Po_2 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 O_2 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 Po_2 in cerebral tissue lead to increased ROS production, followed by increased cortical EEG activity, and finally resulting in the onset of an O_2-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 HBO_2 seizures, particularly at pressures involved with HBO_2T less than 3 ATA.[33]

A relationship exists between high pressures and glycine receptors which indicates possible roles pressure plays on HBO_2 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 HBO_2T, 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]

O_2 under hyperbaric conditions behaves like a drug whose effects on metabolism exceed O_2's common role as a simple oxidizer.[64] The molecular effects of increased Po_2 during HBO_2T affects neural networks in the CNS, resulting in overall network excitability.[37] Much of the research into the molecular mechanisms of CNS O_2 toxicity has focused on the neuroexcitatory and neuroinhibitory effects of neuroactive agents that results from elevated Po_2. 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 O_2 toxicity. CNS O_2 toxicity is an acute exposure to an oxidative environment disrupting neurological function. HBO_2T greatly increases oxygen tension in the brain. Molecular O_2 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 HBO_2 demonstrate that the Po_2 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 HBO_2 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 O_2 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 HBO_2 seizures. Vitamin E deficiency increases the risk of HBO_2 seizures[15]; however, vitamin E failed to prevent HBO_2 seizures.[123] Another example is superoxide dismutase. Superoxide catalyzes superoxide anions to O_2. Therefore, increased levels or activity of superoxide dismutase should decrease levels of ROS; hence, in theory, HBO_2 seizures should be attentuated.[57,93] However, in transgenic mice bred to overexpress human extracellular superoxide dismutase in the brain, inhibition of superoxide dismutase increased resistance to HBO_2 seizures contrary to expectations. By inhibiting superoxide dismutase, the catalysis of superoxide into O_2 (an in vivo antioxidant mechanism) is blocked, allowing superoxide levels to rise unopposed during HBO_2 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 HBO_2-induced reactants.

Gamma-aminobutyric acid (GABA) has long been correlated with HBO_2 seizures.[120,121] Though GABA has been found to be lowered in mammalian neuronal synapses during HBO_2 seizures when exposed to HBO_2 in short intervals,[58] there is evidence to suggest that the increased steady-state levels of GABA over longer intervals may be responsible for O_2-induced seizures.[46] In experiments involving transgenic mice with a HBO_2-sensitivity phenotype, data suggests that the excitatory amino acids, such as aspartate and glutamate, play as important or more important roles in HBO_2 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 HBO_2 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 HBO_2 exposure sensitizes neural networks to HBO_2 seizures.[72] Conflicting evidence exists as to the degree of change in excitatory amino acids prior to and during HBO_2 seizures. Recent evidence suggests that O_2-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 HBO_2 seizures.

Extracellular mediators of physiological functions such as NO also play a role in HBO_2 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 O_2 seizures.[38] Neurons containing nitric oxide synthase (NOS), widespread throughout the cortex, react to HBO_2 by increasing NO production.[1,82] In HBO_2 environments, NO acutely decreases cerebral blood flow but then increases regional cerebral blood flow after prolonged HBO_2 exposure preceding neuronal excitation.[39,51] NO has been associated with changes in cerebral blood flow and HBO_2 seizures.[98] Cerebral blood flow is indirectly proportional to the time of onset of HBO_2 seizures in animal models. Effects of NO with respect to HBO_2 seizures is diagrammed in **Fig. 1**.[68,125] When interstitial NO, aspartate, glutamate, and GABA were measured in vivo in anesthetized rats under HBO_2 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 HBO_2-stimulated neuronal NO production promoted an imbalance between excitatory (glutamate) and inhibitory (GABA) synaptic activity. This in turn contributes to O_2-induced seizures in rats.[38]

The molecular mechanisms involved in HBO_2 seizures are complex. An imbalance of the redundant molecular protective mechanisms that humans have evolved to counter deleterious effects of increased Po_2, as depicted in **Fig. 2**, appears to lead to HBO_2 seizures. Elevated Po_2 causes concomitant saturation of

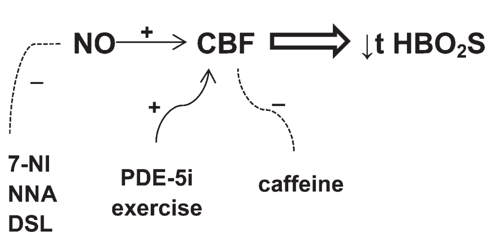

Fig. 1. Schematic of extracellular interactions produced by increased Po_2 that result in CNS HBO_2 seizures. Increased cerebral blood flow (CBF) results in decreased time to onset of HBO_2 seizures ($tHBO_2S$). Extracellular substances such as phosphodiesterase-5 inhibitors (PDE-5i), 7-NI, N-nitro-L-arginine (NNA, a NOS inhibitor), and daurisoline (DSL, a calcium channel blocker) affect CBF. Dotted line = lessened action (-). Bold line = increased action (+). Large arrow = correlation.

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 Po_2 saturates enzymes and maximizes rates of reactions designed to protect against reactive species. For example increased Po_2 saturates superoxide dismutase, increasing superoxide. Superoxide anions can react with NO to yield nitrate (NO_3), a neurologically inert substance; however, the rate of this reaction does not appear sufficient to eliminate risks of CNS O_2 toxicity at sufficiently high Po_2 over time.

A long-standing question regarding hyperbaric oxygen seizures is whether certain regions of the CNS are more susceptible to HBO_2.[112] Neuroanatomic studies have shown that centrally located regions of the brain are most affected by exposure to HBO_2, 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 Po_2 in surrounding tissues when exposed to HBO_2.[50,65] The anatomical localization of neuroactive agents and their effects may also explain anatomical distribution of increased O_2 sensitization.[37,90]

For example, at HBO_2 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 HBO_2 results in an increased firing rate of specific neurons, particularly carbon dioxide (CO_2)/proton-chemosensitive neurons, which are coupled via gap junctions and baroreceptors, in the cerebral and cerebella cortex that demonstrate a high sensitivity to HBO_2, chemical oxidants, and neurotransmitters.[33,40,80]

Certain conditions heighten one's risk to CNS toxicity and HBO_2 seizures. Hypercapnia elevates the risk of O_2 toxicity.[100,119] Hypercapnic-induced intracellular acidosis makes cells more susceptible to ROS. CO_2 causes cerebral vasodilation, increases cerebral blood flow, and heightens CNS exposure to elevated Po_2. Neurons in the solitary complex are particularly susceptible to increased Pco_2 and Po_2, resulting in an increased rate of excitatory firing. Increased Pco_2 in HBO_2 environments may occur by: 1) a decrease in CO_2-carrying capacity of venous hemoglobin since venous hemoglobin may be saturated with O_2; 2) alveolar hypoventilation and CO_2 retention; and 3) CO_2-contamination due to inadequate scrubbing of recirculated breathing gas.[37,100] Exercise also increases the risk of CNS O_2 toxicity, likely related to increased cerebral blood flow and metabolic rate.[2,66] CO toxicity significantly increases the risk of HBO_2 seizures.[52,97]

Current preventative measures to counter O_2 toxicity include minimizing exposure times to increased Po_2, decreasing the inspired Po_2, or inserting periods of air breaks.[11] There is evidence in animal models to suggest that repeated HBO_2 exposures increases risk of seizures.[6,48,75] Data support brain derived neurotrophic factor, 7-nitroindozol (7-NI), and NO as potential

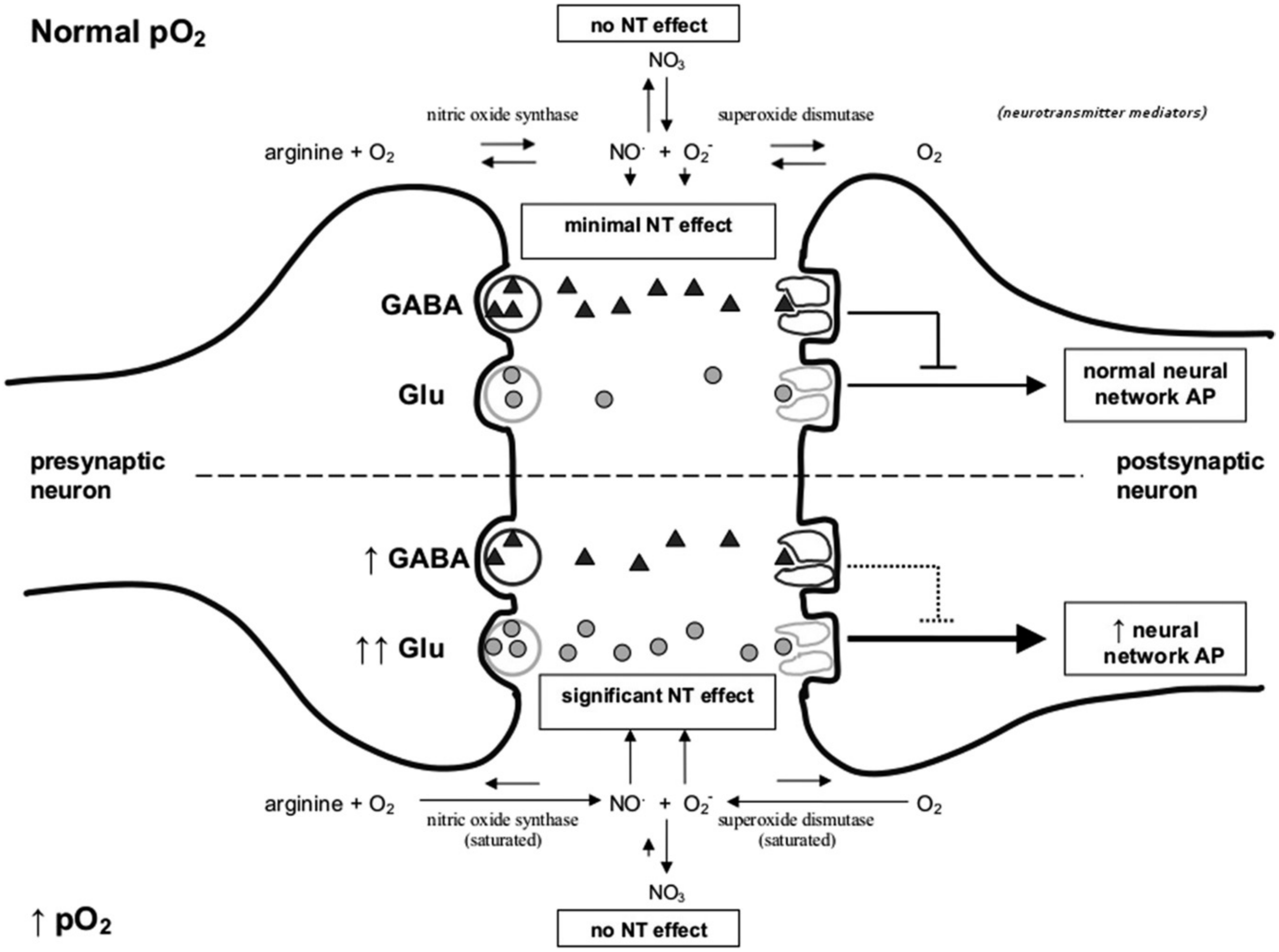

Fig. 2. Schematic of some synaptic changes produced by increased Po_2 and resulting in CNS HBO_2 seizures. The human body has several equilibrated safeguards that minimize effects of ROS on neural networks. Increased Po_2 appears to saturate protective enzymes and unfavorably shift protective reactions 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.

mechanisms for sensitization to repeated HBO_2 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 O_2 toxicity for no apparent reason.[11]

Since the mechanism of CNS O_2 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 O_2 toxicity. Numerous prophylactic treatments for HBO_2-induced seizures have been shown to be effective through in vivo experiments involving rats and mice.

NO is an important mediator of CNS O_2 toxicity.[12] Inhibition of NOS with nitroarginine showed similar prevention of CNS toxicity and O_2-induced seizures in both transgenic and nontransgenic mice.[23,88,115] The potency of NOS inhibitors in preventing CNS O_2 toxicity is indirectly proportional to the disassociation constant of the inhibitor and NOS.[36] Intraperitoneal administration of GABA proved effective in protecting rats from O_2-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 HBO_2 conditions with 7-NI slowed the rate of decline in GABA levels, decreased the glutamate/GABA excitotoxicity index, and minimized EEG spikes associated with O_2 toxicity.[38]

MK-801, an NMDA receptor antagonist, has been shown to prevent EEG spikes associated with O_2 toxicity and O_2-induced seizures.[37,39] Other substances such as disulfiram (Antabuse)[21,47,117] and antioxidants also appear to delay or diminish O_2 toxicity in the brain.[34,37] Additional agents that hasten the onset or increase incidence of HBO_2 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 HBO_2 seizures include: N-nitro-L-arginine (NNA),[22,115] daurisoline (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

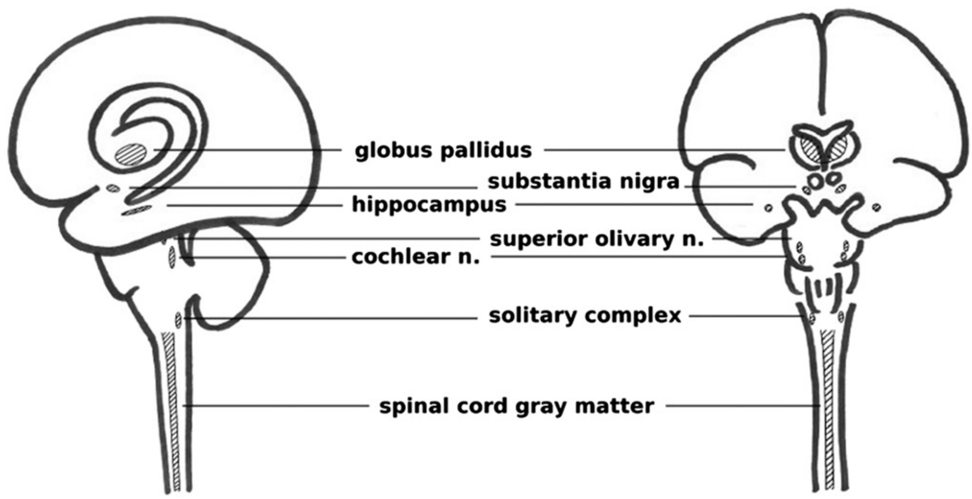

Fig. 3. Brain regions most likely involved in HBO_2-induced seizures. Certain regions of the CNS (including the solitary complex in the dorsal medulla, hippocampus, globus pallidus, substantia nigra, superior olivary nucleus, ventral cochlear nucleus, and spinal cord gray matter) appear more susceptible than others to these effects. Note the central nature of these regions, anatomically similar to CO susceptible regions.

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 HBO_2 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 O_2 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 HBO_2 and only one pertaining to CNS O_2 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 HBO_2-induced CNS toxicity, including: disulfiram (an inhibitor of alcohol dehydrogenase with some evidence of success in preventing HBO_2 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 HBO_2T 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 O_2-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 Po_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 O_2-induced seizures may also negatively affect the therapeutic benefits of HBO_2T, thus adding to the complexity of the study. For example, any antioxidant that can effectively eliminate ROS during HBO_2T may eliminate their role in causing HBO_2 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 O_2-induced seizures such as NO.[96] The excitatory firing rate of dorsal medullary neurons due to HBO_2 can be mimicked by the presence of prooxidants at normobaric conditions,[37] demonstrating that normobaric experimentation might be feasible to shed light on O_2'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 HBO_2 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 O_2 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 O_2 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 HBO_2 come with the risk of CNS O_2 toxicity. The exact mechanism of O_2 toxicity remains a mystery. Prophylactic measures and treatment for CNS O_2 toxicity remain centered on limiting exposure to high Po_2. Better understanding of molecular mechanisms causing O_2 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 HBO_2 seizures in order to better understand how they occur and how to prevent them.

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