CNS oxygen toxicity.

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INTRODUCTION

This short manuscript will briefly present our current knowledge about CNS oxygen toxicity: the clinical manifestations, descriptions and incidence of symptoms, and the time – duration relationship that defines the safety limits and risk factors leading to enhanced toxicity to hyperbaric oxygen. A very general outline will present suggested mechanisms underlying hyperoxia-induced seizures and strategies for protection against the seizures. Unfortunately, not much has been gained in our knowledge and understanding of CNS oxygen toxicity in recent years. Some concluding remarks will be given, as will some suggestions toward further research for increasing our knowledge about mechanisms, and better approaches for protection against the toxic effects of breathing oxygen at high partial pressures.

DESCRIPTION

There is no better description of CNS oxygen toxicity than the personal experience of Christian J. Lambertsen. “The convulsion is usually preceded but not always by the occurrence of localized muscular twitching, especially about the eyes, mouth and forehead. Small muscles of the hands may be involved and incoordination of diaphragm activity in respiration may occur. Eventually an abrupt spread of excitation occurs and the rigid "tonic" phase of the convulsions begins. Vigorous clonic contractions of the muscle groups of head and neck, trunk and limbs then occur becoming progressively less violent over 1 minute” (1). These convulsions are classified as generalized, tonic-clonic (grand mal) seizures (1). A typical electroencephalogram obtained during hyperbaric oxygen (HBO_2) seizures consists of spike and wave discharges (Figure 1) recorded in both hemispheres. They may start simultaneously or at random times in the cortical and subcortical areas (2, 3).

The hyperoxia-induced discharges are believed to be reversible, causing no residual neurological damage, and disappear upon reduction of the inspired oxygen partial pressure (1).

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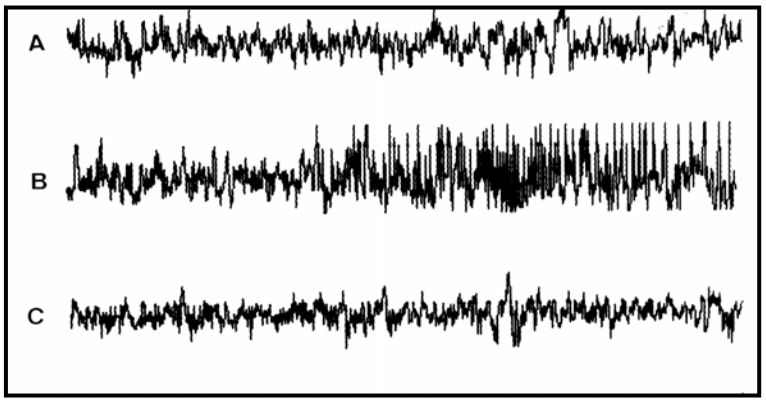


Fig. 1. Typical EEG from a rat exposed to 0.5 MPa oxygen. A) Air at atmospheric pressure. B) Appearance of typical spike and wave electrical discharges at 0.5 MPa oxygen. C) On return to atmospheric pressure. Calibration: 1 sec/50 V.

Hyperoxia-induced seizures are accepted as generalized, although several studies point toward local variations in subcortical brain areas. This might contradict the general nature of the seizure's development and indicate a more localized primary focus for the initiation of the epileptic activity. Several studies demonstrate variations in cerebral blood flow in different brain areas on exposure to HBO_2 (4, 5, 6); others present regional changes in amino acids and ammonia levels (7), variation in lipid peroxide distribution (8), and distribution of antioxidant enzymes (9).

Early changes in cortical electrical activity have been described on exposure to HBO_2 several minutes prior to the full development of the electrical discharges (10, 11). Unfortunately, almost thirty years later despite extensive research, we have no real-time correlate of pre-seizure EEG activity that could serve for the prediction of CNS oxygen toxicity (12, 13, 14).

Symptoms

Few large-scale human studies describing the symptoms of CNS oxygen toxicity are available in the literature (15, 16, 17, 18, 19, 20). The list includes a group of minor symptoms, such as nausea, dizziness, abnormal sensations, headache, disorientation, lightheadedness and apprehension, which are difficult to define. More unambiguous symptoms appearing on exposure to HBO_2 are blurred vision, tunnel vision, and tinnitus. Signs include respiratory disturbances, eye twitching, twitching of lips, mouth, and forehead, and convulsions. There is no consistency in the appearance of symptoms and signs prior to the development of the seizures. Despite our prolonged experience with experimental and accidental CNS oxygen toxicity, there is no consensus about the frequency and incidence of the different symptoms.

Table 1 compares symptoms from about 550 human exposures to hyperbaric oxygen, compiled from those performed by Donald in 1947 (16), Leitch in 1984 (17), and three series of experiments conducted in Panama City by Butler and Thalmann (18, 19, 20). The symptoms of CNS oxygen toxicity are presented in the declining order of their incidences of appearance. As can be seen from the table, there are inconsistencies in the frequency of symptoms' appearance in the different HBO_2 series. This symptom variability reflects the importance of environmental and personal factors on the development of CNS oxygen toxicity.

Dosing

The most famous relationship between inspired oxygen partial pressures and the time for the appearance of symptoms of pulmonary and CNS oxygen toxicity (latent period) is the classic work of Lambertsen and his colleagues at the University of Pennsylvania (Figure 2**)** with exposures to HBO_2 in a dry hyperbaric chamber (21).

TABLE 1

Donald	Leitch	Butler and Thalmann (NEDU)		
1947	1984	1984	1986	1986
Convulsion	Convulsion	Light – Headedness	Nausea	Muscle twitching
Twitching of lips	Unconsciousness	Convulsion	Muscle twitching	Dizziness
Vertigo	Cyanosis	Tinnitus	Dizziness	Blurred vision
Nausea	Limb shaking	Apprehension	Tinnitus	Dysphoria
Respiratory Disturbances	Dizziness	Dysphoria	Dysphoria	Convulsion
Twitching of parts other then lips	Strenuous breathing	Blurred vision	Confusion	Aphasiaia
Sensations of abnormality	Auditory aura	Tunnel vision	Convulsion	Dyspnea
Visual Disturbances	Breathing disturbance	Disorientation	Decreased auditory Acuity	Paresthesias
Acoustic Hallucinations	Nausea	Lethargy	Aphasia	Nausea
Paraesthesiae	Dissociation	Dysphasia	Tingling	Lightheadedness
	Apnoea	Aphasia	Numbness	Air hunger
	Loud cry/groan	Eye twitching	Choking sensation	Tinnitus
	Malaise	Nystagmus	Amnesia	Confusion
	Headache/pulsation	Incoordination	Muscular rigidity	Muscular rigidity
	Apprehension		Lightheadedness	Irritability
	Amnesia		Poor concentration	Hypoacusis
	Facial twitch		Visual disturbances	Hyperacusis
	Lip tremor		Decreased mental alertness	Poor concetration
	Disorientation		Increased respiratory rate	Tunnel vision
N=388	**N=35**	**N=28**	**N=33**	**N=59**

Table 1. Symptoms of CNS oxygen toxicity presented in declining order of incidence. Data from Donald, 1947 (16), Leitch, 1984 (17), & Butler and Thalmann (18,19, 20).

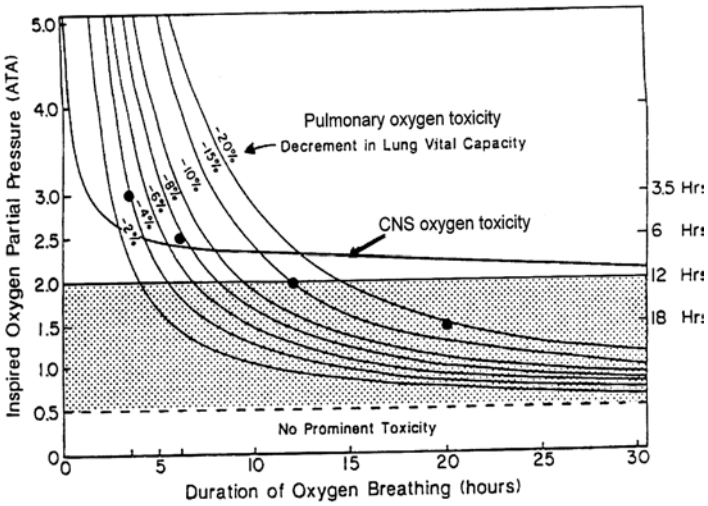


Fig. 2. Pulmonary and neurological oxygen tolerance curves for continuous exposures of normal men to hyperbaric oxygen. Adapted from Lambertsen CJ, Clark JM, Gelfand R, et al, 1987 (21).

Figure 3 displays the depth- time limits for wet (immersed) oxygen diving (19), setting the lower limit for oxygen diving at about 15 msw (50 fsw) for a period of 10 minutes and allowing safe prolonged oxygen diving for about 4 hours at a fairly shallow depth of around 7 meters (20 fsw) (threshold depth). Various environmental and personal factors may modify sensitivity to CNS oxygen toxicity, thus shortening the duration of the latent period and lowering the threshold pressure for the development of seizures.

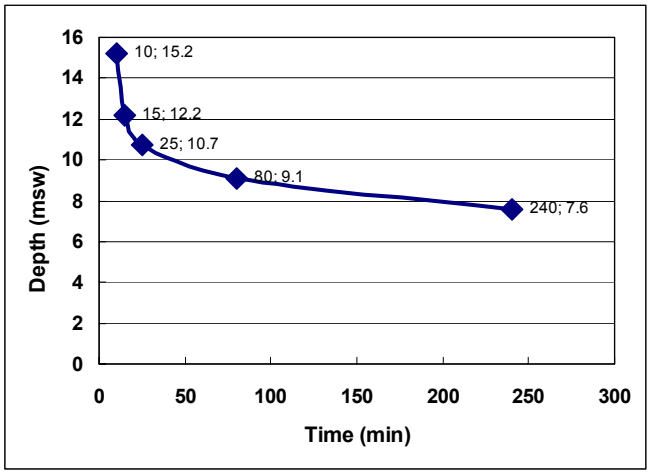
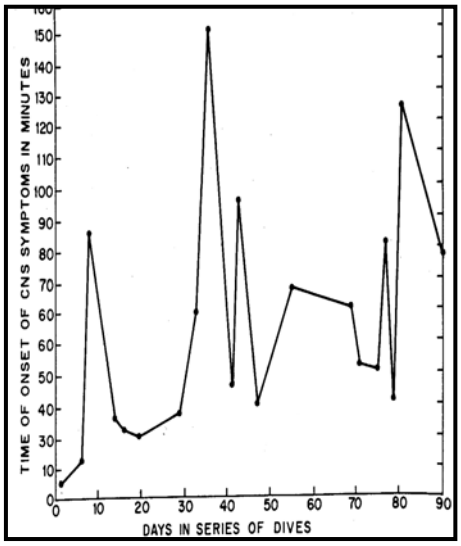


Fig. 3. Time–depth limits for oxygen diving. Data from Butler & Thalmann, 1986 (19).

Risk Factors

The exposure to hyperbaric oxygen in a wet environment increases sensitivity to CNS oxygen toxicity compared to exposure in a dry hyperbaric chamber (1, 16). Elevated concentrations of carbon dioxide (1, 14, 16, 22-25) and physical activity (exercise) dramatically decrease the duration of latent period for hyperoxia-induced seizures (1, 16, 23). The latent period for the appearance of electrical discharges in the EEG is significantly shorter in darkness than in light (26), suggesting the importance of visual input in the modulation of sensitivity to CNS oxygen toxicity. The risk for CNS oxygen toxicity is not determined solely by the partial pressure of the inspired oxygen, and even relatively low partial pressures of inert gases may contribute to hyperbaric-induced seizures (27). The increased sensitivity caused by inert gases could be explained by the involvement of free radical production (28). Circadian rhythm (29), various drugs, age (30), sex (31), interspecies differences and individual day to day variability (16) may contribute to the sensitivity to CNS oxygen toxicity (14). Figure 4 presents data from a unique study by Donald in 1947, in which he exposed a single diver to the same profile of HBO_2 for twenty times within a three month period, until the appearance of neurological symptoms of oxygen toxicity (16). As can be seen, there are large day to day variations in time duration of symptoms, suggesting that there is no fixed, personal, predetermined threshold of tolerance to oxygen toxicity. This finding supports that using the oxygen test as a screening tool for oxygen diver selection is ineffective.



In spite of the known day to day individual variability in tolerance to hyperoxic seizures, and the evidence concerning modulation of environmental and personal factors on the sensitivity to high oxygen pressures, it is surprising that we are still using tables based on statistical methods and predictive models. A more optimal approach would be personal monitoring of oxygen toxicity using a real-time predictive system for detecting the first signs of toxicity.

Fig. 4. Day to day variations in time duration until onset of CNS oxygen toxicity symptoms of a single diver. From Donald, 1947 (16).

Mechanisms

Although hyperoxic-induced seizures have been well described, the effects of HBO_2 on neural elements remain poorly understood. Studies of vertebrate nerves demonstrated decreased excitability and blockage of impulse conduction (32, 33), while increased axonal excitability and an increase in the membrane time constant were demonstrated in the isolated nervous system of the cockroach (34). The synaptic mechanisms seem to play an important role in the development of the HBO_2-induced seizures. Among the main electrophysiological findings is an increase in spontaneous synaptic transmitter release (35), a reduction in the inhibitory transmission and enhancement of evoked excitability activity at the neuromuscular junction of the lobster (36).

HBO_2 is known to affect most of the neurotransmitters and the neurotransmitter enzymes, such as GABA, acetlycholine, glutamate, dopamine, ammonia, norepinepherine, and aspartate (37-44). It also affects neuromodulators, such as nitric oxide (NO) (45). Membrane-bound active transport systems are also impaired on exposure to hyperbaric oxygen (14, 38, 39, 46, 47), with implications on neural activity. These studies were performed in different nerve preparations and synapse models. Some used direct physiological techniques, while others used indirect biochemical methods. They indicate that HBO_2 affects almost all neural elements. However, the primary neural target responsible for development of hyperoxic seizures is still unknown.

It is well accepted that reactive oxygen species (ROS) are increased on exposure to HBO_2, and overwhelming the body's normal antioxidant defenses may mediate the hyperoxic insult (48). An increase in free radical generation in the brain precedes HBO_2-induced convulsions, as demonstrated in brain extracts (49). H_2O_2 is elevated in various brain areas on exposure to HBO_2 (9, 50, 51), and there is a rise in free radical levels in the blood of humans exposed to HBO_2 (52). Nevertheless, a recent study done with awake animals using a microdialysis probe failed to detect an increase in hydroxyl radicals prior to, or during, HBO_2-induced convulsions (53). Currently, the available experimental data does not allow for us to decide whether ROS are the primary cause for hyperoxic seizures activity, or alternatively, that ROS are acting indirectly on neural elements and via second messengers, such as small inorganic molecules or proteins, to elicit the epileptic activity. A study using blood-brain barrier integrity as an index for injury in chronically EEG implanted rats revealed that CNS oxygen toxicity, at its

early stages (onset of electrical discharges), is not associated with the altered permeability of the cerebral microvessels (54).

Protection

Intermittent exposure to hyperbaric oxygen breathing with air breaks at the same pressure is a technical approach for increasing the total time of exposure to hyperoxia (14). This procedure is routinely used in the clinical setting. Various pharmacological strategies have been tested for postponing hyperoxic-induced seizures:

1. Cerebral vascular modulation. Exposure to HBO_2 results in cerebral vasoconstriction, leading to a decrease in CBF (4, 5, 1), which is later followed by cerebral vasodilatation. It has been suggested that the breakpoint in cerebral vasoconstriction is correlative with the development of hyperoxia-induced seizures (4). Therefore, any pharmacological agent that induces cerebral vasoconstriction may have the potential to protect, or at least postpone, the development of the seizures. Caffeine, a well known cerebral vasoconstrictor postpones hyperoxic seizures in a dose-related manner (55). Two nitric oxide synthase inhibitors, L-NAME and 7-nitroindazole (7-NI), significantly prolong the latent period before onset of seizures on exposure to hyperbaric oxygen or to a hypercapnic-hyperoxic stress (56, 57). This supports the involvement of the L-arginine-NO pathway in the pathophysiology of hyperoxia-induced seizures.
2. Neural activity modulation. On the basis of the clinical manifestations of hyperoxic seizures, several anti-epileptic drugs have been studied. A significant prolongation of the latent period before seizures was demonstrated using carbamazepine (Tegretol) (58). Vigabatrin (Gama vinyl GABA), an irreversible inhibitor of GABA transaminase, successfully protected against hyperoxic seizures in a dose-related manner for prolonged periods of 24 hours or more (59).
3. Enhancement of the antioxidant state. Extensive research had been directed toward defining agents that will protect against oxidative stress by increasing the potential for neutralizing or scavenging the ROS. The results up until now are not very promising. It is possible to find contradictory reports on various antioxidants' abilities to protect against CNS oxygen toxicity. For example, Puglia and Loeb (60) found that two of the most studied antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), were protective, but both failed to exhibit protective effects in studies by Block, et al, (61). Others have shown that when entrapped in liposomes, SOD and CAT inhibit hyperoxia-induced seizures (62). No protection was found in transgenic animals over expressing SOD (63), and no effect was shown with knockout animals regarding pulmonary oxygen toxicity (64). Harabin, et al (65) have shown no correlation between the development of oxygen toxicity with intermittent exposures to hyperbaric oxygen and the levels of antioxidant enzymes.

Metal ion chelators, such as Deferoxamine, were not found to be protective against hyperoxic seizure (66). A variety of ROS scavengers and natural and synthetic antioxidants have been tested, showing different levels of protection in animal models (66-71). The Nitroxide spin traps Tempo and Tempol were found to be effective in preventing CNS oxygen toxicity and efficacy, correlated with their lypophilic properties (69, 70). Beta-carotene from natural origin (*Dunaliella bardawil*) was demonstrated to be among the most effective antioxidants after a one-week diet (71). The lack of dramatic protection against CNS oxygen toxicity by antioxidants is consistent with an assertion by two ROS pioneers in a recent review article. Gutteridge and

Halliwell write, "It was soon clear to many researchers that free radicals did not cause a plethora of diseases, neither were 'spoonfuls' of SOD or vitamins going to modify them, let alone cure them" (72). Deprivation of food or water prior to exposure to HBO_2 significantly prolonged the latent period to the onset of hyperoxia-induced seizures in a dose-related manner (73).

Further Research Areas

While trying to evaluate the current understanding of CNS oxygen toxicity, it is surprising that so much is unknown, or rather, that so little is known. Possible explanations for our limited knowledge in this field could be that HBO_2 is not a physiological signal, CNS oxygen toxicity is not a common disease, and for many years, HBO_2 diving was limited to combat military divers. Under such circumstances, not many research institutes or pharmaceutical companies undertake research or provide financial support for basic CNS oxygen toxicity studies. Many technical difficulties are imposed on experiments in hyperbaric conditions (74), whether simulated chamber exposures or deep-water diving (74). The candidate ROS that are suggested to mediate toxic effects have short half lives and are known to be site specific. This combination makes their real-time measurement a difficult task, especially in hyperbaric chambers. Oxygen toxicity is a multi-organ, multi-system toxicity. Therefore, it is difficult to separate the primary symptom from non-specific after effects. An additional reason for limited research may be the nature of the technological solutions available for avoiding CNS oxygen toxicity. They include using various mixtures with the precise control of oxygen partial pressure for diving and hyperbaric clinical use.

CONCLUDING REMARKS

1. An effort should be directed at establishing the importance and utility of hyperoxia-induced seizures as an experimental model of generalized (grand mal) epilepsy (75). Hyperoxia-induced seizures can serve as an excellent epileptic model since the epileptic agent disappears immediately on reduction of the oxygen pressure, and its toxic manifestations are believed to be reversible. Collaborations among scientists from the basic neurological research (especially the mechanisms of epilepsy) will increase our knowledge and improve our ability to use innovative strategies for the prevention of CNS oxygen toxicity.
2. We must continue to expand research efforts on the basic mechanism of oxidative stress and the role of second messengers in the pathophysiology of CNS oxygen toxicity. This approach will increase the need for more sophisticated methods of multimodal monitoring of physiological and biochemical parameters, such as mentioned by Rogatsky, Shifrin, and Mayevsky (76). A future protection strategy should consider the need for a continuous inflow of antioxidants or scavengers to neutralize the ROS or avoid its development in real time, during the entire period of exposure to HBO_2. That is, a patch that releases a continuous flow or an implanted biological generator of ROS scavengers.
3. An extensive effort must be given to having a personalized, real-time profile for any HBO_2 diver or patient, based on his personal, daily-specific sensitivity to HBO_2, instead of using tables of the time–duration relationship. In our technological era, this can be done with miniature sensors and wireless technology, which will follow the physiological parameters and pre-seizure modifications. The future vision for oxygen diving will be in a tailored CNS oxygen toxicity monitor, which will assist in allowing each person to have an optimal level of hyperbaric oxygen without being exposed to its toxicity.

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