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Hyperbaric oxygen therapy

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Abstract
Hyperbaric oxygen therapy (HBOT) is defined as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than sea level (1.0 atmosphere absolute). HBO_2 treatment is carried out by using a mono- (single person) or multi-place (typically 2 to 14 patients) chamber. Pressures applied while in the chamber are usually 2 to 3 atmospheres absolute (ATA), the sum of the atmospheric pressure (1 ATA) plus additional hydrostatic pressure equivalent to one or two atmospheres (1 atmosphere = a pressure of 14.7 pounds per square inch or 101 kPa. Hyperbaric oxygen therapy is a new treatment method with a number of different indications. It is managed by different specialities depending up on the need, but most of the hyperbaric facilities are driven by departments of anaesthesiology, and some of the patients are critically ill. Research using a stricter design that includes, random trials, blind experimentation, multiple centers, and large samples are needed for further confirmation. The mechanism of HBOT in the human body is not fully understood still. Further HBOT study using advanced non-invasive techniques, such as Positron Emission Tomography Computed Tomography (PET-CT) and functional Magnetic Resonance Imaging (fMRI) may help to discover additional mechanisms. HBO-PC helps in the reduction of injury to the body in some cases, and its prospects for clinical application as well as the in-depth study of its mechanism will be of broad interest.

Keywords: hyperbaric oxygen therapy (HBOT), functional magnetic resonance imaging (FMRI)

Introduction
Hyperbaric oxygen therapy (HBOT) can be defined as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than sea level (1 atmospheric pressure) [1]. Hyperbaric oxygen (HBO_2) therapy has been used to treat decompression sickness, but more recently has been used as a primary or adjunctive therapy in number of injuries and medical conditions, many of which commonly affect the aging adult population. It also has potential benefit in conditions such as acute traumatic ischemia, necrotizing soft tissue injuries, nonhealing ulcers, and osteoradionecrosis [2].
HBOT is a treatment that has arised from 1600s. The first oxygen chamber was built and run by a British clergyman named Henshaw. He built a chamber called the domicilium that was used to treat a multitude of diseases. The chamber was pressurized with air and unpressurized using bellows. The idea of treating patients under increased pressure was proposed by the French surgeon Fontaine; he built a pressurized, mobile operating room in 1879. Dr. Orville Cunningham, a professor of anesthesia, ran a hospital known as the "Steel Ball Hospital." The structure, erected in 1928, which are 6 stories high and 64 feet in diameter. The hospital could reach 3 atmospheres of pressure. But unfortunately, the hospital was closed in 1930 because of the lack of scientific evidence indicating that such treatment alleviated disease. It was deconstructed during World War II for scrap.
The military continued work with hyperbaric oxygen. The work of Paul Bert, who demonstrated the toxic effects of oxygen (producing generalized seizures), and also the work of J. Lorrain-Smith, who demonstrated pulmonary oxygen toxicity, were used with Navy divers. These were quantified and tested by measuring the exposure times to oxygen at different depths of water (and, hence, different levels of pressure) based on time to convulsions.
The United States have an inadequate number of HBOT treatment facilities. Of the 361 chambers identified nationwide, only 43 were equipped to handle high-acuity patients. HBOT is instrumental in treating decompression sickness, arterial gas embolisms, and acute carbon monoxide poisoning.

Oxygen chambers
When a patient is given 100% oxygen under pressure, hemoglobin is get saturated, but blood can be hyper oxygenated by dissolving oxygen within the plasma. The patient can be administered systemic oxygen via two basic chambers: Type A, multiplace; and Type B, Monoplace. Both these types can be used for routine wound care, treatment of patients who are in ventilator or critical care unit and also in most dive injuries [3].

Discussion
Hyperbaric Oxygen Therapy an Overview
The term hyperbaric literally means higher pressure (hyper

means over; baric means which is concerned with weight). According to Undersea and Hyperbaric Medical Society (UHMS), HBO_2 therapy involves breathing 100% oxygen within a chamber that has been pressurized to a pressure higher than sea level (ie, >1.0 atmosphere absolute [ATA]). The mechanisms of action, is that increases the partial pressure of oxygen in the tissues of the body to a degree several times greater than that which can be achieved by breathing pure oxygen at a normal atmospheric pressure. The increased atmospheric pressure also increases the amount of oxygen in blood plasma that has greater bioavailability to the tissues than of oxygen in hemoglobin.

HBO_2 therapy can be delivered in one of the three chamber types: high-pressure multiplace, high-pressure Monoplace, or low-pressure Monoplace. The most commonly used one in medical settings are high-pressure chambers, which are designed to hold either one person (ie, Monoplace) or more than one (ie, multiplace) at a time. Most chambers are designed to operate at a pressure in the range of 2.0 to 2.5 ATA [4].

History of Hyperbaric Oxygen Therapy

HBO_2 therapy has been described as a new application of an older, more established technology. The history says that, A British physician Nathaniel Henshaw was the first person to use compressed air in a chamber called a domicilium for an HBO_2 environment. Around this time, Robert Boyle, an Irish chemist, physicist, and inventor, stated that when temperature is held constant, the pressure and volume of a gas have an inverse relationship. Boyle's law is a basis for many aspects of HBO_2 therapy, including a slight increase in ambient temperature within the chamber during treatment sessions.

By 1877 hyperbaric chambers had been used for a wide range of conditions, despite a general lack of scientific understanding or evidence about their mechanism of action or efficacy. It was not until 1917 that German inventors Bernhard and Heinrich Dragger applied pressurized oxygen to successfully treat decompression illness from diving accidents.

The first hyperbaric chamber in the United States was built in New York in 1861 by neurologist James Leonard Corning. Corning's interest in HBO_2 therapy arised from witnessing severe decompression illness among the Hudson Tunnel site workers, they often experience severe muscle pain and paralysis after working below water level every day. He used his chamber to treat such cases and mostly nondecompression-related nervous system disorders. Subsequently, the use of these chambers to treat conditions other than decompression illness was largely discontinued until 1921, when Kansas-based physician Orval J. Cunningham built a hyperbaric chamber in Kansas City. Cunningham built the chamber after observing that morbidity and mortality rates from the "Spanish influenza" pandemic which was greater in higher elevations than in coastal areas. He observed certain success with this therapy. One night, a mechanical failure in his chamber's air compressor which causes the pressure to rapidly decrease to normal atmospheric levels, killing of all its occupants. Not understanding the true mechanism behind his patients' deaths, Cunningham concluded that the HBO_2 therapy had kept them alive and that they could not live in an environment without it. He went on to open the world's largest HBO_2chamber along the shores of Lake Erie in Cleveland, Ohio, in 1928. This million-dollar, 900-ton sphere measured 64 feet in diameter, was 5 stories tall, and was equipped with 12 bedrooms on each floor. The structure was known as the Cunningham Sanitarium and was considered the first "attempt in human history to house people in such a unique structure." Cunningham believed that many illnesses, including diabetes and cancer, are caused by anaerobic organisms that can be killed by exposure to oxygen; subsequently, the chamber was in use for only a short period and dismantled in 1937 for scrap metal. That same year, Albert Behnke and Louis Shaw built on the Draggers' work for decompression illness Shaw built on the Draggers' work for decompression illness and used oxygen in place of compressed air. Their work led to use of the first nitrogen-oxygen mixtures and hyperbaric treatment being used for certain severity of injuries.

The mainstream interest in HBO_2 to treat medical conditions beyond decompression illness was not renewed until 1956, when Dutch cardiac surgeon Ite Boerema reported on the use of HBO_2 as an aid in cardiopulmonary surgery. Thereafter, more promising reports on the use of HBO_2 surfaced, including one by Boerema's colleague, Willem Brummelkamp, who reported in 1961 that anaerobic infections were inhibited by HBO_2 therapy. Since then, HBO_2 has been used in the treatment of numerous medical conditions, including carbon monoxide poisoning, infections, wound healing, and trauma [5].

Mechanism of Action of Hyperbaric Oxygen Therapy

Oxygen is importantly necessary to provide energy and to support cellular respiration. An injury or any disease diminishes the body's ability to transport oxygen to the tissues, so that make increase the process of healing. Conditions such as, exposure to toxins, haemolytic anemia and hemorrhage can affect the body's ability to transport oxygen, whereas in case of edema, decreased perfusion, and micro thrombosis which can affect the distance that oxygen must travel from the capillaries to the cells.

The majority of the oxygen transported in the blood is carried by hemoglobin; however, some oxygen is carried by the plasma. Henry's Law states that the relationship between the volume of gas dissolved in a liquid or tissue and the partial pressure of that gas is proportional or in a reverse relationship. Therefore, based on this law, by increasing atmospheric pressure which will cause more oxygen to dissolve in the plasma, therefore maximizing tissue oxygenation.

By, increasing the concentration of a gas within a fluid which increases its partial pressure within the fluid. The increased partial pressure increases the driving force which is for diffusion and thereby Inca divers [4].

Oxygen chambers

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patients who are in ventilator or critical care unit and also in most dive injuries.

Multiplace chamber

Multiplace chambers treat multiple patients at the same time, generally with a nurse or an observer who monitors the patients and also assists with equipment manipulation or emergencies. Patients in a multiplace chamber breathe 100% oxygen through a mask or close-fitting plastic hood. Multiplace chambers can usually be pressurized to an equivalent of about six atmospheric pressure. If a different mixture of gas (nitrogen or helium mixture) is needed, the mixture can be given, via the mask, only to the patient, not to the employee. All equipment used by patients, such as ventilators and intravenous lines, is put into the chamber with the patient. Since the employee is breathing air during the treatment without mask, his or her nitrogen intake must be monitored, as this arise a risk similar to those sometimes developed by scuba divers (eg, decompression sickness [DCS]).

Monoplace chamber

A Monoplace chamber compresses a single patient at a time, usually in a reclining position. The gas used to pressurize the vessel is usually 100% oxygen. Some chambers have masks which are used to provide an alternate breathing gas (such as air). Employee's contanct to the patient from outside of the chamber and equipment remains outside the chamber. Only certain ventilation ducts and intravenous lines penetrate through the hull. Newer Duoplace chambers can occupy two patients. Their operation is similar to that of a Monoplace chamber.

Other chambers

Two other types of chambers are worth mentioning, although they are not considered HBOT.

Topical oxygen, or Topox, is administered through a small chamber that is placed over an extremity and pressurized with oxygen. The patient does not breathe the oxygen, nor is the remainder of the body pressurized. Therefore, the patient cannot benefit from most of the positive effects of HBOT, which are systemic or occur at a level deeper than topical oxygen can penetrate. Topox is based on the concept that oxygen diffuses through tissue at a depth of 30-50 microns.

Another problem with Topox is the design of the unit. A pressure differential must be created between the machine and open atmosphere to compress the machine. In order to keep the extremity from being pushed out of the pressurized machine, the cuff of the box must fit very tightly around the extremity, thereby creating a tourniquet like effect.

The other type of chamber is the portable "mild" hyperbaric chamber. These soft vessels can be pressurized to 1.5-1.7 atmospheres absolute (ATA). They are only approved by FDA for altitude illness [3].

Hbot in the Treatment of Various Diseases

HBOT in the treatment of periodontitis

HBOT increases oxygen distribution at the pocket base which is deleterious to periodontal pathogens, particularly to the anaerobic microorganisms [33]. Cultivation of plaque microorganisms from sites of chronic periodontitis reveals high percentages of anaerobic (90%) bacterial species.[34] HBO2 increases generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage deoxyribonucleic acid and inhibit bacterial metabolic functions. It also facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria. HBO2 also helps in the improvement of the oxygen-dependent transport of certain antibiotics across bacterial cell walls [34]. Therefore HBOT results in inhibition of bacterial growth [35].

Wound healing

HBO_2 is used to treat delayed radiation injuries and refractory diabetic lower extremity wounds. Clearly, the pathophysiology of these disorders differs but they share several elements include depletion of epithelial and stromal cells, chronic inflammation, fibrosis, an imbalance or abnormalities in extracellular matrix components and remodeling processes, and impaired keratinocyte functions [6]-[8]. Diabetic wound healing is also impaired by decreased growth factor production, while in post-radiation tissues there appears to be an imbalance between factors mediating fibrosis versus normal tissue healing [9]-[12].

The reduction of inflammation

HBOT can reduce inflammation by reducing the release of inflammatory mediators. Such inflammatory mediators include the lymphokine (IL) family and tumor necrosis factor (TNF). For example, HBOT attenuated inflammation via the reduction ofIL-1, IL-6, IL-8, and IL-10expression in rat models of ischemia or injury [19]-[21]. Additionally, HBOT reduced TNF-α in a model of testicular ischemia-reperfusion injury in rats [22]. Besides, HBOT can also reduce inflammation by reducing the incidence of membrane cofactor protein-1(MCP-1), keratinocyte-derived chemokine (KC), and IFN-gamma-inducible protein 10(IP-10) [23]. In addition, the anti-inflammatory effect of HBOT may be related to the inhibition of specific signaling pathways. HBOT may mitigate secondary injury to the spinal cord(SC) by inhibiting inflammatory responses induced by the TLR2/NF-κB and the iNOS mRNA-iNOS-NO signaling pathways, thereby promoting functional recovery in spinal cord injury in rats [24]-[25].

The inhibition of cell apoptosis

HBOT inhibits cell apoptosis by regulating apoptosis-related proteins in a variety of pathological models.[14] HBOT can reduce the secretion of caspase-3, which is critical for apoptosis induced by proteases in different rat models of ischemia [13]. These models include brain ischemia-hypoxia in neonatal rats and cerebral ischemia-reperfusion injury in adult rats [15]. In addition, similar anti-apoptotic effects have been reported in models of myocardial infarction [16]. B-cell lymphoma 2 (Bcl-2) is an inhibitor of the apoptosis protein, Bax, which is a Bcl-2-related protein that pro-apoptotic. The ratio of Bcl-2/Bax is up regulated by HBOT and inhibits cell apoptosis in a rat model of myocardial infarction. In addition, Thioredoxin Reductase (TrxR), an antioxidant, also has an antiapoptotic effect that can involve HBOT [17]. For example, HBOT is beneficial for the improvement of anxiety-like

behavior and cognitive impairments in stressed rats; this effect might be associated with the inhibition of neuronal apoptosis via up regulation of TrxR [18].

The balance of oxygen free radicals

Oxygen free radicals are a product of metabolic processes of the body. Because oxygen free radicals generally exist in the body, their production and scavenging are normally in a dynamic equilibrium. The appropriate levels of oxygen free radicals can facilitate tissue metabolism and cell detoxification, but excessive oxygen free radicals will damage the body [28]. In theory, HBO can increase oxygen free radicals. HBOT initiated soon after acute transient cerebral ischemia in rats increases mitochondrial free radical levels but also increases the activity of superoxide dismutase (SOD), which is important for scavenging free radicals. Thus, the net effect is an increase in oxygen and a reduction in oxygen free radicals, which then protects the body [26, 27].

Brain injury or stroke

When the brain cells die, either due to trauma or lack of oxygen, blood plasma leaks out into surrounding brain tissue results in swelling and reducing the blood flow. These otherwise normal cells go dormant because they are not able to function without the appropriate amount of oxygen. [32] HBOT increases the oxygen carried in the blood plasma, making oxygen available to heal damaged capillary walls, preventing plasma leakage and thereby reducing swelling. As the swelling decreases, blood flow can be restored to the dormant tissue (neovascularization) and those cells then have the potential to function again [33].

Child with cerebral palsy (CP) or traumatic brain injury (TBI)

In CP and TBI patients, some of the injured brain tissues may become "dormant" and non-functioning. HBOT can stimulate these "dormant" tissues and return them to their normal function. In young children, cognitive function and spasticity can also be improved. Hyperbaric oxygen therapy, used in combination with other therapies, ensures the best recovery possible for children with cerebral palsy and traumatic brain injury [33].

Conclusion

This brief review has highlighted some of the beneficial actions of HBO_2 and the data that indicate oxidative stress brought about by hyperoxia can have therapeutic effects. The above study provides a summary of mechanisms, all of which appear to stem from elevations in reactive species. While there has been substantial advancement of the field in recent years, more work is required to establish the place of HBO_2 in 21st century medicine. Investigations of fundamental mechanisms are still needed, and better patient selection criteria would improve cost-efficacy [29-31].

Reference

1. Hampson NB, ed. hyperbaric oxygen therapy: committee report. Kensington MD: Undersea and Hyperbaric Medical Society, 1999.
2. Centers for Medicare & Medicaid Services. Manual section number 20.29: hyperbaric oxygen therapy. In: Medicare National Coverage Determinations Manual. Version Number 3. US Department of Health and Human Services, 2006.
3. British Thoracic Society Guideline for Oxygen Use in Adults in Healthcare and Emergency Settings.
4. Gill AL, Bell CNA. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *QJM:* An International Journal of Medicine. 2004; 97(7):385-395.
5. Edwards ML. Hyperbaric oxygen therapy. Part 1: history and principles. J Vet Emerg Crit Care. 2010; 20(3):284-8.
6. Hendricks P, Hall D, Hunter W, *et al*. Extension of pulmonary O2 tolerance in man at 2 ATA by intermittent O2 exposure. J Appl Physiol. 1977; 42:593-599.
7. Thom SR. Hyperbaric oxygen therapy. J. Intensive Care Med. 1989; 4:58-74.
8. Kemp M, Go YM, Jones DP. Nonequilibrium thermodynamics of thiol/disulfide redox systems: a perspective on redox systems in biology. Fr. Radic. Biol. Med. 2008; 44:921-937.
9. Circu ML, Aw TY. Glutathione and apoptosis. Free Rad Res. 2008; 42:689-706.
10. Valko M, Leibfritz D, Moncol J, *et al*. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007; 39:44-84.
11. Zhang Q, Piston DW, Goodman RH. Regulation of corepressor function by nuclear NADH. Science. 2002; 295:1895-1897.
12. Dennog C, Radermacher P, Barnett YA, *et al*. Antioxidant status in humans after exposure to hyperbaric oxygen. Mutation. Res. 1999; 428:83-89.
13. Chen S, Xiao N, Zhang X. Effect of combined therapy with ephedrine and hyperbaric oxygen on neonatal hypoxic-ischemic brain injury. Neurosci Lett. 2009; 465(2):171-6.
14. Liu XH, Yan H, Xu M, Zhao YL, Li LM, Zhou XH, *et al*. Hyperbaric oxygenation reduces long-term brain injury and ameliorates behavioral function by suppression of apoptosis in a rat model of neonatal hypoxia-ischemia. Neurochem Int. 2013; 62(7):922.
15. Peng Z, Xiao P, Guo H, Liu Q. Effect of early hyperbaric oxygen on neuronal apoptosis and learning and memory of cerebral ischemia-reperfusion injury in rats. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2009; 34(6):468-75.
16. Sun Q, Sun Q, Liu Y, Sun X, Tao H. Anti-apoptotic effect of hyperbaric oxygen preconditioning on a rat model of myocardial infarction. J Surg Res. 2011; 171(1):41-6.
17. Andoh T, Chock PB, Chiueh CC. The roles of thioredoxin in protection against oxidative stress-induced apoptosis in SH-SY5Y cells. J Biol Chem. 2002; 277(12):9655-60.
18. Peng Y, Feng SF, Wang Q, Wang HN, Hou WG, Xiong L, *et al*. Hyperbaric oxygen preconditioning ameliorates anxiety-like behavior and cognitive impairments via upregulation of thioredoxin reductases in stressed rats. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34(6):1018-25.
19. Chen X, Duan XS, Xu LJ, Zhao JJ, She ZF, Chen WW, *et al*. Interleukin-10 mediates the neuroprotection of hyperbaric oxygen therapy against traumatic brain injury in mice. Neuroscience. 2014; 266:235-43.

20. Qi Z, Gao CJ, Wang YB, Ma XM, Zhao L, Liu FJ, *et al*. Effects of hyperbaric oxygen preconditioning on ischemia-reperfusion inflammation and skin flap survival. Chin Med J (Engl). 2013; 126(20):3904-9.
21. Wang C, Ye Z, Zheng J, Liu K, Sun X, Tao H, *et al*. Targeting reactive oxygen species by edaravone inhalation in a rat hyperoxic lung injury model: role of inflammasome. Undersea Hyperb Med. 2013; 40(6):505-11.
22. Zhang Y, Lv Y, Liu YJ, Yang C, Hu HJ, Meng XE, *et al*. Hyperbaric Oxygen Therapy in Rats Attenuates Ischemia-reperfusion Testicular Injury Through Blockade of Oxidative Stress, Suppression of Inflammation, and Reduction of Nitric Oxide Formation. Urology. 2013; 82(2):489 e9-489 e15
23. Hui J, Zhang ZJ, Zhang X, Shen Y, Gao YJ. Repetitive hyperbaric oxygen treatment attenuates complete Freund's adjuvant-induced pain and reduces glia-mediated neuro inflammation in the spinal cord. J Pain. 2013; 14(7):747-58.
24. Tan J, Zhang F, Liang F, Wang Y, Li Z, Yang J, *et al*. Protective effects of hyperbaric oxygen treatment against spinal cord injury in rats via toll-like receptor 2/nuclear factor-kappa B signaling. Int J Clin Exp Pathol. 2014; 7(5):1911-9.
25. Huang H, Xue L, Zhang X, Weng Q, Chen H, Gu J, *et al*. Hyperbaric oxygen therapy provides neuroprotection following spinal cord injury in a rat model. Int J Clin Exp Pathol. 2013; 6(7):1337-42.
26. Lou M, Wang JH, Qian QQ, Wen SQ, Ding MP. Effect of hyperbaric oxygen treatment on mitochondrial free radicals after transient focal cerebral ischemia in rats]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2008; 37(5):437-43.
27. Tian X, Wang J, Dai J, Yang L, Zhang L, Shen S, *et al*. Hyperbaric oxygen and Ginkgo Biloba extract inhibit Abeta25-35-induced toxicity and oxidative stress in vivo: a potential role in Alzheimer's disease. Int J Neurosci. 2012; 122(10):563-9.
28. Wang Q, Liu L. Hyperbaric oxygen medicine course China Military Medical Science Press, 2006.
29. Chen T, Zhou Y, Liu J, Xu B, Wu Z, Li D. Biological effects of hyperbaric oxygen on human severe periodontitis. Undersea Hyperb Med. 2006-2002; 29:159-66.
30. Teughels W, Quirynen M, Jakubowics N. Periodontal microbiology. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, editors. Carranza's Clinical Periodontology. 11th ed. St. Louis, Missouri: Saunders Publication, 2012.
31. Gill AL, Bell CN. Hyperbaric oxygen: Its uses, mechanisms of action and outcomes. QJM. 2004; 97:385-95.
32. Rusyniak DE, Kirk MA, May JD, Kao LW, Brizendine EJ, Welch JL, *et al*. Hyperbaric oxygen therapy in acute ischemic stroke: results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. Stroke. 2003; 34(2):571-4. Pmid: 12574578
33. Sena E, Wheble P, Sandercock P, Macleod M. Systematic review and meta-analysis of the efficacy of tirilazad in experimental stroke. Stroke. 2007; 38(2):388-94. Pmid: 17204689