Hyperbaric Oxygenation – Indications and Contraindications

Abstract: The aim of this work was to conduct a literature review involving the basic concepts of hyperbaric oxygenation, the types of hyperbaric chambers, physiological mechanisms, their indications and contraindications, advantages and disadvantages, volumetric effects, solubility, biochemical and cellular effects; Therapeutic indications and complications associated with hyperbaric oxygenation.

Keywords: tissue hypoxia, hyperbaric oxygen therapy, indications.

INTRODUCTION

Hyperbaric Oxygen Therapy (HBO) is considered to be a method in which the patient breathes 100% oxygen into a hyperbaric chamber at a pressure greater than atmospheric pressure (usually two to three times atmospheric pressure at sea level). Regarding its designation as to etiology, the term hyperbaric is formed by two Greek radicals (Hyper and Baros), meaning the first Excess, and the second Pressure. It is basically oxygen inhalation at high pressure, often associated with artificial respiration. Although hyperbaric oxygenation has therapeutic applications in human beings, it is only expectable that its utilization carries a risk of permanent tissue alteration, once oxygen at increased pressures is relatively employed in synthetic gaseous environment, such as astronauts and aquanauts. In experimental animals, pathologic changes attributable to exposure to excess oxygen have been definitely detected in the lungs, eyes as well as in the Central Nervous System. The aim of this article was to explain the main effects of hyperbaric oxygenation in the human organism, as well as its indication, contraindications, and protocols, according to the Brazilian Society of Hyperbaric Medicine.

LITERATURE REVIEW

General Characteristics of Oxygen and the Living Beings

Oxygen is a nonmetal, colorless, odorless and tasteless element that is used by animals and plants for respiration. Aquatic being also need it, and are able to get it by direct breathing, that is, by emerging from lakes, rivers or from the ocean itself, or also by removing it from the water, such as the majority of the ocean fishes do. Oxygen molecules are not the only form of oxygen present in the atmosphere; it can also be found as ozone (O₃) and carbon dioxide (CO₂). In normal conditions the being that make use of it are totally adapted to its concentration in their environment. However, when it comes to hyperbaric oxygenation, high concentrations of oxygen may help healing pathological conditions, but it can also jeopardize other situations. Pathological changes have been reported in the eyes, lungs and in the Central Nervous System.

Single-celled organisms can easily obtain oxygen and excrete carbon dioxide by simple diffusion between the cell and its environment since the beginning of life on Earth. Eukaryotes, on the other hand, have great amounts of oxygen located in the plasmatic membrane, due to the important fact that oxygen is utilized in the mitochondrias for ATP production, which is used more or less intensively, depending on the cell needs (Baudouin-Cornu, P., & Thomas, D. 2007). In this sense, as mammals developed, a compartmentalization of oxygen began to be arranged in multiple processes which induced the signaling of oxygen levels, in different parts of the cells. This was necessary because the more intense the metabolisms of a cell is, the greater is the amount of oxygen needed, and its storage was then necessary. Additionally, within the same organisms, there have been lots of different cell types with different needs, reaching the number of over 200 different cell types in the human body (Acquisti, C. et al., 2007).
Mammals, the most developed kind of animals concerning cell complexity and interaction, require a more specialized and remarkably complex cardio-respiratory system, so that they can provide the cells with all the nutrients they need to perform their functions and keep homeostasis (Thannickal, V. J. 2009).

The process of arteri alization is essential for the dynamics of breathing and includes oxygen uptake and carbon dioxide excretion of mixed venous blood into the lungs; accomplished by gas exchange, and requires several different interconnected steps. The first of them is ventilation, a cyclic process of inspirations and expirations during which the gas is supplied to and extracted from the alveoli (Berry, M. J. et al., 1996). The second one is diffusion, that is, the process of moving the gases through the alveolar-capillary membrane (Pack, A. et al., 1977). The third step is the pulmonary blood flow, which has the function of transporting gases out of the lungs. The fourth step is the coupling of ventilation and blood flow in various regions of the lung in order to allow the efficient exchange of gases. And finally, the last step, the gas transport of oxygen and carbon dioxide through the blood. Thus, the lungs have secondary functions, such as pH regulation, filtration of air particles from the circulation, and also the function of acting as a blood reservoir. In addition to everything mentioned above, the lungs can also metabolize many vasoactive hormones, including prostaglandins, histamine, serotonin and angiotensin (Felici, M. et al., 2005).

The way that oxygen acts in the living tissue is not entirely understood yet, especially in wound healing. However, it is widely recognized that it plays a role in almost every stage of the wound healing process. Once the body is injured, the cytokines and prostaglandins unleashed by the injured cells begins to interact to chemotactically recruit and attract specialized cell types to the site of injury to repair the damage (Alibardi, L. 2016). It is also necessary to develop increased need for bacterial defense to avoid infection, collagen synthesis to rebuild the destroyed tissues, and more importantly, to develop angiogenesis to allow the blood supply and other reparative functions (Ferrara, N. 2010). It is only expectable that all these processes demand great amounts of energy and effort for tissues to be repaired, and based on this hypothesis, studies have indicated that the main function of oxygen is energy production through cellular respiration within the mitochondria. The phosphorylation process begins with the acceptation of electrons at the end of the transport chain, to convert ADP to ATP (REF). Therefore, when an area of the human tissues does not receive the necessary amount of oxygen supply, a condition known as hypoxia, it can slow or even cease the course of the healing process (Abraham, S. et al., 2005).

Clinical observations have undoubtedly shown that tissues that do not bleed do not heal properly, because the oxygen flow through microcirculation is a vital event for the healing process, including for collagen formation as also for infection resistance, mainly because of the nutritive flow of oxygen which not only provides energy for the metabolism of high producing ATP cells, as it also helps combating anaerobic infection when they are present (REF). ATP is even more necessary for the healing process as a whole because wounded tissues needing repair require cell multiplication and rearrangements in order to reestablish the damaged fragments of the wounds (Van den Thillart, G. et al., 1990; Sade, J., & Fuchs, C. 1996; & Tos, M., & Stangerup, S. E. 1984).

**Hyperbaric Oxygenation Situations**

The reaction of the human terminal airway to hyperbaric oxygen is reminiscent of the changes that can be observed similarly in animal lungs, consisting basically of prominent intra-alveolar fibrin exudate, frequently associated with layering of fibrin on the walls of alveoli, alveolar ducts and also on bronchioles, to form hyaline membranes. In this sense, the alveolar lining cells may become hyperplastic, with a real possibility that the use of 90% to 100% oxygen for a long period is hazardous only for those patients who already suffered from pulmonary infections, preexisting interstitial fibrosis, or pulmonary edema for causes such as congestive failure or uremia. As for what concerns the eyes, high oxygen tension in the infant is retrolental fibroplasia (retinopathy of prematurity), a vasoproliferative reaction consisting of endothelial and mesenchymal cells in the inner layer of the retina and eventually leading to retinal detachment. Necrosis of the visual cell layer of the retina have also been demonstrated in experimental animals.

The lesions of hyperbaric oxygenation may also affect the central nervous system, and consist of selective neuronal necrosis observed in distinct distribution. One of the main representative is the Bert effect, which takes place at oxygen pressures of > 3 ATA. Support for the occurrence of the lesions being related to excessive tissue oxygenation arises from the observation that unilateral cerebral ischemia (induced by unilateral carotid artery ligation) protects the ipsilateral half of the animal brain form the oxygen-induced lesions.

**Hyperbaric Chamber** (Types Monopatient Camera)

According to the Brazilian Society of Hyperbaric Medicine, the installation of monopatient chambers should follow the guidelines of the ABNT Standards. NBR 12188 (Swarts, J. D. et al., 2012; & Cinamon, U., & Sadé, J. 2003). In those cases where the compression has to be performed with air, it will be necessary to install specific valves properly identified by the manufacturer, being essential that the applied air has the medicinal characteristics. This type of camera is designed for a person in exclusive hospital use, ensuring and ensuring comfort and privacy, and enhancing safety even
more, since the hospital environment provides Intensive Care Unit with infusion pump and mechanical ventilation at the time of implementation of the treatment. The hyperbaric chamber could be described as a sealed compartment, where pure oxygen is pumped through properly calibrated and hospital compressors.

It has a cylindrical shape, made of steel, with the upper part made in acrylic so that its exterior can be easily seen. Doors should have perfect seals to withstand air pressurization at three absolute levels: normobaric (one atmosphere); superbaric (two atmospheres); and hyperbaric (above two atmospheres). This pressurization is done directly with 100% oxygen and in each session of 60 minutes an average of 30 cubic meters of oxygen is consumed (variable values according to the pressurization chosen and adjusted). In order not to cause claustrophobia in treatment patients, this type of chamber has the advantage that only the patient is compressed by the inhalation of pure oxygen and can be decompressed instantly if necessary. It is also operable by only one person, with the help of a doctor and a trained nurse. The cost of individual chambers is much lower as well as the space they occupy in a much smaller hospital resuscitation center. These chambers, for reasons of ergonomics and practicality, can be taken to the emergency room in ambulances. With regard to disadvantages, the patient is in fact more isolated and the use of pure oxygen increases the danger of fire and explosion since this gas is the fundamental element for combustion, demanding compliance with severe safety standards (Wittmaack, K. 1918).

Multi-Patient Camera

The multi-chambered chambers, as the name says, were designed to hold more than one patient inside. They are pressurized with compressed air, the oxygen being inhaled by masks or hoods. They also allow the stay of other people with the patient(s) (Wittmaack, K. 1918).

Advantages - Enable follow-up by the physician, which can become important in severe hyperbaric accident. In cases of surgery it is essential to use this type of camera. In addition, a possible case of Decompressive Disease or Arterial Gas Embolism is better attended by these chambers, who can withstand the pressures necessary to treat these accidents (Weitz, J.I. 2011).

Disadvantages - Stationary chambers are complex units. Its installation demands the solution of some technical problems of certain amount. It needs qualified personnel for the operation of the chamber, and there may be organizational problems within the hospital structure. The cases that need a wide contact of oxygen with the tissues cannot be fulfilled, since the use of oxygen throughout the chamber, besides implying a high cost, would increase the risk of fire and explosion. Usually takes up large physical space. The medical and nursing team (internal guide) is exposed to the hyperbaric environment, which implies in the selection of qualified people for this situation, with admissional medical examination (selection) and mandatory periodic control.

Physiological Mechanisms

Under normal conditions, we are all subjected to atmospheric pressure corresponding to an atmosphere of pressure - 1 atm. However, at every 10 (ten) meters of depth, an atmosphere increases under pressure on the pressurized body. Hyperbaric treatments use a pressure ranging from 2.5 to 3.0 ATA (ATA: atmospheric pressure + depth pressure). In these pressures we suffer physical effects, explained by the laws of diving physics.

Effects on partial pressure (PP) of gases

According to Dalton’s Law, the total pressure of a gas equals the sum of the partial pressures of this gas in the mixture, that is, as we increase the pressure inside the hyperbaric chamber, we increase the partial pressures of the gases in the chamber. The increase of PPO2 in turn leads to an increase in its plasma solubilization (Cinamon, U. 2009; Lee, D. H.et al., 2005; & Colhoun, E. N. et al., 1988). Volumetric effects According to Boyle-Mariotte’s law the pressure and volume vary in inverse proportion (at constant temperature). It means that all the aerial organic cavities, especially the pneumatic objects, will suffer the same volume variations (digestive tract, ears, paranasal sinuses) (Mangabeira-Albernaz, P. 1933; & Bento, R. F. et al., 1992).

Effects on solubility

According to the precepts of Henry’s law, when we breathe pure oxygen in the hyperbaric environment, we observe a significant increase of the arterial oxygen pressure that can exceed 2000 mmHg to an environmental value of 3 ATA. Oxygen is then dissolved and transported by plasma more than 22 times. Thus, by calculating the plasma content of dissolved oxygen in plasma, it is observed that, at sea level, the amount of oxygen carried by the plasma is about 0 ml / dl, while at 3 ATA, the dissolved oxygen is approximately 6 ml / dl. This latter value is sufficient for the consuming cells at rest without need of any contribution of oxygen bound to the hemoglobin.
Biochemical and Cellular Effects

Direct Effects

The increase of PPO2, according to Dalton's law, and above all the great increase of transport and the availability of plasma O2 by Henry's law, oxygen inhaled through hyperbaric therapy would be able to act in all pathologies whose etiologies were linked tissue hypoxia. An example is the rise of hyperbaric O2 by capillarity to terminal ischemic territories and its transfer by simple diffusion gradient (Lee, D. H. et al., 2005; & Colhoun, E. N. et al., 1988).

Indirect Effects

Infected tissues have most of the time, and depending on other concomitant pathologies, such as cardiac diseases, for example, decreased capacity of PMN neutrophils (Mangabeira-Albernaz, P. 1933; & Bento, R. F. et al., 1992). By reversing tissue and cellular hypoxia through oxygen-therapy, this type of first-line immune defense is also restored, as is the phagocytic capacity of some bacteria. Taking into account also that some bacteria live exclusively in the absence of oxygen, such as anaerobes, for example Clostridium perfringens, it is expected a bactericidal effect for such species, and bacteriostatic for others, such as some species of Escherichia and Pseudomonas.

OHB is also able to suppress the clostridial production of alpha-toxin (Doyle, W. J. 2000; Swarts, J. D. et al., 2010; & Koç, A. et al., 2003), contributing to the reversion of hypoxia in the injured tissues, and stimulating the formation of the collagen matrix, essential for angiogenesis and healing. It is also well known that the alternation hyperoxia/normoxia constitutes a potent stimulus for vascular neoformation of healing areas (Cinamon, U. 2009; Lee, D. H. et al., 2005; & Colhoun, E. N. et al., 1988), consequently improving microvascular perfusion. This effect is most likely related to the increased synthesis of nitric oxide (NO) supplied by hyperbaric oxygen. In tissues submitted to acute ischemia, HBO also showed benefit. In fact, animal studies using models of reperfusion injury and cutaneous grafts show that HBO inhibits neutrophil adhesion and post-ischemic vasoconstriction (Lee, D. H. et al., 2005; & Colhoun, E. N. et al., 1988; Siegel, M. I., & Doyle, W. J. 1975). In acute carbon monoxide (CO) poisonings, carboxyhemoglobin (HbCO) is formed, a molecule about 240 times more stable than oxyhemoglobin. The half-life of HbCO in ambient air is 520 minutes. By breathing 100% O2 at atmospheric pressure it decreases to 80 minutes, and with hyperbaric oxygen at 3 ATA it is reduced to 23 minutes. Studies with both animals and clinical trials have found that early administration of HBB resulted in a decrease in the appearance of neurological lesions / sequelae due to exposure to carbon dioxide.

Therapeutic indications

The Brazilian Federal Council of Medicine, through CFM Resolution no. 1.457 / 95, approved the indications below for HBOT, establishing criteria and guidelines for the proper application of HBO to be performed by a physician or its supervision, not considering hyperbaric oxygen therapy as pure oxygen in normobaric environments or topical applications by pressurized tents. The currently recognized clinical indications of HBO are:

- Decompressive diseases;
- Gas emboli;
- Traumatic air embolism;
- Carbon monoxide poisoning or inhalation of smoke;
- Poisoning by cyanide or cyanide derivatives;
- Gaseous gangrene - Fournier's Syndrome;
- Other necrotizing soft tissue infections: cellulites, fascitis and myositis;
- Acute traumatic ischemias: crush injury, syndrome compartmental, reimplantation of amputated extremities and others;
- Acute vasculitis of allergic, drug or toxin etiology (arachnids, snakes and insects);
- Thermal and electrical burns;
- Refractory lesions: skin ulcers, pre-diabetic lesions, decubitus, autoimmune vasculitis ulcer, suture dehiscence;
- Radiation damage: radiodermatitis, osteoradionecrosis and actinic mucous membranes; - compromised or risky patches or grafts; and
- Osteomyelitis
- Acute anemia (in cases of impossibility of blood transfusion)

According to Protocol of the Brazilian Society of Hyperbaric Medicine the HBO is reserved for (3):

- Recovery of suffering tissue;
- Clinical conditions in which it is the only treatment;
- Serious and / or complex injuries; - Failure to respond to usual treatments; - Injuries in need of surgical debridement;
- Fast worsening with risk of death;
- Lesions in noble areas: face, hands, feet, perineum, genitalia, breasts
• Refractory lesions; frequent recurrences.

Protocols
The protocols vary widely according to the case in question and are influenced by the pathology underlying treatment, especially if acute or chronic due to the predominant cell types in each type of inflammation, including subclinical inflammation. In general, the treatments are performed in sessions of 90 to 120 minutes duration, with pressures ranging from 2 to 3 ATA, at the discretion of the physician and the pathology. In specific situations such as diving accidents or gas intoxication, larger pressures and longer duration of treatment may be required. The sessions can vary from one to three per day and depending on the stage of the treatment may be used to use the sessions on alternate days. The number of sessions varies on average from 10 to 30 sessions for acute cases and from 30 to 60 in chronic cases (Sade, J., & Fuchs, C. 1996; Tos, M., & Stangerup, S. E. 1984; & Swarts, J. D. et al., 2012). The HBV has side effects that are related to the variation of oxygen pressure and/or toxicity, depending on the dose of hyperbaric oxygen offered and the time of exposure to the hyperbaric treatment. Adverse effects may include: pulmonary toxicity; pulmonary edema, dry cough, retrosternal pain, hemoptotic sputum; neurological toxicity (paraesthesia, paresis and seizure); otological barotraumas; discomfort in sinuses and transient visual changes. The vast majority of side effects and complications from hyperbaric therapy are due to Boyle's Law, manifesting during compression (increased pressure within the hyperbaric chamber).

Barotraumas
These are traumas caused by incapacity of pressure equalization in closed cavities. When the air is decompressed, it can expand and traumatize the walls of the cavities, causing pain, bleeding or perforations. The most commonly affected cavity is the OM, which can cause varying degrees of TM injury culminating in rupture. The injury occurs when the pressure equalization inside the OM and the external environment cannot be equalized through the auditory tube. By a similar mechanism there may be barotraumas in the paranasal sinuses or other air spaces, such as cavities closed in teeth, behind diving masks and more rarely of the inner ear with acute vertigo syndrome (Diamant, M. 1940; Wittmaack, K. 1918; & Hill, C. A. 2011).

Gas Artery Embol
Gas Arterial Embolism is rare in HBV clinics, occurring much more commonly in divers because of rapid pressure variations (Weitz, J.I. 2011; & Ho, W.K. 2010). It happens at the end of the treatment, during the decompression when the patient does not exhale the air of his lungs. By Boyle's law, the pressure inside the chamber decreases, so that if there is no exhalation of air there will be a pulmonary rupture with air entering the arterial circulation. This complication can occur in patients with pneumopathies that trap air in the alveoli due to obstructed bronchioles (Wells, P. S. et al., 2000).

Decompressive Disease (DD)
DD is caused by nitrogen bubbles that form during decompression after hyperbaric exposure. These blisters can form in the blood, blocking the microcirculation and in various tissues, such as the skin, the nervous system and the joints. Besides noncompliance with the norms of the decompression tables, other factors may facilitate the onset of the disease: fatigue, stress, dehydration, etc. (Lippmann, J., & Mitchell, J. 2005). Patients treated with hyperbaric oxygen are not at risk for DD, since they are eliminating nitrogen throughout the treatment. In a multipatient chamber, if air is inadvertently administered by the mask as opposed to oxygen, DD becomes a theoretical possibility. With a clinical protocol breathing O2 for 2 hours at 2 ATA, the DD would not cause problems, even if the treatment had gone wrong. A 2.4 ATA could be a problem. It is important that there are free mechanisms of failure that can assure the administration of O2 to the patients. The main concern is with the internal guide who is supervising the patients, since he/she breathes compressed air and therefore is subject to DD in case of omission of the decompression (pathologies that demand prolonged treatment or to great depths require stops for decompression) or situation that increases its metabolic demand. Therefore, the internal guides should be oriented on the main symptoms of DD and to recognize their signs; if they present them, they should seek immediate assistance to be recompressed, at the risk of worsening the condition that can lead to sequelae (Mangabeira-Albernaz, P. 1933). The DD is classified into two clinical presentation forms: DD type 1 and DD type 2. DD type 1 predominates cutaneous and articular signs and symptoms: skin rash, pruritus, arthralgia, fatigue. In DD type 2, which may be an evolution of type 1 DD when it is not treated, neurological symptoms such as paralysis (monoparesis or plegia due to spinal cord injury, hemiplegia) or coma due to brain injury are present (Thom, S. R. et al., 2015).

INTOXICATION BY OXYGEN
Neurological Toxicity
The symptoms of neurological toxicity (Paul Bert effect) are acute and include: facial pallor, diaphragnostic spasms, diaphoresis, bradycardia, anguish, visual field impairment, tinnitus, auditory hallucinations, vertigo, seizures, nausea, vomiting, syncope, lips, malar, nose and eyelids (Udwaadia, F. E. 2000). Seizures are very rare and usually only
occur in treatments with pressures close to or above 3 ATA, or in those individuals with predisposing conditions: hyperthyroidism, fever, history of seizures, etc.

**Pulmonary Toxicity**
Symptoms of pulmonary toxicity (Lorraine Smith Effect) are more insidious and less significant in conventional HBO sessions where exposure to O2 and treatment pressures are limited. However, there are differences in individual susceptibility to pulmonary toxicity and care should be taken in cases where the patient is ventilated with high concentrations of O2 at intervals between two sessions of HBV, or if HBOT is very intense (more than one treatment per day long-term) or prolonged (one treatment per day for a long period) (Demchenko, I. T. et al., 2007).

**Contraindications**
The contraindications are relatively few. However, some pre-existing conditions or concurrent therapies may be considered as absolute or relative contraindications to HBO (Demchenko, I. T. et al., 2007).

**Absolute contraindications**
The untreated pneumothorax is the only absolute contraindication that is a consensus among the authors (Koç, A. et al., 2003). Hemodynamic instability and some drugs are also described: adriamycin, bleomycin, disulfiram, cisplatin, sulfamilon, cyclophosphamide, doxorubicin.

1. **Doxorubicin (Adriamycina)**
Experiments in guinea pigs have shown that this chemotherapeutic produces 87% mortality when combined with HBO. It is recommended to wait at least one week after the last dose of this medicine to restart HBOT.

2. **Disulfiram (Antabuse)**
This drug blocks the production of superoxide dismutase, which is the body's greatest protection against oxygen poisoning. For this reason it is contraindicated in patients who need to undergo several HBO sessions.

3. **Cis-Platinum**
This drug is used in the treatment of various types of cancer and interferes with DNA synthesis, retarding fibroblast production and collagen synthesis. It appears that HBOT can increase the cytotoxic effect of this drug on the tissues, preventing the healing of wounds.

4. **Acetate Mafenide (Sulfamylon)**
This product is very effective in the treatment of bacterial infection in burned, surpassing the therapy by silver nitrate. This drug is an inhibitor of carbonic anhydrase, resulting in hypercapnia and, consequently, causing peripheral vasodilation. If a burned patient should be subjected to HBOT, all mafenide ointments should be carefully removed. It is recommended that silver sulfadiazine (Silvadene, Demazine and others) be replaced (Commons, K. H. et al., 2013).

5. **Untreated Pneumothorax**
Patients with "untreated pneumothorax" are not placed in a hyperbaric environment, since there is a risk of hypertension.

6. **Asthma**
Patients with asthma should not be placed in a hyperbaric environment.

7. **Equipment**
Some chips with electric current used in orthopedic surgeries, especially spine, makes it necessary to contact the engineer responsible for manufacturing the material, as a rule do not treat it in a hyperbaric chamber due to static electricity.

**Relative Contraindications**
Infections of the Upper Respiratory Tract and Chronic Sinusitis These pathologies make it difficult to compensate for the OM and the paranasal sinuses. It is prudent to interrupt the hyperbaric treatment for 3 (three) or 4 (four) days while proceeding to clinical treatment (Demchenko, I. T. et al., 2011).

- Convulsive Pathologies Patients with convulsive pathology are more susceptible to O2 intoxication (Paul Bert effect). If HBO is essential, it is recommended to use preventive anticonvulsive medication, such as benzodiazepines (Üstündağ, A. et al., 2012).
Other relevant contraindications are emphysema with CO₂ retention, history of spontaneous pneumothorax, history of thoracic surgery, history of otosclerosis surgery, viral infections, high fever, congenital spherocytosis, claustrophobia, and history of optic neuritis.

- Diabetes monitoring of the glycemia of these patients and perform an insulin regimen, according to medical prescription.

**CONCLUSIONS**

Hyperbaric therapy has a wide range of indications, with some specific contraindications. Its use is indicated for patients whose pathologies have as etiological agents, tissue hypoxia. However, its use must be performed with medical criteria and careful diagnosis to avoid complications due to high concentrations of oxygen.

**REFERENCES**