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New Developments in Hyperbaric Oxygen Therapy

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Abstract

Hyperbaric Oxygen Therapy, or HBOT, is a form of treatment based on the inhalation of 100% pure oxygen while subjected to closed chamber or room at pressures greater than sea level (1 atmosphere, ATA) (Howell et al., 2018; Kocaman, 2020). HBOT is administered through either a mono-place chamber or a multi-place chamber. Mono-place chambers are pressurized with oxygen and are equipped to handle a single person at a time. Multi-place chambers, on the other hand, can accommodate up to 20 people at a time, including medical personnel and intubated patients. These chambers are pressurized with air, and pure oxygen is administered via facemask, hood tent, or endotracheal tube (Gill & Bell, 2004; Howell et al., 2018). Oxygen is primarily used by the body in the formation of ATP, the molecule responsible for fueling cellular processes. When body tissues are injured or damaged, the energetic demand increases, and consequently more oxygen is needed (Kahle & Cooper, 2020). HBOT increases the body's arterial and tissue oxygen tension, augmenting the amount of oxygen that the blood plasma can carry. This can create a number of beneficial biochemical, cellular, and physiologic effects (Tibbles & Edelsberg, 1996).

Keywords

Hyperbaric Oxygen Therapy, Environmental Physiology, Decompression Illness, Carbon Monoxide Poisoning, Chronic Wound Treatment, Hyperbaric Chamber

Disciplines

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INTRODUCTION

Hyperbaric Oxygen Therapy, or HBOT, is a form of treatment based on the inhalation of 100% pure oxygen while subjected to closed chamber or room at pressures greater than sea level (1 atmosphere, ATA) (Howell et al., 2018; Kocaman, 2020). HBOT is administered through either a mono-place chamber or a multi-place chamber. Mono-place chambers are pressurized with oxygen and are equipped to handle a single person at a time. Multi-place chambers, on the other hand, can accommodate up to 20 people at a time, including medical personnel and intubated patients. These chambers are pressurized with air, and pure oxygen is administered via facemask, hood tent, or endotracheal tube (Gill & Bell, 2004; Howell et al., 2018). Oxygen is primarily used by the body in the formation of ATP, the molecule responsible for fueling cellular processes. When body tissues are injured or damaged, the energetic demand increases, and consequently more oxygen is needed (Kahle & Cooper, 2020). HBOT increases the body's arterial and tissue oxygen tension, augmenting the amount of oxygen that the blood plasma can carry. This can create a number of beneficial biochemical, cellular, and physiologic effects (Tibbles & Edelsberg, 1996).

The first documented use of Hyperbaric Therapy occurred in 1662, even before oxygen was discovered, when a British physician created an airtight container, called a 'domicilium', in which the pressure could be altered using bellows and valves (Carden, 2020; Gill & Bell, 2004). It was not until 1872 that this process was scientifically explained by Paul Bert, who wrote about the physiological effects of oxygen under increased pressure which granted him the title of 'the Father of Hyperbaric Medicine' (Carden, 2020; Gill & Bell, 2004). After this point, physicians and scientists began to explore the use of HBOT to treat a variety of diseases and conditions, including diabetes, arthritis, syphilis, and carbon monoxide intoxication, despite the lack of

empirical evidence supporting its efficacy (Carden, 2020; Kocaman, 2020). Since then, however, extensive research on the use of hyperbaric oxygen has been performed, especially by the United States Naval Academy in the context of deep-sea diving and the treatment of decompression sickness (Behnke, 1945; Carden, 2020)

PHYSIOLOGY

As noted previously, Hyperbaric Oxygen Therapy uses pure oxygen at high pressure in a closed environment to treat numerous pathologies. The primary effect of HBOT is hyperoxia while the secondary effects are the result of controlled oxidative stress (Choudhury, 2018). These phenomena, in principle, are governed by the Gas Laws (Choudhury, 2018; Kocaman, 2020; Leach, 1998; Tibbles & Edelsberg, 1996).

Dalton's law states that in a mixture of gases, the sum of the partial pressures of the gases will equal the total pressure in the system (Cosgrove & Bryson, 2001; Choudhury, 2018; Gill & Bell, 2004).

Henry's law states that at a constant temperature, the amount of gas that dissolves in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (Cosgrove & Bryson, 2001; Choudhury, 2018; Kocaman, 2020).

Primary Effects

Oxygen is transferred to cells via plasma, and the initial diffusion of oxygen into the plasma can be understood by the application of Dalton's Law and Henry's Law (Cosgrove & Bryson, 2001; Choudhury, 2018). Air is composed of approximately 21% oxygen and 79% nitrogen (Cosgrove & Bryson, 2001). The consequence of Dalton's Law is that the partial pressure of oxygen in the air is solely based on the percentage of oxygen in the atmosphere and

the ambient pressure, which may vary based on altitude and other factors (Choudhury, 2018). The partial pressure of oxygen (PaO_2) in air at sea level (1 ATA = 760 mmHg) is calculated as 160 mmHg (Cosgrove & Bryson, 2001). Air in the trachea, however, has a similar partial pressure to humidified water (47 mmHg); thus, a more appropriate calculation of inspired oxygen at sea level would result in a PaO_2 of 150 mmHg. Deoxygenated blood entering the lung contains a PaO_2 of 40 mmHg. After the diffusion of oxygen from the environment to the lungs, the final PaO_2 in the blood is 100 mmHg (Choudhury, 2018) and 50 mm Hg in the tissues (Gill & Bell, 2004). These PaO_2 values are dependent on the gradient between the partial pressure present in the alveoli and in the deoxygenated blood (Choudhury, 2018). Therefore, a larger difference in these two partial pressures produces greater oxygen diffusion from the alveoli into the plasma (Tibbles & Edelsburg, 1996). Henry's law can be used to determine how much oxygen is *dissolved* in plasma. According to calculations using the O_2 solubility coefficient, the PaO_2 in the blood and tissues at normobaric conditions allows for the maximum delivery of 0.3 mL oxygen per deciliter of blood (Choudhury, 2018; Tibbles & Edelsburg, 1996) but tissues require 5-6 mL O_2/dL of blood for homeostasis (Choudhury, 2018). Hemoglobin makes up for this difference; in fact, most oxygen carried in the blood is bound to hemoglobin (Gill & Bell, 2004).

Hyperbaric Oxygen Therapy takes advantage of both Dalton's law and Henry's law to increase the alveoli-plasma gradient and solubility of oxygen, respectively. To portray this numerically, administering 100% oxygen at 3 ATA increases arterial oxygen tension to 2000 mmHg and tissue oxygen tension to 500 mmHg, allowing the delivery of 6 mL O_2/dL (Gill & Bell, 2004). Evidently, following HBOT, the dissolved oxygen carried by the plasma is sufficient in maintaining homeostatic conditions without a contribution from hemoglobin (Kocaman,

2020). As a result, this oxygen can be carried to tissues even with impaired hemoglobin oxygen carriage, such as the case in carbon monoxide poisoning and severe anemia. The other advantage of using plasma to distribute oxygen rather than hemoglobin is that with plasma, oxygen can reach physically obstructed areas (like clots or occlusions) where red blood cells cannot pass (Gill & Bell, 2004).

Secondary Effects

The primary effects of HBOT include correcting the hypoxic state by increasing oxygen delivery and tension, but it is important to note that the application of HBOT to treat many diseases derives from the secondary effects of hyperoxia at pressure (Choudhury, 2018). The secondary, or indirect effects of HBOT, include the increase of the generation of oxygen free radicals (ROS), the increase in the body's healing ability & immunity, vasoconstriction, angiogenesis, and the decrease in edema (Sureda et al., 2016; Choudhury, 2018; Kahle & Cooper, 2020). These effects will be specifically addressed in relation to their clinical application(s) in the following pages.

THERAPEUTIC APPLICATIONS

Decompression Illness

Decompression illness denotes two pathological syndromes—arterial gas embolism (AGE) and decompression sickness (DCS)—that are caused by intravascular bubbles formed as a result of a reduction in environmental pressure (Vann et al., 2011). Another gas law, Boyle's law, explains the root of these syndromes as well as the beneficial effects of HBOT for treating them. *Boyle's law* states that at a constant temperature, the volume of gas in an enclosed space is proportional to the pressure exerted on it (Tibbles & Edelsburg, 1996; Gill & Bell, 2004).

Arterial gas embolism and decompression sickness have historically been associated with recreational diving (Diaconu et al., 2018). As a diver descends in the water column, the increasing barometric pressure has two major effects. The first is mechanical: in the context of Boyle's law, the volume of any gas-containing space in the body is reduced. Thus, if one starts off with X volume in the lungs on the surface and breaths to a depth without breathing any additional gas, X will be halved (X/2). If one breathes from a gas source while at that depth, the lungs will return to X. Should the diver then swim back to the surface, the X will double (2X). This enlarging volume of gas is typically exhaled, but in cases that it is not (such as breath holding or rapid ascent) then mechanical forces can result in disruption of lung tissue, causing pulmonary overinflation (Vann et al., 2011; Hamm, 2019; Neuman, 2002). An example of a pulmonary overinflation syndrome is AGE. In this condition, expanding gas ruptures alveoli capillaries (pulmonary barotrauma) and is forced into the pulmonary vasculature and arterial circulation (Neuman, 2002; Vann et al., 2011). Aside from diving injury, arterial gas embolism may be caused by a number of iatrogenic reasons including mechanical ventilation, central line placement, and hemodialysis (Kocaman, 2020; Gill & Bell, 2004). In non-fatal cases, air bubbles partially block circulation. The clinical picture is aggravated, however, when platelets, leukocytes, fibrinogen, and thrombin adhere to the bubble, initiating the thrombotic process and causing deterioration of the vessel (Kocaman, 2020). These situations are manifested in the clinical effects, which range from muscle and joint pain to more life-threatening problems like Acute Respiratory Distress Syndrome (ARDS), brain edema, lack of brain metabolism, and sudden death (Kocaman, 2020; Gill & Bell, 2004; Vann et al., 2011).

The second category of physiological problems associated with decompression is based on Dalton's law and Henry's law (see page 3) (Choudhury, 2018). As a diver descends, the

partial pressures of the gases they breathe is increased, which is reflected in alveolar gas and arterial blood. Eventually, increasing amounts of gas are driven into solution in the body tissues. When using air as a breathing medium, nitrogen gas is driven into solution. Depending on the amount of gas driven into solution, a varying number of bubbles will form during decompression due to the reduction in ambient pressure (Vann et al., 2011; Neuman, 2002). This gas phase causes the signs and symptoms that are collectively referred to as DCS. Like AGE, these run on a spectrum from rash to extreme joint pain ('the bends') paralysis, seizures, and even death as a result of the blocking of lymphatics, veins, and arteries by the gas bubbles (Tibbles & Edelsburg, 1996; Vann et al., 2011; Hamm, 2019; Neuman, 2020).

HBOT is widely accepted as the only treatment for decompression sickness and arterial gas embolism (Vann et al., 2011; Kocaman, 2020). During pressurization, also known as the compression phase of HBOT, a contraction occurs in the gas-containing cavities of the body (as predicted by Boyle's law), which helps to decrease the air bubbles and relieve the pressure present in the tissue and intravascular area (Kocaman, 2020; Tibbles & Edelsburg, 1996; Gill & Bell, 2004). Additionally, hyperbaric oxygen hastens the dissolution of the inert gas bubble by replacing the inert gas with oxygen, which is then rapidly metabolized by the tissues. It can also serve to oxygenate compromised tissues and ameliorate the inflammatory responses that contribute to tissue injury (Vann et al., 2011). In one case, administering 100% oxygen at 2.8 ATA reduced bubble volume by almost two thirds (Tibbles & Edelsburg, 1996).

Carbon Monoxide Poisoning

Carbon monoxide poisoning is the most common cause of death by poisoning in the United States (Tibbles & Edelsburg, 1996). Upon inhalation, CO binds to hemoglobin due to its high affinity as a gas, creating reduced arterial oxygenation and hypoxia within the cell at the

mitochondrial level (Kocaman, 2020; Gill & Bell, 2004). This creates a number of symptoms from dizziness and headache to seizures, dysrhythmias, and coma. CO also binds to cytochrome-c oxidase and myoglobin, causing delayed neurological symptoms including cognitive deficits, cortical blindness, and psychosis (Gill & Bell, 2004). The primary effects of HBOT can be observed in its use to effectively treat CO poisoning (Choudhury, 2018). HBOT speeds up the separation of CO gas from hemoglobin, shortening the time it takes to be excreted from the body and correcting intracellular hypoxia (Kocaman, 2020). While breathing room air, this process takes 300 minutes, but with HBOT the time is shortened to 32 minutes. Additionally, HBOT restores cytochrome-c oxidase and myoglobin, which helps to prevent the delayed neurologic sequelae (Latham, 2020). Studies describe mixed conclusions about the use of HBOT for CO poisoning. In one severe case of CO poisoning, HBOT preserved cognitive function but lesions in peripheral nerves persisted, which suggests partial resolution of neurological dysfunction via HBOT (Sinkovi et al., 2006). Another recent study suggested performing HBOT within 22 hours after poisoning to fully prevent delayed neurological sequelae (Liao et al., 2018). More studies are needed to confirm the optimal timing for commencing HBOT in patients with CO poisoning.

Chronic Wounds

Normal wound healing is a positive feedback system that proceeds through stages of hemostasis, removal of infectious agents, resolution of the inflammatory response, reestablishment of a connective tissue matrix, angiogenesis, and resurfacing (Tal et al., 2017). Chronic wounds are those which do not proceed completely through this process due to an intrinsic or extrinsic problem occurring in one or more of the healing phases (Kocaman, 2020; Latham, 2020). These include diabetic wounds, venous stasis ulcers, arterial ulcers, and pressure ulcers (Latham, 2020). Infection and ischemia are the most common causes of wound healing

delay with hypoxia as their defining feature (Kocaman, 2020). The infection causes an exaggerated response in the inflammatory phase of wound healing, resulting in rapid depletion of oxygen in the tissue and insufficient blood flow as a result of edema. Ischemia occurs when the tissue lacks oxygen, causing a delay in cellular activity and consequential interruption the healing process (Kocaman, 2020; Gill & Bell, 2004).

Hyperbaric Oxygen Therapy helps to restore the healing process by increasing the amount of oxygen in the blood and providing a favorable gradient for the diffusion of oxygen into the affected tissues (Kocaman, 2020; Sureda et al., 2016). Adequate oxygen is essential to healing since fibroblast proliferation, collagen synthesis, angiogenesis, and infection resistance are oxygen-dependent processes (Latham, 2020; Sureda et al., 2016). HBOT has also been shown to modulate the inflammatory process through the production of reactive oxygen species (ROS) (Kocaman, 2020; Sureda et al., 2016). In large amounts, ROS production is detrimental for cells; however, a moderate increase can be beneficial since they act as cellular messengers in many signal transduction pathways. In this case, vascular endothelial growth factor (VEGF) and endothelial-1, key promoters of the angiogenic process and myofibroblast differentiation, are upregulated via ROS production which in turn advances chronic wound healing (Thom, 2009; Sureda et al., 2016). In a study performed by Nguyen et al. on diabetic mice, treatment with hyperbaric oxygen was shown to increase ROS and accelerate wound healing compared to untreated mice, with more completed and extended reepithelization (2020).

POTENTIAL NEW INDICATIONS

Alzheimer's Disease

The prevalence of age-related disorders is on the rise as a result of the increase in life expectancy. For example, Alzheimer's Disease (AD) is the most common cause of dementia in older adults and is ranked as the sixth leading cause of death in the United States. Despite its predominance, however, there is presently no cure for this disease and no effective treatment to slow progression (Shapira et al., 2018; Louisiana State University, 2019). HBOT is currently being examined as an alternative treatment for AD, as it has been shown to improve neurological functions and life quality in other similar incidents such as stroke and traumatic brain injury. AD is characterized by senile plaques formed by deposits of beta-amyloid and neurofibrillary tangles, which ultimately lead to loss of synapses and degeneration of neurons (Shapira et al., 2018). Recent evidence suggests that hypoxia in the brain tissue plays a major role in AD pathogenesis as a result of reduced cerebral perfusion pressure that promotes the acceleration of beta-amyloid deposition. As a result, hyperoxic conditions have the potential to increase cerebral perfusion, slow beta-amyloid deposition, and boost brain function (Louisiana State University, 2019). In 2019, Harch et al. demonstrated the largest improvement in brain metabolism of any therapy for Alzheimer's disease through the use of HBOT. After undergoing 40 HBOT treatments, the patient reported increased memory and concentration, sleep, conversation, appetite, resolved anxiety, and decreased disorientation (Harch et al., 2019).

Gastrointestinal Diseases

Ulcerative colitis (UC) and Chron's disease (CD) are characterized by chronic mucosal ulcers and increased frequency of bowel movements, often accompanied with lower gastrointestinal bleeding (Latham, 2020). Treatment options for these patients are limited and often invasive (Landsdorp et al., 2020). As a result of chronic inflammation, mucosal hypoxia results, therefore, HBOT has been hypothesized as an alternative treatment option. Previous

studies demonstrated the effectiveness of HBOT in a model of experimental colitis by decreasing tissue damage. Although its mechanism of action is not totally clear, expression levels of inflammatory mediators in the damaged tissue as well as neutrophil infiltration was reduced by HBOT (Parra et al., 2020). More studies are needed to confirm the optimal number of HBOT sessions for UC and CD patients.

COVID-19

The current COVID-19 pandemic has become an unprecedented event for healthcare systems worldwide, with a dramatic loss of human life that continues to grow each day despite the technological advancements that have led to a vaccine. The infectious disease is caused by SARS-CoV-2, which causes damage to tissues and organs of the infected host by direct infection of target cells or indirectly by prolonged activation of host defense responses (De Maio & Hightower, 2020). Symptoms presented by an infected person can range from asymptomatic to respiratory illness and death (Latham, 2020). Morbidity and mortality from this condition are due to the incidence of Acute Respiratory Distress Syndrome (ARDS) which is characterized by low arterial oxygen concentration and is likely the product of inflammation mounted by the patient's own response to the infection (De Maio & Hightower, 2020). Dr. Richard Levitan recently made the striking observation that oxygen saturation levels fall to below 50% in the initial stage of COVID-19 before the onset of respiratory symptoms. This initial stage is now being understood as "silent hypoxia" (Levitan, 2020). This discovery may be critical in preventing respiratory failure, and HBOT has the potential to facilitate this as soon as a reduction of arterial oxygen concentration is detected. Currently, a COVID-19 multicenter trial is taking place to investigate the effects of HBOT on infected patients admitted to the hospital requiring oxygen (Latham,

2020). Hopefully, HBOT can be verified as a legitimate treatment for COVID-19 and can help to reduce the number of lives lost as a result of the pandemic.

RISKS AND LIMITATIONS

As with any medical therapy, treatment brings both risks and benefits. The oxidative stress that occurs as a result of high concentrations of oxygen may cause cell and tissue damage including harm to DNA. If not adequately repaired, this can lead to mutations and therefore has the potential to initiate cancer (Speit et al., 2002). Despite this concern, however, a review of the scientific literature showed that the vast majority of published studies failed to demonstrate such an effect (Feldmeier et al., 1994). Patients may experience mild-to-severe pain from rupture of the middle ear, cranial sinuses, and (in rare cases) the teeth or lungs as a result of rapid pressure changes (Tibbles & Edelsburg, 1996). This can be avoided by teaching the patient mitigation strategies such as the auto inflation technique (Latham, 2020). Some limitations of HBOT exist in the United States despite the growing list of diseases and syndromes that it can treat. In relation to cost, HBOT is rather expensive, with an average 90-minute session costing between $300 and $400. The cost of 30-40 sessions can therefore range from $9,000 to $16,000. An economic analysis of hyperbaric-oxygen therapy in patients with osteoradionecrosis, however, reported a savings of $96,000 as compared with in-hospital, nonhyperbaric-oxygen therapy (Tibbles & Edelsburg, 1996). Next, a limited number of technical staff available makes the installation of hyperbaric chambers difficult, as this is a heavily regulated process in the US that requires strict adherence to manufacturer specifications (Howell, 2018). Finally, the number of medical schools who teach hyperbaric medicine is slim. The Undersea & Hyperbaric Medical Society (UHMS) offers fellowships at several universities for hyperbaric preventative and emergency medicine in an effort to increase the expertise in this promising field (UHMS, 2020).

CONCLUSION

Hyperbaric Oxygen Therapy is a branch of science that has many indications for treatment due to its ability to counter oxygen deficits, promote healing and angiogenesis, fight infection, and control inflammation. HBOT has been described as a “therapy in search of diseases” (Tibbles & Edelsburg, 1996) since it is open to development and progress given the wide range of diseases that it has been explored to treat. Evidence for its use in decompression illness, carbon monoxide poisoning, and chronic wounds is strong, but more research is needed for its use in Alzheimer’s disease, GI diseases, and COVID-19. Although there are risks associated with HBOT, it is accepted as a safe procedure when administered properly. Overall, Hyperbaric Oxygen Therapy is a relatively new treatment for the standards of contemporary medicine. As medical technology has matured, it is the proper time to complete clarification on the potential uses of HBOT. Supported research, advanced technological equipment, and funding are necessary in order to develop HBOT as a mainstream treatment.

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