Hyperbaric oxygen therapy. Part 1: history and principles

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Abstract

Objective – Review the historical development and physiologic principles of hyperbaric oxygen therapy (HBOT) based on human and veterinary experimental literature and current equipment in use.

Data Sources – Review of basic physiologic concepts. Data from human and veterinary journals were reviewed through Pubmed and Veterinary Information Network database searches as well as reference searches on several articles covering hyperbaric therapy in clinically applicable situations.

Human Data Synthesis – HBOT has been gaining acceptance as an adjunctive treatment in human medicine. The understanding of the physiology and application of hyperbaric therapy is increasing through ongoing research and greater access to hyperbaric equipment.

Veterinary Data Synthesis – Several animal models have been utilized to examine the effects of HBOT. Most models utilize dogs and rats but pigs, cats, and other species have been studied.

Conclusions – Hyperbaric therapy utilizes several physiologic principles of how gases respond under pressure and more specifically of how oxygen responds under pressure. The increase in concentration of oxygen in solution, based on its solubility under pressure, increases the diffusion gradient for its delivery deeper into tissues, which is the premise of HBOT. Ultimately the increases in dissolved oxygen generated by hyperbaric therapy have several physiologic effects that can alter tissue responses to disease and injury. As this technology becomes more available to clinical practice, HBOT should be considered as a therapeutic option.


Keywords: HBOT, hyperbaric chambers, oxygen concentration, pressure

Introduction

Hyperbaric therapy, although a relatively old therapy, is increasing in use as a treatment option in both human and veterinary medicine as more chambers become available and knowledge of its benefits increase. It has several applications in emergency conditions such as carbon monoxide poisoning, envenomation from spider and snake bites, compartment syndrome, and central nervous system injury, as well as in more chronic disease states such as delayed wound healing. The aim of this article is to review the history, physiology, and equipment available for hyperbaric therapy. A companion article will review the human and veterinary literature examining the indications, contraindications, animal research literature, and current clinical usage of hyperbaric therapy.

History

In 1662, a British physician, Henshaw, first utilized compressed air for hyperbaric therapy. An English scientist named John Priestly first discovered oxygen in 1775, which ultimately would have a profound effect on hyperbaric medicine. Unfortunately, Lavoisier and Seguin reported ill-defined toxic effects of concentrated oxygen in 1789, thereby increasing the hesitation to use hyperbaric oxygen therapy (HBOT). In 1878, Paul Bert documented more clearly the toxic effects of oxygen on the central nervous system that were manifested as seizures. In spite of the prevailing idea that excess oxygen was toxic, Arntzenius did a review in 1887 noting up to 300 references in the literature to hyperbaric therapy indicating that early interest in hyperbaric medicine was blooming. During this time, several historic hyperbaric chambers were built, including the first
hyperbaric chamber constructed in North America, built in 1860 in Oshawa, ON, Canada, followed closely in 1861 by the first chamber in the United States that was built in New York. Cunningham in Kansas City, KS built the most well known and utilized hyperbaric chamber in the United States in 1921, which became the only operational chamber in the world by 1925. In 1928, he built the largest chamber in the world in Cleveland, OH that measured 64 feet in diameter, was 5-stories tall and had 12 bedrooms on each floor.1

References on the use of hyperbaric oxygen in animals can be traced back to 1887 when Valenzuela studied the effects of HBOT on rabbits demonstrating a decrease in febrile events and increased survival after they had been injected with the putrid contents from a dead rabbit.2 In 1937, Behnke and Shaw first used hyperbaric oxygen successfully for the treatment of decompression sickness. Since that time, HBOT has been utilized in the treatment of numerous medical conditions3 including carbon monoxide poisoning, infections, and trauma, and research continues to prove its effectiveness in several others such as wound healing in diabetics.4,5

**Gas Laws**

The principles of HBOT are based on how gases of different solubilities, most importantly oxygen, behave under changing pressures and volumes, within tissues and fluid described by Henry’s, Fick’s, and Boyle’s Laws of gas behavior. Henry’s Law describes how the pressure of a gas affects its concentration within a tissue or fluid. Henry’s Law states that the concentration of a dissolved gas (\(C_{\text{Concgas}}\)) equals the pressure (\(P\)) times the solubility coefficient (\(\text{Sol}\)) of that gas.

\[
C_{\text{Concgas}} = P(\text{Sol})
\]

Henry’s Law

The 3 main gases of concern in HBOT are oxygen, carbon dioxide, and nitrogen. The solubility coefficients of these gases at normal body temperature are as follows:

- Oxygen: 0.024
- Carbon dioxide: 0.57
- Nitrogen: 0.012

From this, it is evident that carbon dioxide is 24 times more soluble than oxygen and 48 times more soluble than nitrogen and that oxygen is twice as soluble as nitrogen. The delivery of a gas to the tissues is dependent, not only on the concentration of a gas in solution, but also on its diffusion into the tissue, both of which can be affected by pressure. Where Henry’s Law determines the concentration of a gas within a tissue or fluid, Fick’s Law describes the rate of diffusion of a gas through tissues or fluids.

Fick’s Law states that the gas flow (volume of gas per unit time [\(V_{\text{gas}}\)]) through a tissue or membrane is equal to the area (\(A\)) divided by the thickness (\(T\)) multiplied by the diffusion constant (\(D\)) times the difference in partial pressures (\(P_1 - P_2\)) of the gas across the tissue or membrane. The partial pressure of a gas is calculated by multiplying the pressure of the mixture of gases times the percentage of that mixture that is a particular gas.

Fick’s Law

\[
V_{\text{gas}} = \frac{A}{T} D(P_1 - P_2)
\]

As the area and thickness of a tissue or membrane is usually unmeasurable, the equation is often reduced to gas flow is equal to the diffusion constant times the change in partial pressure.

Fick’s Law

\[
V_{\text{gas}} = D(P_1 - P_2)
\]

The diffusion constant is proportional to the solubility of the gas (\(\text{Sol}\)) divided by the square root of the molecular weight (\(\text{MW}\)) of the gas.

Diffusion constant

\[
D = \frac{\text{Sol}}{\sqrt{\text{MW}}}
\]

Carbon dioxide is slightly heavier than oxygen in molecular weight, but as mentioned above, the solubility coefficient of carbon dioxide is 24 times greater. This means that carbon dioxide will diffuse through tissue 22 times faster than oxygen over the same distance and under the same pressure. If there is an increase in the partial pressure difference (driving pressure) between 2 tissue areas, not only the rate of diffusion, but the distance the gas diffuses into the tissue will increase. The driving pressure of a gas can be increased by either increasing the fraction of an inspired gas or the atmospheric pressure. In this way, inspiring oxygen enriched air under hyperbaric conditions, the pressure gradient of oxygen is increased allowing the oxygen to diffuse further into tissues especially those that may be increased in thickness secondary to inflammation or those that have decreased blood flow. Another method of increasing the relative oxygen concentration is through vasoconstriction of well-oxygenated tissues so that the body can divert oxygen to less well-oxygenated tissues.

Finally, Boyle’s Law relates to how volumes of gas behave under pressure. Boyle’s Law states that with increasing pressure (\(P\)) the volume (\(V\)) of a gas decreases proportionately.

Boyle’s Law

\[
P_1 V_1 = P_2 V_2
\]
This means a volume of gas will be halved when the pressure is doubled and conversely that the volume of a gas will double when the pressure is halved. This becomes important when gases are trapped in various cavities during compression and decompression of the patient and is the main cause of barotrauma. When the patient is compressed if there is air trapped within a body cavity the volume will contract and may alleviate some clinical conditions. Alternatively, when the patient is decompressed the trapped gas will expand and may cause complications.

**Physiology**

Oxygen is needed to provide energy and support cellular respiration. Decreased delivery of oxygen can affect cell survival. Injury or disease decreases the body’s ability to transport oxygen to the tissues, increases the tissue demands for oxygen, and may increase the distance that the oxygen must travel from the capillary to reach the cell. Conditions such as hemolytic anemia, toxin exposure, and hemorrhage can affect the body’s ability to transport oxygen. Infections and tissue healing can increase the demands for oxygen. Edema, decreased perfusion and microthrombosis can affect the distance that oxygen must travel from the patent capillaries to the cells.

There are several pressure gradients that exist to help bring oxygen to the cells as well as to transport by-products, most notably carbon dioxide, away from the cells. In an ideal system the gradients for oxygen, called the oxygen cascade, start with ambient air that has a PO$_2$ of 160 mm Hg at sea level. The air then enters the respiratory tract and becomes diluted by water vapor to yield an alveolar PO$_2$ of 104 mm Hg. The mixed venous blood coming into the lungs has a PO$_2$ of approximately 40 mm Hg so oxygen diffuses down the pressure gradient from the alveoli into the blood reaching an arteriolar PO$_2$ of 95 mm Hg. The arteriolar PO$_2$ is a reflection of oxygen bound to hemoglobin for transport as well as oxygen that is dissolved in the plasma phase of the blood. In the capillaries, the oxygen again flows down the pressure gradient to 40 mm Hg in the interstitium. From here, the oxygen diffuses into the cells, which have a PO$_2$ of 3–40 mm Hg but average about 3 mm Hg. The cells require an intracellular PO$_2$ of 1–3 mm Hg to fully support metabolic processes$^6$ (Figure 1). The absolute values in any given area in the pulmonary or circulatory system depend on many variables including, but not limited to, barometric pressure, inspired oxygen concentration, ventilation, and oxygen delivery and uptake to name of few. However, the general principle still holds that a pressure gradient is required to allow oxygen diffusion.

![Oxygen Cascade](image)

**Figure 1**: The diffusion gradients along the oxygen supply chain to the tissues of a normal body at sea level. Modified with permission from Nunn’s Applied Respiratory Physiology$^{11}$ (Elsevier Publishing Inc.).

Oxygen is far more soluble in lipid than in water so the diffusion of oxygen in tissues becomes limited by its rate of diffusion through the fluid portions of the system (ie, plasma, interstitial fluids, and cytoplasm). Under normal atmospheric pressure, there is a limit to the amount of oxygen that can be carried in blood, which is quantified by the equation for arterial oxygen content (CaO$_2$). The CaO$_2$ equals 1.34 times the hemoglobin concentration (Hgb) times the arterial saturation of oxygen (SaO$_2$) plus 0.003 times the arterial partial pressure of oxygen (PaO$_2$).

**Arterial oxygen content**

\[
CaO_2 = (1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)
\]

Because the hemoglobin is 97% saturated in the normal body at sea level, limited improvement in oxygen delivery to tissues can be achieved by increasing hemoglobin saturation. However, the concentration of dissolved oxygen in the plasma can be influenced greatly with hyperbaric therapy. Based on Henry’s Law, increased pressure will cause more gas to go into solution, and therefore more oxygen will be transported in the plasma. Increasing the concentration of a gas within a fluid increases its partial pressure within the fluid. The increased partial pressure increases the driving force for diffusion and thereby increases its diffusion distance as defined by Fick’s Law. Additionally, it is the oxygen dissolved in plasma that is most bioavailable to the tissues. By increasing the PaO$_2$ in arterial blood, more oxygen can be delivered deeper into the tissues. Increasing the pressure from 1 atmosphere absolute (ATA) to 2–2.5 ATA, which is the typical work-
ing pressure with hyperbaric therapy, the oxygen dissolved in plasma increases approximately 3-fold if the patient is breathing room air. If the inhaled oxygen concentration is increased to 100% under pressure, the plasma oxygen concentration increases by almost 17-fold. In theory, with 100% oxygen at 2.5 ATA, enough oxygen can be dissolved in plasma to meet the normal requirements of the body at rest without the need for hemoglobin.

The delivery of oxygen is also affected by perfusion and by variable degrees of vasodilation and vasocostriction within different tissues. Typically, arterioles and venules vasoconstrict at high oxygen tensions (PO$_2$ > 500 mm Hg) and primarily is thought to be related to a decrease in the availability of endogenous nitric oxide. This is a protective mechanism in response to hyperoxia to protect tissues from increased oxidative damage. Despite the decrease in blood flow, overall tissue oxygenation remains normal because of the increased PO$_2$. In ischemic and postischemic tissue, these vasoconstrictive mechanisms are impaired, thus, allowing for improved oxygen delivery. Additionally, carbon dioxide build up in these areas contributes to vasodilation and is a more potent vasodilator than the oxygen is a vasoconstrictor. This vasodilation and enhanced oxygenation of injured tissues helps to preserve the ATP levels and to inhibit swelling and edema formation by maintaining energy-dependent cellular functions.

Although carbon dioxide removal from the tissue is impaired by the saturation of the hemoglobin with oxygen, it has minimal effects on the venous PCO$_2$, with increases as little as 5 mm Hg. As the hemoglobin transport system is responsible for only 20% of CO$_2$ removal from tissues, the bicarbonate system and increased plasma carrying capacity limit the overall impact of decreased hemoglobin removal thereby limiting any further rise in venous or tissue PCO$_2$ levels.

In addition to its effects on cellular function, HBOT affects the immune system. Oxygen has an antimicrobial effect especially in anaerobic infections. The oxygen-derived free radicals that are formed in the reperfusion state have bactericidal affects. Likewise, HBOT stimulates phagocytosis within affected tissues. HBOT also has been shown to have beneficial effects on fibroblast activity, angiogenesis, and modulation of neutrophil activity, which will be discussed further in a companion article reviewing the experimental literature.

**Equipment**

There are currently 3 types of chambers in use for delivering hyperbaric therapy. In human medicine, the most common chambers are high-pressure multipurpose and monoplace chambers with low-pressure monoplace chambers being relatively new. A multipurpose chamber is designed to be compressed with air and accommodate several patients who are individually breathing oxygen usually through a mask or hood. The multipurpose chambers allow for a higher volume patient load as well as being adaptable for more critically ill patients by allowing an attendant to be present in the chamber during therapy to address any complications that may arise. Monoplace chambers are designed for a single person and the compressed gas is oxygen, negating the use of a mask or hood. These are more frequently used in smaller facilities allowing for more individualized therapy and are often found in chronic wound treatment centers. Most of these chambers are designed to operate at high pressure usually in the 2–2.5 ATA range. Newer low-pressure collapsible monoplace chambers are available that operate in the 1.2–1.3 ATA pressure range. These chambers are currently used most frequently for in-home use, and by plastic surgeons to improve postoperative recovery. They may be more attractive in some situations due to their portability, lower cost, and increased availability. Because these low-pressure chambers are relatively new, differences in therapeutic benefits have not been researched; however, based on the principles of hyperbaric therapy, tissue oxygen delivery will be improved even though it will not be to the same degree as with the high-pressure units.

**Conclusions**

Henry’s, Fick’s, and Boyle’s Laws of how gases behave under pressure are crucial in the understanding of how hyperbaric therapy exerts its physiologic effects. These physiologic effects include enhanced, or improved oxygen delivery to cells, antimicrobial effects, stimulation of phagocytosis, stimulation of fibroblasts, modulation of neutrophils, and angiogenesis. Hyperbaric therapy has been in existence for over 350 years suggesting it has stood the test of time and is deserving of consideration as a therapeutic modality.

**References**


