Hyperbaric Oxygen Therapy

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Abstract: Hyperbaric oxygen therapy (HBOT) is emerging in veterinary medicine as an effective treatment or adjunct therapy for a variety of disorders in which improving oxygen delivery to tissues is a priority. The primary mechanisms of action of HBOT are (1) immediate hyperoxygenation of plasma and tissues and (2) decreased gas bubble (air embolus) size. With each hyperbaric “dive,” secondary physiologic effects are set into motion. This article provides an introduction to HBOT, as well as its benefits, potential indications, contraindications, complications, and future directions in small animal veterinary medicine.

Hyperbaric oxygen therapy (HBOT) is the therapeutic use of a pressurized, 100% oxygen atmosphere. While HBOT is emerging as an effective treatment or adjunct therapy for a wide variety of medical and surgical conditions in small animal veterinary medicine, it may be underutilized, in part because practitioners may not be sufficiently familiar with how it works and when it may be efficacious. This article gives an overview of HBOT in human and veterinary medicine.

History of Hyperbaric Oxygen Therapy
The scientific study of the effects of HBOT began as early as 1895, when Scottish physician John Scott Haldane evaluated its effect on carbon monoxide toxicosis in humans. The first clinical application of HBOT in the early 1930s is attributed to Brazilian physician Alvaro Osorio de Almeida. De Almeida’s work also addressed the complication of central nervous system toxicity encountered while treating cancer patients with HBOT.

Following De Almeida’s work, the US Navy tested HBOT in an effort to find a better therapy for decompression illness in people, which is why an HBOT treatment session is called a “dive.”

By the late 1950s, sufficient HBOT research had accumulated for clinicians to study the effects of HBOT on a wide range of human medical and surgical conditions. Notable among these studies were the findings of Ita Boerema, a Dutch cardiovascular surgeon who performed various surgical procedures in a hyperbaric oxygen environment, and of I. Churchill Davidson, who launched a clinical trial evaluating HBOT as a potentiatior for radiation therapy in cancer patients at St. Thomas Hospital in London.

Veterinarians first used HBOT in the late 1990s to treat traumatic brain injury patients, and the Veterinary Hyperbaric Medicine Society was formed in 2006 to “educate professionals and the public about hyperbaric medicine and its application, collaborate in the discovery of new knowledge, and promote operator and patient safety.” The number of facilities offering HBOT to veterinary patients continues to grow. A list of some of these facilities may be found on the Web site of the Veterinary Hyperbaric Medicine Society (www.vet.utk.edu/vhms/centers.html).

Gas Laws in the Context of Hyperbaric Oxygen Therapy
Four physical laws pertaining to the properties of gases are important in understanding HBOT (BOX 1). In the context of HBOT, because the patient is receiving 100% oxygen, the partial pressure of oxygen (P02) and, therefore, the density and solubility of oxygen are all maximized.

**Box 1. Gas Laws of Importance in Hyperbaric Oxygen Therapy**

- **Dalton’s law** (also called Dalton’s law of partial pressures) describes the relationship of the pressure of individual gases in a mixture of gases to the total pressure of the gas mixture. It states that the total pressure exerted by a mixture of gases is equal to the sum of the pressure of each individual gas in the mixture.

- **Boyle’s law** relates the volume and density of a gas to the pressure of the gas at a constant temperature. It states that the volume of gas is inversely proportional to the pressure, while the density of a gas (e.g., oxygen) is directly proportional to the pressure.

- **Graham’s law** describes the relationship of pressure (concentration) of a gas to how it moves. It states that oxygen and carbon dioxide (and other gases) move independently, and at different rates, from areas of high pressure to areas of lower pressure.

- **Henry’s law** relates the amount of gas that can be dissolved in a liquid to the pressure of the gas above the liquid. It states that the solubility of a gas in a liquid is directly proportional to the pressure of the gas in contact with the liquid.
Physiology of Hyperoxygenation

Oxygen delivery (DO₂) depends on cardiac output, arterial oxygen content (CaO₂), and blood flow. CaO₂ can be calculated using the hemoglobin (Hb) concentration, hemoglobin saturation (SaO₂), and arterial partial pressure of oxygen (PaO₂) as follows:

\[
\text{CaO}_2 = (1.36 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)
\]

The contribution of dissolved oxygen (0.003 × PaO₂) is normally very small; however, under high-pressure hyperbaric conditions (2 atmospheres absolute [ATA]), the content of dissolved oxygen in the plasma can be increased up to 15 times normal. This increase in the oxygen-carrying capacity of the blood is independent of red blood cells (hemoglobin); therefore, in areas where capillary flow is compromised, tissues have a greater opportunity to receive much-needed oxygen.

Mechanism of Hyperbaric Oxygen Therapy

Most veterinary high-pressure HBOT sessions use pressures of 2.0 to 3.0 ATA, while low-pressure therapy may be conducted at 1.5 to 2.0 ATA. When lower pressure is used, treatment times may be longer. The average treatment time at 2 ATA is 45 to 60 minutes. Small animal patients are typically treated every 8 to 12 hours; however, large animals have been treated up to six times in a 24-hour period, depending on the severity of the condition. A standard HBOT protocol is outlined in Box 2.

When a patient is placed into the hyperbaric chamber and pressurization begins, the action of replacing the room air in the hyperbaric chamber with 100% oxygen gradually increases the fraction of inspired oxygen (FiO₂) in conjunction with the atmospheric pressure (Figure 1). The increased concentration of oxygen molecules increases the partial pressure of oxygen (Dalton’s law), so as the patient breathes, the concentration of oxygen molecules delivered to each alveolus and, therefore, the alveolar partial pressure of oxygen (Pao₂) are increased. This increase in partial pressure leads to a corresponding increase in the density of the oxygen molecules in the alveoli (Boyle’s law), resulting in more oxygen being available for diffusion into pulmonary capillaries.

Because gases move from areas of higher pressure to areas of lower pressure (Graham’s law), the increased Pao₂ results in an increase in oxygen molecules diffusing across the alveolar epithelium into the blood. The high density and pressure of oxygen in the alveoli also increase the solubility of oxygen in the blood (Henry’s law), resulting in a significant increase in the arterial partial pressure of oxygen (Pao₂; Figure 2). In turn, this high Pao₂ creates a pressure gradient that determines the movement (amount and rate of diffusion) of oxygen from the blood through the capillary endothelium, the interstitial space, and the intracellular compartment (Graham’s law; Figure 3). Therefore, a significantly
Figure 2. A high $P_aO_2$ increases the solubility of oxygen in the adjacent blood (Henry’s law), resulting in a significant increase in $P_aO_2$.

Figure 3. A high $P_tO_2$ creates a pressure gradient with adjacent tissue ($P_tO_2$) that increases the amount and rate of diffusion of oxygen from the blood through the capillary endothelium, the interstitial space, and, ultimately, the intracellular compartment (Graham’s law).

increased $P_aO_2$ ultimately results in an increased rate of oxygen delivery into the interstitial space and then into the cells (FIGURE 3).

Hyperbaric Chambers

Human HBOT chambers are either monoplace (accommodating one person) or multiplace (accommodating several people at one time). Veterinary practices can acquire previously owned monoplace equipment from human facilities to treat their patients. Veterinary-specific hyperbaric chambers are also available, with some being large enough for ambulatory equine patients. Access to hyperbaric oxygen as a treatment modality is currently limited due to the modest number of facilities with the appropriate equipment.

Benefits of Hyperbaric Oxygen Therapy

The primary effects of HBOT are hyperoxygenation and decreased gas bubble size. As described above, hyperoxygenation increases the oxygen-carrying capacity of the blood and, subsequently, the diffusion of oxygen into tissues (Graham’s law). Tissue $P_O_2$ may remain elevated by more than 10% above normal for up to 3 hours after a single hyperbaric dive.

Decreased gas bubble size is paramount in the treatment of mechanical vascular obstruction from decompression sickness or air embolism; smaller bubbles pass through the vasculature more easily, thereby clearing the obstruction. Additionally, the smaller surface area of smaller bubbles reduces the activation of platelets, complement, and Hageman factor (factor XII).

Other beneficial effects of HBOT include increases in leukocyte oxidative killing capacity, modulation of nitric oxide production, and modification of growth factors and cytokine effects through regulation of their levels and/or receptors. HBOT also decreases production of clostridial toxins and is synergistic with some antibiotics such as fluoroquinolones, amphotericin B, and aminoglycosides, all of which use oxygen to cross the cell membrane. An additional benefit is decreased vasogenic edema. Although the mechanism has not been conclusively elucidated, it is proposed that hyperoxic vasoconstriction to normal tissues may be involved while blood supply to ischemic tissues remains unaffected.

Potential Indications for Hyperbaric Oxygen Therapy

In veterinary medicine, scientific evaluation of HBOT is scarce; therefore, HBOT applications and protocols are largely adopted from human studies. Literature searches on HBOT in veterinary medicine yield primarily anecdotal case reports and conference proceedings. In 2000, I (D. T. C.) discussed more than 1400 hyperbaric oxygen treatments given to dogs and cats over a 2-year period. This report covered HBOT for a wide variety of conditions, such as sepsis, peritonitis, osteomyelitis, encephalitis, spinal cord injury, traumatic shearing and crush wound injury, snake envenomation with resultant swelling and necrosis, and aortic thromboembolism, with the results assessed as “extremely favorable” in most cases. Failure to respond to HBOT was noted as a prognosticator of an unfavorable outcome. I have also reported retrospective studies on the use of HBOT that demonstrated benefits in veterinary patients with spinal cord injuries/compressions, head injuries, or stroke-like conditions as well as in wound healing.

Hyperoxygenation is potentially indicated in conditions characterized by ischemic insult, such as aortic thromboembolism, gastric dilatation-volvulus, traumatic brain injury, and stroke, and after cardiopulmonary-cerebral resuscitation. It has been documented that an increased oxygen gradient between a wound and its surrounding environment will stimulate angiogenesis and, subsequently, increased proliferation of fibroblasts; therefore, HBOT may also be useful for nonhealing wounds, skin flaps or grafts, radiation injuries, and crush injuries. Patients with sepsis, osteomyelitis, diskospondylitis, gangrene, fungal infections, and necrotizing fasciitis may benefit from HBOT’s effect on leukocyte killing capacity, antibiotic synergy, and clostridial toxin production. Additionally, the modification of growth factors and cytokine effects induced by hyperoxygenation is helpful in inflammatory conditions such as pancreatitis, heatstroke, and envenomation.

A series of neurologic cases treated with HBOT presented at the 2007 American College of Veterinary Internal Medicine Forum and the 2008 International Veterinary Emergency & Critical
Care Society Symposium, included patients with global ischemia, head trauma, fibrocartilaginous emboli, intervertebral disk extrusion, and inflammatory central nervous system disease.12,21 The presenter felt that the adjunct use of HBOT was instrumental in the improvement and recovery of these patients.

At our facility (Pet Emergency & Specialty Hospital, Thousand Oaks, CA), more than 1700 HBOT sessions have been administered to treat a wide variety of conditions, including wounds, envenomation, central vestibular disease, osteomyelitis, traumatic brain injury, and pancreatitis. We retrospectively evaluated HBOT as an adjunct therapy in the management of emergent central nervous system conditions. The favorable results obtained prompted an ongoing international, multicenter, prospective study. In our experience, veterinary small animal practitioners often do not recognize situations in which their patients could benefit from this treatment modality.

**Contraindications**

Awareness of contraindications to HBOT is important to providing safe, optimal care. In veterinary medicine, HBOT contraindications are often inferred from human studies.

Absolute contraindications to HBOT include the following33:

- Untreated pneumothorax or pneumomediastinum
- High risk of aspiration, as in comatose, unconscious, or semiconscious patients
- Respiratory failure requiring mechanical ventilatory assistance (if using a monoplace chamber)
- Implantation of older types of pacemakers
- Uncontrolled seizure activity
- Nonmammalian species, due to differences in respiratory physiology and/or anatomy

Relative contraindications to HBOT include the following:

- Upper respiratory infections
- Asthma
- Pregnancy
- History of spontaneous pneumothorax

**Complications**

As with contraindications, complications of HBOT are mostly inferred from human medicine. Oxygen toxicity from the formation of reactive oxygen species (ROS) is a potentially serious complication of HBOT.29 ROS originate from the addition of an electron to molecular oxygen (i.e., the reduction of the molecule). Because this electron is unpaired in its valence shell, the resultant molecule is highly reactive and can cause significant cellular damage.48 Cellular oxidant stress (and subsequent damage) is determined by the relationship between ROS formation and ROS elimination by antioxidant defenses.49 Natural antioxidant defenses within the central nervous system can become overwhelmed if they are overexposed to oxygen; when this occurs, oxygen-induced seizures may result.48,49 Careful decompression for oxygen-induced seizures is recommended; anticonvulsant therapy is not required.48,49 Seizures typically do not recur if future hyperbaric treatments are conducted at a lower pressure or shorter length of exposure.48 While ROS are implicated in pulmonary toxicity in human studies,48 no published veterinary reports citing this relationship presently exist.

Confine anxiety and aural barotrauma (ear discomfort) are less serious complications of HBOT.13 If aural barotrauma is noted during compression or decompression, the rate of the process is slowed. For containment anxiety, anxiolytic medication is recommended. However, patients receiving anxiolytics must be assessed before HBOT to ensure that they are not profoundly sedate and therefore at risk for aspiration.

**Future Directions**

Further scientific research is necessary to maximize the potential of HBOT in small animal veterinary medicine. Treatment protocols need to be standardized. Studies are needed to compare the effectiveness of low-pressure versus high-pressure HBOT and to determine the optimal length and frequency of individual treatments for specific conditions. No published reports to date delineate long-term outcomes from HBOT, present a cost-benefit analysis, or identify potential differences in treatment sensitivity or complications by species and breed.

**Conclusion**

HBOT is an underutilized treatment modality that is potentially beneficial for a variety of disorders in which improving oxygen delivery to tissues is a priority. It also may have positive effects in infectious and inflammatory conditions. Knowing the physiology, mechanisms of action, indications, contraindications, and possible complications of HBOT can help small animal veterinary practitioners be better prepared to identify patients that may benefit from this important emerging therapy.

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**References**

1. Oxygen delivery depends on
   a. cardiac output.
   b. arterial oxygen content.
   c. blood flow.
   d. all of the above

2. The primary effects of HBOT are hyperoxygenation and
   a. decreased edema.
   b. enhanced antimicrobial effectiveness.
   c. increased fibroblast proliferation.
   d. decreased gas bubble size.

3. After a single HBOT dive, tissue $P_O_2$ can remain elevated by more than ___ above normal for up to 3 hours.
   a. 5%
   b. 10%
   c. 20%
   d. 50%

4. The secondary effects of HBOT do not include
   a. increased leukocyte killing ability.
   b. increased flow of fluid into tissues.
   c. increased fibroblast proliferation.
   d. decreased clostridial $\alpha$ toxin production.

5. ________ law relates the volume and density of a gas to the pressure at a constant temperature.
   a. Boyle’s
   b. Dalton’s
   c. Graham’s
   d. Henry’s

6. ________ law relates the amount of gas that can be dissolved in a liquid to the pressure of the gas above the liquid.
   a. Boyle’s
   b. Dalton’s
   c. Graham’s
   d. Henry’s

7. Which of the following is not a contraindication for HBOT?
   a. untreated pneumothorax
   b. nonmammalian species
   c. unconscious patient
   d. controlled seizures

8. What is the most significant potential complication of HBOT?
   a. containment anxiety
   b. aural barotrauma
   c. decreased proprioception
   d. oxygen toxicity

9. If signs of aural barotrauma are observed during decompression,
   a. the rate of decompression should be slowed.
   b. the rate of decompression should be increased.
   c. decompression should be discontinued.
   d. the chamber should be represurized.

10. Which of the following is a potential indication for HBOT in veterinary medicine?
    a. nonhealing wounds
    b. osteomyelitis
    c. head trauma
    d. all of the above