Hyperbaric oxygen therapy. Part 2: application in disease

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Abstract

Objective – Review the mechanisms of action and clinical application of hyperbaric oxygen therapy (HBOT) based on human and veterinary clinical and experimental literature.

Data Sources – Pubmed and Veterinary Information Network databases were searched for human and veterinary journal articles on hyperbaric therapy in clinically applicable situations. Historical reference searches on several articles in addition to basic physiologic concepts were also reviewed.

Human Data Synthesis – HBOT has gained acceptance as an adjunctive treatment in clinical conditions other than diving-related injuries, such as select problem wounds and central nervous system diseases, in human medicine. Access to hyperbaric therapy has increased and ongoing research has furthered understanding of the mechanisms and potential therapeutic uses of HBOT.

Veterinary Data Synthesis – Several animal models have been utilized to examine the effects of HBOT; primarily rodents (mice, rats) and rabbits but also dogs, cats, and pigs. Data related to animal model research as it pertains to clinical application of HBOT is reviewed.

Conclusions – There is a substantial body of literature that has examined the adverse and beneficial effects of HBOT in animal models. As technology becomes more readily available to clinical practice and more clinical trials are performed to define its effectiveness, HBOT may be considered as an additional therapeutic option in many conditions including select problem wounds, spinal cord injury, and cerebral ischemic injury. Understanding the mechanisms by which HBOT exerts its effects will help guide research and use of the modality in clinical patients.


Keywords: angiogenesis, HBOT, nitric oxide, reperfusion injury, sepsis, wound healing

Clinical Application

Historically, citations can be found in the literature regarding the use of hyperbaric oxygen therapy (HBOT) in several conditions in animals (primarily rats and dogs) dating back to the 1950s and 1960s. Cited conditions include bowel obstruction, myocardial ischemia, anaphylactic and hypovolemic shock, severe anemia, and anaerobic infections. The more recent literature discusses uses in immunomodulation, wound healing, central nervous system injury and disease, and sepsis. A companion article reviewed how gases behave under pressure to understand how HBOT exerts some of its physiologic effects. Briefly, the volume of a gas decreases as pressure increases (Boyle’s law); the solubility of a gas is proportional to the pressure of the gas in equilibrium with the liquid (Henry’s law); and diffusion radius increases as the concentration gradient increases (Fick’s law). These principles determine the rate and distance of diffusion of gases within body tissues and fluids. Gas volume and solubility changes created by changes in pressure are the main causes of adverse effects associated with hyperbaric therapy. The aim of this article is to review the mechanisms of action of HBOT and some of the conditions where it might be useful in a clinical setting as well as indications and contraindications for its use.

Mechanisms of Action

In a hyperbaric oxygen environment, the effects of pressure, and changes in solubility and diffusion characteristics of gases lead to several of the physiologic effects seen with this therapy. The physiologic effects of HBOT include intravascular and tissue gas bubble reduction, improved oxygenation, vasoconstriction, increased antimicrobial activity, modulation of inflammation and immune function and angiogenesis. The following is a
with HBOT through improvement of wound oxygen sufficiency and diabetes in humans. A prospective experimental pig model, HBOT decreased the deleterious effects of cerebral air embolism on intracranial pressure (ICP) and brain metabolism. A retrospective human clinical study identified HBOT, with or without conventional nasogastric or intestinal tube decompression, to be beneficial in ameliorating symptoms of gas accumulation in bowel loops caused by postoperative paralytic ileus.

Improved oxygenation
Blood and tissue oxygen tensions were documented to remain elevated for over an hour following a single HBOT treatment in an experimental rat wound model. Improved oxygenation is the mechanism by which HBOT has its primary beneficial effect in conditions such as carbon monoxide (CO) toxicity and select problem wounds. HBOT is widely accepted for the clinical treatment of CO toxicity. In a prospective experimental pig model, HBOT decreased the deleterious effects of cerebral air embolism on intracranial pressure (ICP) and brain metabolism. A retrospective human clinical study identified HBOT, with or without conventional nasogastric or intestinal tube decompression, to be beneficial in ameliorating symptoms of gas accumulation in bowel loops caused by postoperative paralytic ileus.

Gas bubble reduction
The use of HBOT to reduce gas bubbles in the circulation and tissues is 1 of the oldest applications of this therapy. HBOT is widely accepted for the treatment of air or gas embolism because increased pressure decreases the volume of the gas in addition to increasing the solubility of gases such as nitrogen and carbon dioxide, which aids in resorption and elimination of the air or gas embolism. Gas emboli can be seen as a complication after various surgical and diagnostic procedures, such as neurosurgery or angiography, as well as being the cause of decompression sickness in divers, commonly called the bends. In a prospective experimental pig model, HBOT decreased the deleterious effects of cerebral air embolism on intracranial pressure (ICP) and brain metabolism. A retrospective human clinical study identified HBOT, with or without conventional nasogastric or intestinal tube decompression, to be beneficial in ameliorating symptoms of gas accumulation in bowel loops caused by postoperative paralytic ileus.

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Vasoconstriction
In experimental rat models, normal vasculature constricts in response to hyperoxia while tissue oxygenation is maintained because of the increased arterial dissolved oxygen content. Experimentally in animals, vasoconstriction decreases tissue exposure to reactive oxygen species (ROS) such as superoxide that are generated under hyperbaric conditions. Vasoconstriction also helps reduce tissue edema formation. Nitric oxide (NO) is an important smooth muscle relaxant that leads to vasodilation. In ischemic tissue in experimental rat models, increased NO activity can inhibit progressive arteriolar vasoconstriction, which could explain differences in healthy and ischemic tissue reactions to HBOT. In contrast, the ability of HBOT to decrease inducible nitric oxide synthase (iNOS) expression in several rat lipopolysaccharide-induced septic shock models, reduces NO production and helps maintain vascular responsiveness as evidenced by minimal changes in mean arterial pressure. Maintenance of vascular responsiveness has been correlated to decreased mortality in some studies. Decreased vasogenic edema has been demonstrated in animal models of cerebral ischemic events and traumatic brain injuries. In addition, experimental rodent models have demonstrated that hyperoxic vasoconstriction decreases brain blood flow and blood brain barrier permeability, thereby decreasing ICP and improving ICP dynamics. Correction of blood brain barrier permeability changes and ICP dynamics decrease mortality and neurologic deficits.

Antimicrobial activity
HBOT enhances endogenous antimicrobial activity in several ways. HBOT helps restore tissue oxygen tension, which is required for leukocytes to function normally with regards to oxidative killing mechanisms. In addition, increased tissue oxygen levels have direct
bacteriostatic or bactericidal effects on various infectious organisms.59 These effects were reported in a combined experimental guinea pig model and clinical human case series of clostridial myositis where HBOT improved outcome.9 Rat models have also demonstrated the antibacterial effects of HBOT in aerobic bacterial infections.60,61 HBOT was shown in an experimental human clinical study to stimulate phagocytic activity of neutrophils in diabetic patients with infected foot wounds in conjunction with standard therapy including intensive insulin therapy, antimicrobials, and surgical debridement.62

Finally, HBOT has been shown to have synergistic effects with antimicrobials. In an experimental rat model of Escherichia coli-induced sepsis, HBOT was found to be a useful adjunct to antimicrobial therapy in eliminating histopathologic injury and biochemical derangements of the liver. Changes in ROS bactericidal effects and increased antioxidant levels were the proposed mechanisms for the improvements seen.25 Other rat models have shown decreased Staphylococcus aureus-induced osteomyelitis when HBOT is used in combination with antimicrobials administered either locally or systemically.60

Inflammation and immune modulation
HBOT has been shown to modulate neutrophil and macrophage function, which explains many of its effects during reperfusion injury, inflammation, and immune-mediated disease. In an experimental model of CO poisoning, HBOT inhibited the formation of xanthine oxidase, which thereby decreased lipid peroxidation in the brain during ischemia/reperfusion.64–66 Increases in NO generation with HBOT have been associated with decreased neutrophil adhesion and sequestration, both from functional inhibition of the neutrophil β2 integrin,66,67 and through downregulation of endothelial intracellular adhesion molecule-1 expression.68 In several laboratory models, decreased neutrophil adhesion reduces ROS formation, especially during the reperfusion phase,46,64,66,68 which decreases production of inflammatory mediators. Laboratory rat models have demonstrated the ability of HBOT to decrease neutrophil sequestration in various tissues such as the lung,69–73 brain,74 and intestinal mucosa75 in response to inflammation.

In a rat stroke model, HBOT decreased cerebral neutrophil accumulation, which in turn decreased infarct volume and reperfusion injury in the ipsilateral hemisphere and improved neurologic outcome.74 HBOT-induced decreases in microglia (proinflammatory) and increases in astrocytes (neuroprotective) explain some of the improvements in infarct volume.76 By decreasing neutrophil adhesion to the endothelium, neutrophil infiltration into tissues is limited. Decreased neutrophil infiltration is associated with improved neurologic outcomes in several experimental rat models including permanent ischemic,77,78 and transient ischemic events.79 Alterations in neutrophil migration and ROS activity during HBOT have also been proposed as explanations for improved neurologic outcomes and attenuated neuronal injury in a postresuscitation cardiac arrest model in dogs.80

In addition to its anti-inflammatory effects, HBOT has other immunomodulatory actions. HBOT attenuates disease severity in experimental models of autoimmune disease,11 and improves graft tolerance through major histocompatibility complex protein changes.12 In a cecal ligation and puncture-induced sepsis model in mice, HBOT showed protective effects that appeared to be linked to enhanced interleukin 10 (IL-10) expression by macrophages.10 HBOT also decreases the serum concentration of tumor necrosis factor-α (TNF-α) as shown in reperfusion71 and heatstroke13 rat models.

Angiogenesis
Experimental animal models have demonstrated HBOT creates the necessary oxygen gradients between the blood and injured tissues to promote angiogenesis81 and increased blood flow (on the order of 20% increase in mean perfusion).16,82 Oxygen gradients have been shown to be mandatory in angiogenesis during wound healing through regulation of macrophage-derived growth factors, specifically vascular endothelial growth factor.16,83,84 Neovascularization is important in helping fight infection as well as in the later phases of wound repair as it facilitates the migration of fibroblasts and epithelial cells that continue the healing process. Improved angiogenesis with HBOT has been associated with improvements in healing in such diverse experimental animal models as burns, cartilage and skin grafts,17,66,85,86 dermal wounds,82,85,87 and bone healing.88

Indications in human medicine
In human medicine the accepted indications for the use of HBOT vary between organizations as well as countries. Few randomized-controlled clinical trials exist on the use of HBOT. Many of the widely accepted uses in human medicine are based on experimental animal models and clinical case experience.28 The Undersea and Hyperbaric Medical Society performs an evidence-based medicine review of the available literature and publishes a list of indications that is referenced by Medicare and other third party carriers in reimbursement determinations in the United States.28 HBOT is currently covered by Medicare in the United States for reimbursement in the treatment of several acute conditions including decompression sickness, CO toxicity,
Clostridial myonecrosis and crush injuries, in addition to chronic conditions including refractory osteomyelitis, radionecrosis, and select diabetic wounds. A complete listing of approved indications from Medicare and the Undersea and Hyperbaric Medical Society are provided in Tables 1 and 2.28,29 A list of conditions not covered for reimbursement by Medicare or considered nonapproved/research conditions is provided in Table 3 for comparison.

**Clinical investigational use in veterinary medicine**

There are no prospective randomized controlled studies on the indications for HBOT in veterinary medicine. The investigational uses of HBOT in veterinary patients are often based on accepted human indications and are similar to those (approved and nonapproved) reported in human medicine. In small animal medicine, clinical investigational cases include: brain and spinal cord injury, postoperative patients with intervertebral disc herniation, pancreatitis, peritonitis, pyothorax (especially Nocardiosis and Actinomycosis), postcardiopulmonary cerebral resuscitation neurologic impairment, severe soft tissue inflammation, aortic embolization, and post-traumatic and reperfusion myocardial injury.89 Additional references also include treatment for skin flaps,90 refractory osteomyelitis, clostridial infections, acute traumatic ischemias,91 and rattlesnake envenomations.9 In equine medicine, proposed applications include: laminitis, osteomyelitis, desmitis/tendonitis, postsurgical wounds, slow-healing wounds, thermal burns, smoke inhalation, rhabdomyolysis, head trauma, peripheral nerve trauma, anaerobic infections, lymphangitis, intestinal surgeries, envenomations (spider and rattlesnake),92,93 internal abscesses, dummy foals,94 and infertility.95 Another proposed use for HBOT is to enhance recovery from athletic performance in horses.93

**Table 1:** This table presents a list of indications for hyperbaric oxygen therapy covered for reimbursement by Medicare29

<table>
<thead>
<tr>
<th>Acute conditions</th>
<th>Chronic conditions</th>
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<tbody>
<tr>
<td>Acute carbon monoxide intoxication</td>
<td>Actinomycosis (only when refractory)</td>
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<tr>
<td>Acute peripheral arterial insufficiency</td>
<td>Preparation and preservation of compromised skin grafts</td>
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<tr>
<td>Acute traumatic peripheral ischemia</td>
<td>Diabetic wounds meeting select criteria</td>
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<tr>
<td>Crush injuries and suturing of severed limbs</td>
<td>Chronic refractory osteomyelitis</td>
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<tr>
<td>Cyanide poisoning</td>
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<tr>
<td>Decompression sickness</td>
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<td>Gas embolism</td>
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<td>Gas gangrene</td>
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<tr>
<td>Osteoradionecrosis</td>
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<tr>
<td>Progressive necrotizing infections (necrotizing fasciitis)</td>
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**Table 2:** This table presents a list of accepted indications for hyperbaric oxygen therapy from the Undersea and Hyperbaric Medical Society28

<table>
<thead>
<tr>
<th>Acute conditions</th>
<th>Chronic conditions</th>
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</thead>
<tbody>
<tr>
<td>Air or gas embolism</td>
<td>Enhancement of healing in selected problem wounds</td>
</tr>
<tr>
<td>Carbon monoxide poisoning with or without cyanide poisoning</td>
<td>Osteomyelitis (refractory)</td>
</tr>
<tr>
<td>Clostridial myositis and myonecrosis (gas gangrene)</td>
<td>Skin grafts and flaps (compromised)</td>
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<tr>
<td>Crush injury, compartment syndrome, and other acute traumatic ischemias</td>
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<tr>
<td>Decompression sickness</td>
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<tr>
<td>Delayed radiation injury (soft tissue and bony necrosis)</td>
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<tr>
<td>Exceptional blood loss (anemia)</td>
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<tr>
<td>Intracranial abscess</td>
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<tr>
<td>Necrotizing soft tissue infections</td>
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<tr>
<td>Thermal burns</td>
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**Table 3:** This table presents a list of nonapproved/research conditions for hyperbaric oxygen therapy from Medicare, and the Undersea, and Hyperbaric Medical Society28,29

<table>
<thead>
<tr>
<th>Nonapproved/Research conditions</th>
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<tbody>
<tr>
<td>Acute cerebral edema</td>
</tr>
<tr>
<td>Acute frostbite</td>
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<tr>
<td>Acute or chronic cerebral vascular insufficiency</td>
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<tr>
<td>Acute thermal and chemical pulmonary damage (smoke inhalation with pulmonary insufficiency)</td>
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<tr>
<td>Aerobic septicemia</td>
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<tr>
<td>Anaerobic septicemia and infection other than clostridial</td>
</tr>
<tr>
<td>Arthritic diseases</td>
</tr>
<tr>
<td>Brown recluse spider bites</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Cardiogenic shock</td>
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<tr>
<td>Chronic peripheral vascular insufficiency</td>
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<tr>
<td>Cognitive performance, psychology, and chronic neurology (including senility and cerebral palsy)</td>
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<tr>
<td>Cutaneous, decubitus, and stasis ulcers</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Hearing loss</td>
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<tr>
<td>Hepatic necrosis</td>
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<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Nonvascular causes of chronic brain syndrome (including Alzheimer’s disease)</td>
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<tr>
<td>Organ storage</td>
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<tr>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Pulmonary emphysema</td>
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<tr>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Sports and athletic performance</td>
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<tr>
<td>Tetanus</td>
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Contraindications in Human Medicine

In human medicine, pneumothorax is the only absolute contraindication for HBOT. This contraindication can be overcome by inserting a thoracostomy tube with a Heimlich valve attached during the HBOT treatment. Relative contraindications include emphysema with bulla formation, asymptomatic pulmonary lesions, history of thoracic or ear surgery, uncontrolled high fever, pregnancy, claustrophobia, and upper respiratory infection. Many of these contraindications are related to the known adverse effects of HBOT, such as barotrauma that can be exacerbated by upper respiratory infection and emphysema, or seizures for which an uncontrolled high fever can be a predisposing factor. Adverse effects from some of these conditions can often be mitigated with medications such as anxiolytics or decongestants administered before HBOT.

Complications

Complications with HBOT are related to the toxic effects of oxygen, including myopia and cataracts, barotrauma, decompression sickness, oxidative stress associated with lipid peroxidation as well as the generation of ROS, oxygen-induced seizures, and pulmonary oxygen toxicity.

Barotrauma is related to Boyle’s law and the pressure trauma caused by volume changes of gases in closed spaces. Sinus and middle ear pain are potential problems during compression and decompression as the gas in these enclosed rigid structures contracts or expands causing pressure differentials across the structure and is the most common form of barotrauma. Pulmonary barotrauma occurs mainly during decompression as gas in the lungs expands. If the lung becomes over-distended it can rupture, which can lead to air embolism, mediastinal emphysema (which can cause cardiovascular compromise), or tension pneumothorax. Barotrauma, especially pulmonary barotrauma, is more problematic in monoplace chambers (single occupant) where the clinician cannot get to the patient until the chamber is decompressed, which may take several minutes even in an emergency. Barotrauma effects are difficult to diagnose in veterinary patients but common sense suggests they should be considered. The patient should be monitored for any sign of anxiety or discomfort during compression or decompression such as head shaking or pawing at the head. If such signs are noted the clinician should evaluate the situation and appropriate steps such as slowing compression, immediate decompression, or premedication before further therapy should be taken.

Decompression sickness, related more to Henry’s law, occurs when gas bubbles (primarily nitrogen) form in tissues as solubility is reduced on decompression. Decompression sickness is less common than barotrauma in HBOT and can be treated through recompression of the patient and slowing of the decompression cycle.

The oxidative effects are well correlated with increasing pressure, however, in several experimental rodent studies HBOT has been demonstrated to decrease overall oxidative stress by increasing ROS scavengers and anti-inflammatory mediators.

HBOT can cause oxygen-induced seizures as NO effects can increase excitatory CNS activity. The incidence of oxygen-induced seizures in humans has been shown to be less than 0.03%, and an existing seizure condition unrelated to oxygen therapy is not considered a contraindication to HBOT. There are species differences in susceptibility to oxygen toxicity, based on basal metabolic oxygen consumption, therefore, dogs may be more sensitive to oxygen-induced seizures than humans.

Pulmonary oxygen toxicity is another concern with HBOT. Pulmonary oxygen toxicity is dependent on the concentration and duration of exposure to high oxygen concentrations in addition to species and individual variability. Patients receiving supplemental oxygen therapy may be predisposed to pulmonary oxygen toxicity with HBOT. Many patients who may benefit from HBOT also have conditions that require supplemental oxygen therapy. Strategies such as using the lowest inspired oxygen concentrations possible between sessions and using moderate pressure (1.5–2 ATA) short duration (45 min to 1 h) therapy sessions may help reduce the risk of pulmonary oxygen toxicity in these patients.

Because many of these complications are associated with the increased formation of ROS that overwhelm the intracellular and extracellular antioxidant defense systems, maintaining proper nutritional support and dietary antioxidants such as vitamin E may help to decrease sensitivity to oxidative stress caused by HBOT.

Practical considerations in veterinary medicine

Veterinary patients are reported to accept treatment well. Most will fall asleep during a session but some patients do require an anxiolytic before placement in the chamber. Because sparks from static electricity can cause fires in the 100% oxygen environment in some chambers used in veterinary medicine, metal collars should be removed and preferably metal skin staples be covered. Cotton has less risk of developing static compared with other materials and should be considered...
when selecting towels or bandaging materials for use with HBOT patients. The chamber should be grounded and the use of static ground limb straps should be considered.⁸⁹,¹¹⁸

Monoplace chambers are most commonly used in veterinary medicine, which presents challenges for patient access and monitoring such as vital signs, ECG, or perfusion parameters should problems arise. Although HBOT chambers can be rapidly decompressed it still takes several minutes for this to occur, depending on where the patient is in their treatment cycle, and concerns for barotrauma and decompression sickness increase. Some chambers are equipped with integrated monitors or pass through ports to allow monitoring, IV therapy, or mechanical ventilation during HBOT, which mitigates some of these concerns. Additionally, personnel should be properly trained in patient monitoring, chamber safety, and operations.¹²⁰

Conclusion

HBOT in veterinary medicine is in its infancy and current prospective clinical research is lacking. Understanding the physiology and mechanisms of action of HBOT will help guide case selection and clinical research in HBOT and help establish indicated veterinary uses as well as standardized treatment protocols. Areas of interest may include smoke inhalation, wound healing, and air embolism but also more challenging areas such as postcardiac arrest resuscitation, spinal cord injury, systemic inflammatory response syndrome, and sepsis.

Footnote

* Edwards ML, unpublished data.

References


