

wound healing perspectives®

A CLINICAL PATHWAY TO SUCCESS

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→ HYPERBARIC OXYGEN THERAPY

Necessity of Oxygen

Of all the elements on the periodic table, it is the 8th element, oxygen, that is the most marvelous of them all. It is oxygen and oxygen alone, that drives the biological pulse of the entire planet! Given the physiological importance of this molecule, it is understandable that people have sought to use oxygen to treat many disorders. In this issue of Wound Healing Perspectives, you will find a succinct overview of some of the applications of hyperbaric oxygen.

Given the importance of oxygen to biological systems, it is often asked why there is so little clinical research in this area. The answer lies in the fact that most clinical trials are sponsored by drug companies that stand to profit from new drugs. Accordingly, they are prepared to risk the millions of dollars required to design and execute large scale studies. Because oxygen is a natural substance, it cannot be patented or easily controlled. Hence, the financial forces or incentives that normally fuel the advances of medicine are conspicuously absent in oxygen research.

Nonetheless, in scientific circles, oxygen is experiencing a renaissance period as new technologies such as electron paramagnetic resonance are now opening powerful new windows of understanding on how nature uses oxygen in its grand design.



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Basics of HBO

Hyperbaric oxygen therapy (HBO)—breathing 100 percent oxygen while enclosed in a chamber pressurized between 1.5 – 3.0 times atmospheric pressure, which results in systemic hyperoxia by increasing the dissolved fraction of oxygen in plasma—has been proven to help wounds, especially infected wounds, heal more quickly. In experimental and clinical studies of chronic wound management, HBO has been demonstrated to accelerate granulation tissue formation and wound closure [Boykin, 2001].

According to Medline Plus, in addition to helping heal wounds (e.g., diabetic foot ulcers) and necrotizing soft tissue infections, HBO can also be helpful in the following conditions: gas gangrene, decompression sickness (also known as “the bends”), air or gas embolism, carbon monoxide poisoning, osteomyelitis (bone infection), radiation injuries, skin grafts, and burns. Although used for a variety of diseases and conditions today, history will show that HBO has been under ongoing scrutiny by reimbursement agencies and others since the mid-1970’s.



OXYGEN AT GREATER THAN ATMOSPHERIC PRESSURE STIMULATES COLLAGEN PRODUCTION AND CAPILLARY ANGIOGENESIS. AS TREATMENTS CONTINUE, CAPILLARY DENSITY INCREASES UP TO 80%.



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Hyperbaric oxygen: from past to present

HBO's use for medical purposes can be traced back to 1662 when British physician Henshaw first altered atmospheric pressure for medical use. Henshaw believed that chronic diseases—such as scurvy, arthritis, and rickets—might respond to a reduction in pressure while acute conditions such as fever and inflammation might best be treated with an increase in atmospheric pressure. It is doubtful, however, that Henshaw succeeded in treating these diseases this way since more than 100 years would pass before another attempt to use pressure for therapeutic purposes would be made [Bartlett, 2002].

Part of the delay in developing oxygen's therapeutic uses was a report in 1789 that highlighted the possible toxic effects of oxygen. By 1830, though, hyperbaric facilities using compressed air were beginning to be used in health spas throughout Europe due, in part, to Dr. Marcel Junod's enthusiastic results. The Swiss doctor had constructed a copper chamber and used air pressure of 2-4 ATA to treat patients with pulmonary problems, cites Bartlett.

By 1870 the creation of mobile, pressurized

operating rooms by Fontaine, a French surgeon, allowed patients to recover quicker from anesthesia. In 1878, Paul Bert conducted further testing on the use of oxygen by conducting experiments with oxygen in animals and humans and found oxygen under elevated pressure to be toxic [Bartlett].

The evidence of oxygen's beneficial effect was revealed in 1895 by John Scott Haldane, a Scottish physiologist who showed that a mouse placed in a jar containing oxygen at 2 ATA failed to develop signs of carbon monoxide poisoning. By 1928, Dr. Orval J. Cunningham, a leading exponent of hyperbaric air therapy, began to treat a variety of diseases (diabetes, hypertension, syphilis, and cancer), but due to a lack of controlled studies and a failure to report data, Cunningham was censured by the AMA and the hospital he was affiliated with closed in 1930 [Bartlett]. Seven years later, American medical professor and inventor Louis A. Shaw and Dr. Albert R. Behnke developed oxygen-based decompression and treatment protocols for the management of decompression sickness. Though this was the first use of hyperbaric oxygen to treat a medical

disorder, it would be 30 years before the U.S. Navy fully adopted the oxygen-based treatment protocols. [Bartlett].

Nineteen fifty-nine starts the modern age of hyperbaric medicine when Dr. Boerema uses the combination of pressure and oxygen as an adjunct to cardiac surgery. Churchill-Davidson investigated the possible use of HBO to improve the radio sensitivity of tumors to external beam radiation, which led to the development of the oxygen-compressed monoplace hyperbaric chamber [Bartlett].

By 1961, Boerema teams with another surgeon to publish the first paper detailing the utility of hyperbaric oxygen as an adjunct in the management of anaerobic infections (gas gangrene). This paper helped spark international interest in the therapeutic potential of oxygen under pressure.

In 1966, survivors of a coal mine disaster who sustained both thermal burns and CO poisoning were treated with HBO. Patients treated with HBO appeared to heal faster and were discharged sooner

(continued on page 3)

Advantages of multiplace chambers

- Maximum working pressure of 6 ATA is possible
- More space and patient contact is possible (ICU activities, pneumothorax management)
- Ability to use some electrical equipment in the chamber
- Entrance and exit of staff during therapy

Advantages of monoplace chambers

- Low cost
- Nominal space requirements
- Modest engineering requirements
- Chamber is relatively mobile
- Treatment protocol is specific for the condition and patient
- Modest staffing requirements
- No risk of iatrogenic decompression sickness

The UHMS: an overview

Founded in 1967 as the Undersea and Medical Society by physicians and scientists interested in diving and high pressure physiology, the rapid growth of clinical hyperbaric oxygen therapy prompted the society less than 20 years later to add the term “Hyperbaric” to its name, officially becoming the Undersea and Hyperbaric Medical Society in 1986.

The primary reference for appropriate uses of hyperbaric oxygen therapy is contained in the Report of the Undersea and Hyperbaric Medical Society’s Hyperbaric Oxygen Committee, which was established by the UHMS in 1976, following a request from the Social Security Administration, which administered the Medicare program at the time, and Blue Cross, who

were concerned with the growing number and variety of claims for reimbursement.

The committee’s first report (released in 1977) stratified disorders into four categories—disorders with scientific and clinical evidence to support the use of HBO, disorders with clinical evidence to support the use of HBO, disorders with a scientific rationale, and disorders treated without scientific or clinical evidence [Wood]. However, most of the clinical evidence cited in the report to support the use of HBO in many disorders was based on case reports and retrospective studies, not on double-blind, placebo-controlled studies, which was considered controversial at times [Wood].

The committee and its report would evolve over time. Certain conditions would be added and later removed (as was the case with cerebral edema, for example) while other conditions would be extended (such as with soft tissue radiation injury).

According to Wood, a new version of the report is released every three to five years. The current version of the report was issued in 2003, and a new version is expected to be released in late 2008. Today, the committee has developed a specified process for adding new indications. New indications for HBO are considered for acceptance at the meeting of the Hyperbaric Oxygen Committee during the annual meeting of the Undersea and Hyperbaric Medical Society [Wood]. ■

Patients treated with HBO will have the following bedside testing completed prior to each treatment:

- A complete set of vital signs will be obtained
- All diabetics will have a finger stick blood sugar prior to, and following each, hyperbaric procedure

Hyperbaric oxygen *(continued from page 2)*

than those patients who did not suffer concurrent CO poisoning and did not receive HBO. In 1967, six U.S. Navy medical officers formed an organization dedicated to diving and undersea medicine. By 1977, the era of formal indication began, thanks to the Undersea Medical Society, which formed an advisory committee to sort through the many “claimed indications” by examining the evidence. What resulted is the Hyperbaric Oxygen

Therapy-A Committee Report, used as important guidelines for reimbursement agencies. The National Board of Diving and Hyperbaric Technicians formed in 1991, administering credentialing examinations for diver medics, certified hyperbaric technicians, and hyperbaric nurses. By 1999, HBO was formally recognized by the American Board of Medical Specialists as a physician subspecialty. The American Board of

Medical Specialists went on to approve a request by the American Board of Preventive Medicine for Certification of Added Competency in Undersea Medicine. In 2002, a new ACHM exam was developed, which is offered to the medical community on an international basis [Bartlett]. ■



HBO's potential anti-cancer effects on breast cancer cells



One of the most significant new findings from this study was that the total metastatic load in the lung is reduced after HBO.

Approved Indications

The following indications are approved uses of hyperbaric oxygen therapy as defined by the Hyperbaric Oxygen Therapy Committee:

- Decompression illness ("the bends")
- Acute peripheral arterial insufficiency
- Acute traumatic peripheral ischemia
- Air or gas embolism
- CO and Cyanide poisoning
- Clostridial gas gangrene
- Compromised skin grafts and skin flaps
- Crush injury; compartment syndrome, and other acute traumatic ischemias
- Delayed radiation injury (soft tissue and bony necrosis)

Despite the notion that HBO could actually have cancer-enhancing effects, it is frequently administered to cancer patients. Therefore, Haroon, Patel, and Al-Mehdi in a 2007 study, decided to evaluate the growth of murine breast cancer cells in the lung after hyperbaric oxygen treatment in an experimental metastasis assay.

To do this, young nu/nu mice were injected intravenously with $3 \times 10(3)$ 4T1-GFP tumor cells per g body weight followed by lung isolation, perfusion, and intact organ epifluorescence microscopy one to 37 days after injection. A group of animals ($n=32$) was exposed once daily for five days a week to 45 minutes of 2.8 ATA

hyperbaric oxygen in a research animal chamber. Control animals ($n=31$) were not subjected to HBO, but received similar intravenous administration of $3 \times 10(3)$ 4T1-GFP tumor cells. Single tumor cells and colonies were counted in the subpleural vessels in areas of about 0.5 cm² of lung surface [Haroon et al].

What Haroon et al found was that HBO treatment did not lead to an increase in the number of the large or small colonies in the lungs. Instead, there was a significant reduction in the number of the large colonies when observed at varying periods of time after hyperbaric treatment. Most importantly, there was a significant decrease in large colony size in the HBO group

during all periods of observation. The results indicate that HBO is not prometastatic for breast cancer cells, but, instead restricts the growth of large tumor cell colonies [Haroon et al]. One of the most significant new findings from this study was that the total metastatic load (the combined mass of large colonies, small colonies, and the single cells in the target organ) in the lung is reduced after HBO. What's more, HBO treatment did not lead to an increase in the combined number of metastatic foci in the lung. The load reduction was accomplished because the size of the colonies was limited, states Haroon et al.

Studies reveal that there is no adverse effect of HBO on tumor growth. In fact, the research suggests that HBO may have an anti-cancer effect with breast cancer cells. Use of HBO in human breast cancer patients did not have any adverse effects in a recent long-term follow up study and is even considered for treating lymphedema associated with breast cancer surgery. ■

HBO: A useful adjunct in the treatment of frostbite

According to Folio, Arkin, and Butler in a 2007 article, anecdotal evidence in the literature reveals that HBO may be a useful adjunct in the treatment of frostbite. The case highlighted in the Folio et al article examined a healthy 28-year-old female climber who experienced frostbite on all fingers because of a series of events during a mountain climb where severe unexpected weather occurred. The experienced climber had no significant medical history, no metabolic disorders, nor did she have a history of smoking or significant occupational exposure, and was in excellent physical condition.

After enduring four days of freezing temperatures, the climbing team was rescued and the female patient presented with frostbite on all fingers of both hands; however, only three had turned black, representing dry eschar on the tip; the rest were gray/white. According to Folio et al, a physical examination at that time revealed that the fingers had not refrozen, based on the appearance and temperature of the fingers. It was also difficult to establish the exact time of frostbite

onset, noted the authors. After initial primary-care treatment (the patient was released to a warm environment with a gauze wrap and aloe gel), the patient was able to obtain HBO treatment with no reports of adverse effects or contraindications. The patient received a total of 21 treatments over a span of three months and gained full function of all fingers, with only cosmetic defects on one finger.



No fingers required amputation; however, HBO physicians performed some debridement of superficial tissue after the first few weeks of treatment. The patient maintains normal neurological motor function and only mildly decreased sensation (especially under cold conditions) on the tip of the misshapen finger [Folio et al].

According to Folio et al, from a mechanistic viewpoint, HBO has great potential benefit for patients, including improved red blood cell count, theological features, decreased edema, improved oxygenation, interrupted leukocyte adhesion, diminished lipid peroxidation, and increased capillary density. Since few cases of HBO-treated frostbite have been reported (only 14 reported cases before 1971 and then two since 2001), this report adds value to the literature until a case series is reported or a large prospective study is undertaken. However, according to the authors of this study, the human data are anecdotal and the animal data are conflicting. Therefore, a systematic research program using animal models and human cases is needed before HBO is deemed the standard of care. ■

Approved Indications

cont'd

- Diabetic lower extremity wounds that meet appropriate criteria
- Intracranial abscess
- Necrotizing soft tissue infections
- Osteoradionecrosis
- Refractory osteomyelitis
- Selected problem wounds
- Thermal burns
- Acute exceptional blood loss anemia (not CMS approved)

SOURCE: UNDERSEA AND HYPERBARIC MEDICAL SOCIETY; NATIONAL HEALING CORPORATION

HBO therapy for acute traumatic ischemia and crush injury

Pneumothorax: contraindication for HBO

An absolute clinical contraindication for HBO is a patient with an acute pneumothorax or with a significant history of recent and/or recurrent pneumothorax development. In the hyperbaric setting, a recurrent pulmonary leak at the parietal or visceral pleura could lead to the rapid development of a tension pneumothorax and significant cardiovascular compromise. Other contraindications for treatment include recent or significant ear or sinus surgery; chemotherapy (especially with oxygen-free radical-based agents, such as adriamycin); and an acute or significant history of seizure disorders, especially if poorly controlled with anti-seizure medications. In addition, claustrophobia is a relative contraindication for 10-15 percent of patients selected to receive HBO.

SOURCE: JOSEPH V BOYKIN, ADVANCES IN SKIN & WOUND CARE, 2001

Although the use of hyperbaric oxygen therapy as an adjunct in the management of surgical disease is still considered controversial, HBO therapy has been recommended as an adjunct treatment in acute traumatic ischemia and crush injury, according to Garcia-Covarrubias, McSwain, Van Meter, and Bell in a 2005 article.

The authors performed a systematic review of the literature, extracted and summarized the data of said research and examined study design, patient traits (including number of subjects and type of injury), HBO protocol, outcome, and data class. Some problems with the HBO reports were encountered, noted the authors, including variability in mechanisms of injury (which influenced outcomes) as well as some anecdotal reports of patients whose severity of injury and functional outcome post-injury were unclear [Garcia-Covarrubias et al].

The authors also reviewed the evidence-based recommendations for the management of the injured extremity developed by the Eastern Association for the Surgery of Trauma (EAST) Ad Hoc Committee on Practice Management

Guidelines, which evaluates the clinical experience with HBO in the management of crush injury and/or acute traumatic peripheral ischemia. These guidelines are based on class II and class III data, including more than 7,000 patients [Garcia-Covarrubias et al]. Although several publications favored using HBO in the management of these patients, only nine documents fulfilled the inclusion criteria for the authors' study. What's more, only eight class III studies and one class I article (for a total of 150 patients) existed, which confirms the need for more well-designed, randomized controlled studies, state Garcia-Covarrubias et al. In addition, the review conducted by Garcia-Covarrubias et al revealed the existence of several animal models, which have shown to provide significant reduction in loss of muscle function, edema, and muscle necrosis when HBO is used in crush injury and compartment syndrome, even in the presence of hypovolemic shock. HBO preserves ATP levels and attenuates glutathione depletion when administered immediately after reperfusion. It also attenuates ischemia-reperfu-

sion injury that appears to be mediated by downregulation of key adhesion molecules such as intercellular adhesion molecule-1 and beta-2 integrins [Garcia-Covarrubias et al].

Furthermore, adjunctive HBO is not likely to be harmful in the management of crush injury and acute traumatic ischemia. Pathophysiologic mechanisms, animal data, and clinical studies (level I and III evidence) suggest it could be helpful, note Garcia-Covarrubias et al. If available, HBO should be administered early. Meanwhile, transcutaneous oximetry may prove useful as an objective measure to triage patients needing amputations. What's more, surgery should never be delayed, and prophylactic fasciotomies should be the standard of care in acute compartment syndrome [Garcia-Covarrubias et al]. Due to limited evidence, additional clinical studies are needed, state Garcia-Covarrubias et al, especially those that include an accepted injury scoring system, mechanism of injury, delay to treatment, standardized HBO protocol, amputation and wound infection rate, healing time, long-term function, and cost-effectiveness. ■

The benefits of hyperbaric oxygen in superficial dermal wounds

Significant experimental data support the adjunctive use of hyperbaric oxygen therapy for burn injuries. Microscopically, hyperbaric oxygen is believed to preserve the microcirculation in the partially injured tissue, thereby decreasing the overall size and depth of the wound, according to Niezgodka, Cianci, Folden, Ortega, Robin, Slade, and Storrow [1997]. The potential benefits of hyperbaric oxygen therapy in burn patients include reducing edema, preserving marginally viable tissue, enhancing host defenses, promoting wound closure, reducing morbidity and mortality, shortening hospitalization, and reducing hospital costs.

Clinical reports and various series of non-randomized burn patients treated with hyperbaric oxygen provide mostly favorable data, noted the authors. However, according to the Niezgodka et al study most burn unit physicians believe there is insufficient objective evidence to justify hyperbaric oxygen use in burn treatment plans.

Niezgodka et al designed a protocol to either confirm or challenge these previous findings and conducted a double-blinded randomized study of 12 healthy, non-smoking volunteers (seven males, five females) to provide a more objective assessment of hyperbaric oxygen use in burn patients. The volunteers were screened for contraindications to hyperbaric oxygen therapy (active cancer, acute sinusitis, otitis media, pneumonia, pregnancy, pneumothorax) and given a single test hyperbaric exposure.

A standardized wound model was used for the painless creation of a volar forearm lesion on volunteers by applying a suction device to form a blister, excising its epidermal roof, and irradiating the exposed dermis with ultraviolet light. Subjects were randomized into either a hyperbaric oxygen group (100 percent oxygen at 2.4 ATA, n=6) or the sea-level air-breathing equivalent control group (8.75 percent oxygen at 2.4 ATA, n=6). Both groups then under-

went standard hyperbaric therapy. Each subject received two dives per day over a three-day period. The wounds were studied noninvasively prior to treatment and once per day over six days for size, hyperemia, and exudation, with epithelialization as the endpoint.

The hyperbaric oxygen group showed a 42 percent reduction in wound hyperemia, a 35 percent reduction in the size of the lesion, and a 22 percent reduction in wound exudation (p values of 0.05, 0.03, and 0.04, respectively). Moreover, there was no significant difference when epithelialization was used. Therefore, Niezgodka et al noted that these findings suggest that observed differences in wound size, hyperemia, and exudation were attributable to hyperbaric oxygen therapy.

More importantly, this protocol supports some of the earlier conclusions that hyperbaric oxygen is beneficial in superficial dermal wounds [Niezgodka et al].■

Relative risks of HBO

Patients with the following conditions may run a health risk when using HBO:

- Upper respiratory infections and chronic sinusitis
- Seizure disorders
- Emphysema with CO2 retention
- High fever (above 100 F)
- Patients who are pregnant
- Patients who are taking steroids, narcotics, or phenergan

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Frequently asked questions about HBO:

Q: Why is HBO thought to be effective in wound management?

A: Two predominant mechanisms are believed to be responsible for enhanced wound healing with HBO—wound hyperoxia and increased cellular wound nitric oxide (NO) production. The hyperoxic response during wound repair satisfies several of the oxygen-dependent biologic needs of cutaneous wounds that are critical for normal wound healing. These include: the need for increased aerobic metabolism; increased inflammatory and cellular requirements for oxidative microbial killing and phagocytosis, collagen production and cross-linking; osteoclast resorption and bone formation; and epithelialization

and wound matrix formation; and the creation or enhancement of a significant oxygen gradient between the hypoxic wound and peripheral tissues that act to stimulate the process of neovascularization.

Q: What types of wounds respond best to HBO?

A: Generally, wounds that respond best to HBO have been acutely or chronically compromised by hypoxia and/or infection or pathologic conditions that have led to a substantial, but reversible, impairment related to these problems. Clinical conditions associated with these types of wounds are peripheral vascular disease, diabetes, radiation necrosis, mixed soft tissue infections, refractory osteomyelitis, and selected traumatic wounds.

Q: Is there a specific protocol for HBO used to manage wounds?

A: With rare exception, HBO is utilized adjunctively in wound management and its application should not preclude the implementation of established practices for standard wound care, including debridement, antibiotic therapy, revascularization, or surgical reconstruction. Protocols that have been developed for the use of HBO in wound management uniformly use an initial phase of wound evaluation, diagnosis, debridement, quantitative cultures and biopsies, surgical evaluations and, if indicated, noninvasive venous and arterial studies (Doppler examination).

INDICATIONS FOR HYPERBARIC OXYGEN TREATMENT

- Actinomycosis
- Acute peripheral arterial insufficiency
- Acute traumatic peripheral ischemia
- Chronic refractory osteomyelitis
- Crush injuries and suture (reattachment) of severed limbs
- Diabetic foot ulcers
- Osteoradionecrosis
- Preparation and preservation of compromised skin grafts
- Progressive necrotizing infections
- Soft tissue radiation injury