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INVITED ARTICLE

Hyperbaric oxygen for chronic wounds

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ABSTRACT: Hyperbaric oxygen therapy (HBOT), the administration of pressurized 100% oxygen, is used as an adjunct to aid healing in selected chronic wounds. Though the therapy has had a controversial history, research is now elucidating the mechanisms by which HBOT helps to heal wounds. HBOT increases growth factors and local wound signaling, while also promoting a central stem cell release of endothelial progenitor cells from the bone marrow via nitric oxide pathways. The clinical data continue to accumulate in support of HBOT to help hasten wound healing, and reduce the amputation rate in diabetic ulcers. In appropriate patients, HBOT is an effective, noninvasive, adjunct modality that can be used to hasten chronic wound healing.

KEYWORDS: diabetes, hyperbaric oxygen, wound

Chronic wound physiology

The role of oxygen in the physiology of wound healing has been well established (1–3). Etiologies ranging from surgical incisions to diabetic neuropathic injury cause infarcted, hypoxic tissue within the wounded region (4). This local ischemia is often superimposed on preexisting arteriopathy and chronic ischemia, which may have been clinically silent prior to the initiation of a wound. The cascade of events that follows wound creation involves a complex interplay of cellular activity. Platelets degranulate at the site of injury, followed by an influx of macrophages and fibroblasts, and eventually leukocyte migration (5). The increased cellular activity in the wounded area further diminishes the local oxygen availability (4).

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Wound healing mechanisms become impaired by the decreased local oxygen tensions. There is impaired phagocytosis by macrophages, oxidative killing of bacteria, and fibroblast deposition of collagen (3,6). Extra cellular matrix formation ultimately relies on conversion of pro-collagen to collagen (via hydroxylation of proline). Prolyl hydroxylase and lysyl hydroxylase, oxygen-dependent enzymes, effect this conversion (5). Oxygen tensions of at least 30–40 mmHg have been shown as required to complete steps in wound healing including production of reactive oxygen species, neutrophil bacterial killing, and collagen formation (1,5–7). Oxygen levels within many wounds have been found to be substantially lower than this (1,2). Simple supplemental oxygen administered by mask has even been shown to decrease wound infection rates (8).

History of hyperbaric therapy

Hyperbaric oxygen therapy (HBOT) describes the inhalational administration of 100% oxygen while

under increased pressure (exceeding atmospheric pressure, normobaric conditions, or one-atmosphere absolute, ATA). Hyperbaric conditions are created via a specially constructed patient chamber that allows for pressurization, usually up to 3.0 ATA.

Initial reports of the therapeutic administration of oxygen began to emerge in the early 1900s, with Haldane reporting on its use (9). In the 1920s, word spread of Dr. Orval J. Cunningham of Kansas City, MO. Dr. Cunningham had constructed a tank to pressurize oxygen and treat a variety of conditions including diabetes, pernicious anemia, syphilis, asthma, and carcinoma (10). Dr. Cunningham had also partnered with industrialist H. H. Timken to build an enormous, spherical hyperbaric chamber (or sanitarium) in Cleveland. Though Dr. Cunningham may have actually been a pioneer of hyperbaric medicine, he was ridiculed at the time. The *Journal of the American Medical Association* chastised him, stating "Dr. Cunningham advances a thesis that is altogether without scientific proof," and his treatment "seems tinctured much more strongly with economics than with scientific medicine." (10) The Journal celebrated the deconstruction of the tank in 1942 (and the contribution of the scrap metal to the war effort), asserting that the "useless tank to become useful tanks." (11) The reality is that Dr. Cunningham was correct in his assumptions, but not his indications. The general distrust of his methods was likely due to the medical community's ignorance of oxygen physiology at the time. One critique explicitly incorrectly stated, "to claim that oxygen may be made to reach the tissues at higher tensions is only to display ignorance of the mechanism by which oxygen is transported." (12)

Enthusiasm returned over time, as physicians noted the benefits of increased oxygen for the effects of radiation therapy and in the field of anesthesia. By 1967, The Undersea and Hyperbaric Medical Society (UHMS) was formed, and is currently responsible for publishing the indications for HBOT.

Physiology of hyperoxia

Though Dr. Cunningham was unable to produce scientific rationale for his assertions, the physiology surrounding oxygen transport was rapidly elucidated. The equation for concentration of oxygen in arterial blood (Ca_{O2}) is:

$$Ca_{O2} = (1.34 \times Hb \times Sa_{O2}) + (0.003 \times Pa_{O2})$$

where Hb denotes hemoglobin, Sa_{O2} is arterial oxygen saturation, and Pa_{O2} is the partial pressure of oxygen in the blood (13). Under normobaric conditions, the contribution of dissolved oxygen to the total oxygen in arterial blood ($0.003 \times Pa_{O2}$) is negligible. However, when the partial pressure of oxygen becomes significantly elevated under hyperbaric conditions, this value increases substantially. Alveolar oxygen concentrations can be doubled, or even tripled under hyperbaric conditions, leading to partial pressures of oxygen exceeding 2000 mmHg.

There are several indications for hyperbaric therapy (as it relates to chronic wounds). Increasing hydrostatic pressure will, according to Boyle's law, decrease the volume of gases, thus making hyperbaric therapy an effective treatment for divers suffering decompression sickness, or caisson disease suffered during construction (14). The importance of HBOT for chronic wounds, however, rests on its ability to raise the alveolar partial pressure of oxygen. Thousands of genes have been identified whose regulation is affected in cells exposed to HBOT, and these effects persist for up to 24 hours following treatment (15).

The molecular effects of hyperoxia, though not completely understood, appear related to the production of reactive oxygen species, and reactive nitrogen species (including nitric oxide, NO) (14). Reactive oxygen species act as signal transducers, promote growth factors, and participate in other pathways of inflammatory mediation (14,16,17). Hyperoxia effects the production of nitric oxide via stimulation of the three isoforms of nitric oxide synthase (NOS) (18–20).

Nitric oxide, specifically produced by eNOS, has been shown to be requisite for release of endothelial progenitor cells (EPC) from the bone marrow (21). These EPC are responsible for vasculogenesis (the process of bone marrow stem cell derived neovascularization) (22). This is contrasted with angiogenesis, the extension of locally existing capillaries into adjacent tissue (23). Early work hypothesized that hyperoxia stimulation of NOS could increase the bone marrow NO production, and lead to peripheral mobilization of EPC to aid in wound healing. This was found to be the case, with HBOT resulting in peripheral EPC mobilization from the bone marrow via a NO mechanism, and increased wound healing (24,25). This finding, combined with prior data suggesting hyperoxia can raise local wound growth factor levels (26),

FIG. 1. A monoplace hyperbaric oxygen chamber.

paints a picture of combined local and systemic hyperbaric oxygen effects on wound healing.

Diabetic patients are known to suffer from chronic nonhealing wounds, and at the same time, have been demonstrated to have decreased mobilization of EPC (27–29). This finding has specifically found to be ameliorated by the use of HBOT, which causes an increase in the number of circulating progenitor cells in diabetic patients (27,28,30). This increasing body of evidence for the combined peripheral and central effects of HBOT begins to explain the observed clinical benefits seen in diabetic patients with chronic wounds.

Mechanisms of administration

Hyperbaric oxygen therapy is administered to patients in a completely enclosed vessel capable of raising the pressure within to up to three times atmospheric pressure. Monoplace chambers are designed for a single patient, and are often cylindrical structures built of translucent acrylic, or other similar materials. (FIG. 1) Monoplace chambers are filled with 100% oxygen, and masks are present that patients can use to breathe air ("air breaks"). Specialized interfaces allow for monitoring, communications with the patient during therapy, and entertainment.

Multiplace treatment chambers are available for varying numbers of patients, both seated and confined to stretcher (FIG. 2). The tanks are pressurized with air, and the patients breathe 100% oxygen via mask or hood. Treatment in either multiplace or monoplace chambers occurs for 90–120 minutes. Treatments are often scheduled daily, but can be more frequent depending on the diagnosis.

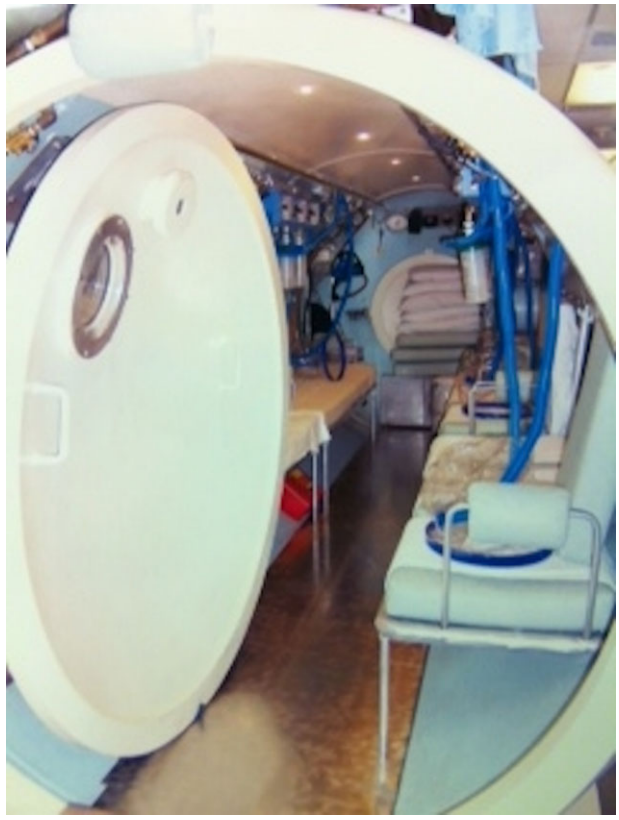

FIG. 2. A multiplace hyperbaric oxygen chamber.

In an effort to reduce the cost, difficulty, potential systemic complications, and improve

availability, the concept of "topical hyperbaric oxygen therapy" (THOT) has been developed. Although attractive in concept, THOT is not an equivalent therapy to true HBOT administered in a hyperbaric chamber. THOT consists of surrounding a wounded region or extremity with a device (airtight sleeve or chamber) that then becomes mildly pressurized with humidified oxygen. Despite the claims of wound penetration of oxygen up to 2 mm deep (based on animal studies), there is little to no pressurization above atmospheric pressure achieved by the setup, making "hyperbaric" a misnomer in this setting (31–33). Additionally, evidence supporting this practice is weak, with cited studies consisting of small numbers of patients, sometimes run by investigators with ties to the device manufacturer, and with varying outcomes (32–34). In 2005, the UHMS issued a position statement, concluding that THOT is not equivalent to HBOT, it should be subject to the same scrutiny as true HBOT, the data currently existing are weak, and at this point in time, the treatment should not be reimbursed or used outside of a clinical trial until more substantial data has been collected (35).

Newer devices continue to arrive looking for faster and easier methods for providing wounds with increased oxygen availability. A recent publication highlights a device that combines hyperoxygenated saline applied to a wound with a surface acoustic waveform low-frequency ultrasound device (36). As variants of topical oxygen therapy begin to appear, they continue to be hampered by a lack of supporting evidence, and small numbers of patients in nonrandomized trials. Finally, all types of topical oxygen therapy delivery devices lack the ability to exploit the central (bone marrow stem cell) effects of true hyperbaric oxygen delivery (discussed previously).

Indications

There are 14 approved indications for HBOT as defined by the UHMS (37). "Enhancement of healing in selected problem wounds" is the most relevant indication with regard to chronic wounds; however, we will include the discussion of compromised flaps and grafts, as well.

The most common chronic wound presenting for evaluation and therapy with hyperbaric oxygen will likely be a refractory diabetic ulcer. In fact, the indication for use of hyperbaric therapy as an adjunct is for ischemic, infected (Wagner grade 3) diabetic ulcers. Chronic diabetic ulcerations are often characterized by ischemia, decreased growth factors, impaired angiogenesis, impaired extracellular matrix production and deposition, and decreased number and function of bone marrow-derived endothelial progenitor cells (27,38–40). Treatment for diabetic foot ulcers usually occurs at 2.0–2.5 ATA for 90–120 minutes, once or twice daily, for between 20 and 40 treatments (or more), with variations to these protocols based on clinical assessment (7,41). Wound healing in diabetic subjects is associated with collagen synthesis during hyperbaric therapy (42).

The use of transcutaneous pressure of oxygen (TcpO2) measurements can be another useful data point in predicting both propensity to heal, as well as the likelihood that HBOT will provide a benefit. This measurement involves the placement of a noninvasive electrode over the skin adjacent to the wound. The electrode heats the area, causing a local hyperemia and aiding in diffusion of oxygen to the sensor. Measurements of less than 40 mmHg have been correlated with impaired wound healing, whereas values above 40 have been shown to have little benefit from the addition of hyperbaric oxygen (7,39,43). Monitoring trends in TcpO2 readings can predict outcomes, and response to therapy during treatment (44). "Oxygen challenge" can also be performed, where TcpO2 readings are taken while in 2.5 ATA hyperbaric oxygen. Values of >200 mmHg are predictive of improved wound healing with the addition of HBOT (7,45).

Compromised flaps and skin grafts pose a unique challenge for management. Often, flaps (in the case of amputation or post-irradiation) are located in areas of relative ischemia, as are skin grafts for wounds. Skin grafts have long been shown to benefit from hyperbaric oxygen, having increased survival and area of "take" (46). Following amputation, the resultant tissue flaps used to close the extremity can have tenuous blood supply, and in threatened flaps, hyperbaric oxygen can reduce oxygen deficits, decrease edema, and stimulate both angiogenesis and vasculogenesis, improving survival (4,47).

Evidence for hyperbaric oxygen and chronic wounds

Since its inception, HBOT was faced with a good deal of skepticism from the scientific and medical communities. Early criticism stemmed from the lack of understanding of gas physiology, and the seemingly random application of the treatment to various disorders without regard for mechanism.

Since the formation of the UHMS, both the science behind hyperbaric oxygen and the clinical benefit it confers have been clarified. Effectiveness has been measured to date in decreased wound size and lowered rate of amputation.

In 2003, Abidia et al. published a double-blind, randomized controlled trial comparing HBOT to hyperbaric air for the treatment of ischemic non-healing diabetic ulcers. Sixteen patients were randomized to air or 100% oxygen, treated for 30 sessions in a multiplace chamber and followed out to 1 year. The results demonstrated a significantly improved wound healing rate (5/8 vs. 0/8, $p = 0.026$) for those treated with hyperbaric oxygen. Common criticisms include the small number of patients, the vague description of ischemia (ankle-brachial index < 0.8, toe-brachial index < 0.7), and the exclusion of patients with planned vascular reconstruction.

The HODFU trial (Hyperbaric Oxygen Therapy in Diabetics with Chronic Foot Ulcers), published by Löndahl et al. in 2010, is widely cited as one of the largest studies supporting the use of HBOT (48). This single-center, double-blinded, placebo-controlled trial randomized 94 patients with Wagner grades 2, 3, 4 ulcers to hyperbaric oxygen and hyperbaric air. The HODFU study demonstrated improved ulcer healing rates at 1 year, especially in those undergoing >35 treatments.

In 2004, a Cochrane Review systematically evaluated the data available at that time with regard to efficacy of hyperbaric oxygen (41). While subject to the usual criticisms of meta-analysis and reviews, the conclusion (based on pooled data from three trials studying 118 patients) was that hyperbaric oxygen reduced the risk of major amputation in diabetic foot ulcer patients (risk ratio 0.31, 95% confidence interval (CI) 0.13 to 0.71). The review concluded that four patients were needed to treat to avoid one amputation. This review was updated in 2012, adding a substantial number of studies (49). Five trials were included that examined reduction in amputation (total of 309 patients), and at this time, no statistically significant reduction in amputation rate was found due to HBOT (47,48,50–52). The 2012 Cochrane Review did continue to find an increased rate of ulcer healing in those treated with HBOT (three pooled studies with 140 patients, $p = 0.02$) (48,51,53).

Goldman published yet another meta-analysis in 2009, based on OVID/Medline database searches for HBOT trials. The review concluded that HBOT "reduces chance of amputation (odds ratio (OR) 0.242, 95% CI: 0.137–0.428) (7 studies) and improves chance of healing (OR 9.992, 95% CI: 3.972–25.132) (6 studies)" (54). Criticisms of this, and most meta-analyses, focus on the diversity of studies pooled, and those excluded. Studies looking at the efficacy of HBOT are particularly difficult to evaluate in this fashion due to the significant number of patient and trial variables including patient demographics, length and extent of diabetic disease, extent of ischemia, varying wound location, differing controls, differing hyperbaric protocols, definitions of conservative therapy (requirements for wound care), length of follow-up, outcomes measured, and varying numbers of enrolled patients.

Current trials continue to demonstrate benefits of HBOT with regard to both wound healing rates, as well as decreased rate of amputation (44). Additionally, due to the concern of the low quality of previous studies and inconsistent data, a new trial has been initiated in Canada. This trial is a double-blind, randomized controlled trial examining the efficacy of HBOT (2.4 ATA for 90 minutes, 30 total treatments) for Wagner grades 2–4 diabetic ulcers (55). Primary outcome will be freedom from amputation. This should add data from a well-designed trial to our current knowledge of the efficacy of hyperbaric oxygen.

Complications

Hyperbaric oxygen therapy has been successfully used safely for decades throughout the world. However, there are complications associated with the therapy ranging from mild to catastrophic. Claustrophobia is a common complaint, especially in monoplace chambers (56,57). As a systemic therapy, the increased oxygen can have an effect on glucose levels (often problematic hypoglycemia as many treated are diabetic) (32,48). Oxygen toxicity has been reported, but is generally well tolerated due to the short course of therapy and "air breaks" can lessen the incidence as well. This toxicity can be manifested by neurotoxicity (grand mal seizures), and progressive myopia (which is usually self-limiting) (14,56). Middle ear barotrauma can often be prevented by patient maneuvers (e.g., yawning or swallowing) to equalize their middle ear pressures, but can result in the need for myringotomy or pressure equalization tubes (4,47). Untreated pneumothorax remains an absolute contraindications for treatment, though bullous emphysematous changes are treated with caution as well (4,56). The use of certain drugs in combination with hyperbaric oxygen including doxorubicin, bleomycin, disulfiram, cis-platinum, and mafenide acetate worsens outcomes and potentially increases mortality (4).

The most worrisome complication associated with HBOT is chamber fires or explosions. Three components are required for fire: ignition, oxygen, and fuel. Oxygen-enriched hyperbaric chambers have a substantially lower energy required for ignition, and thus pose a significant fire hazard to patients while enclosed. This is mitigated somewhat in multiplace chambers, as they are filled with air, not 100% oxygen. Due to strict regulations regarding the presence of electronics, metallic objects, and other sources of ignition, hyperbaric chamber fires are rare occurrences, though unfortunately nearly uniformly fatal when they occur (58). Prior to 2009, there had not been a fatality in North America in a hyperbaric chamber (59). In May of 2009, a young boy and his grandmother were victims of a chamber fire in south Florida that they did not survive (60). The boy was being treated for an unapproved indication (cerebral palsy), and numerous contributing factors to the accident were identified including incorrect clothing, absence of static guards (static spark was cited as the cause of ignition), presence of metallic objects and alcohol-containing objects within the chamber, poor maintenance of the chamber electrical systems, and insufficient supervision of the patients during treatment (61).

Conclusions

From its inception, HBOT was found to benefit patients. Since that time, much effort has been focused on the mechanisms and correct indications. As hyperbaric research progresses, we are elucidating the mechanisms of wound healing, both via the local action of growth factors and the central action via mobilization of stem cells. Clinically, many trials have shown the benefit of treating chronic wounds, especially diabetic foot ulcers. Unfortunately, meta-analyses have been tempered in their enthusiasm, mostly due to the heterogeneity of the clinical trials studied. It may be more prudent to evaluate these studies going forward on their own merit, rather than pool the data into meta-analyses. Further experimentation, both with regard to molecular mechanisms of action, and to clinical effectiveness is certainly warranted. Despite this need for further study, HBOT is currently able to offer a safe, effective, noninvasive adjunct to help healing in selected chronic wounds.

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