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REVIEW ARTICLE

Hyperbaric Oxygen Therapy: Descriptive Review of the Technology and Current Application in Chronic Wounds

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Summary: Hyperbaric oxygen therapy (HBOT) serves as "primary" or "adjunctive" therapy in a wide range of pathologies. It is considered the mainstay of management for potentially life-threatening conditions such as carbon monoxide poisoning, decompression illness, and gas embolisms. Moreover, HBOT has been utilized for decades as an adjunctive therapy in a variety of medical disciplines, including chronic wounds, which affect approximately 6.5 million Americans annually. In general, chronic wounds are characterized by hypoxia, impaired angiogenesis, and prolonged inflammation, all of which may theoretically be ameliorated by HBOT. Nonetheless, the cellular, biochemical, and physiological mechanisms by which HBOT achieves beneficial results in chronic wounds are not fully understood, and there remains significant skepticism regarding its efficacy. This review article provides a comprehensive overview of HBOT, and discusses its history, mechanisms of action, and its implications in management of chronic wounds. In particular, we discuss the current evidence regarding the use of HBOT in diabetic foot ulcers, while digging deeply into the roots of controversy surrounding its efficacy. We discuss how the paucity of high-quality research is a tremendous challenge, and offer future direction to address existing obstacles. *(Plast Reconstr Surg Glob Open 2020;8:e3136; doi: 10.1097/GOX.0000000000003136; Published online 25 September 2020.)*

Hyperbaric oxygen therapy (HBOT) serves as a "primary" or "adjunctive" therapy in a wide range of pathologies. It is considered the mainstay of management for potentially life-threatening conditions such as carbon monoxide poisoning, decompression illness, and gas embolisms.[1–3] Additionally, HBOT has been utilized for decades as an adjunctive therapy in a variety of medical disciplines, including chronic wounds.[4–9] A 2017 report by Kaiser Health News estimated that nearly 1,300 hospitals in the United States have installed hyperbaric facilities.[10]

Chronic cutaneous wounds are defined as "wounds that have failed to proceed through an orderly and timely series of events to produce a durable structural and functional closure."[11] Major etiologies that exhibit such wounds include diabetes, pressure, venous insufficiency, and peripheral arterial disease. Chronic wounds pose a significant burden of disease, affecting approximately 6.5 million Americans, with the care costs in the United States alone exceeding $50 billion annually.[12] Those afflicted experience decreased quality-of-life, pain, restricted mobility, loss of limb, and even loss of life. The incidence of chronic wounds is on the rise due to an increasing elderly population and growing prevalence of obesity and diabetes.

In general, chronic wounds are characterized by hypoxia, impaired angiogenesis, and prolonged inflammation, all of which may theoretically be ameliorated by HBOT (Fig. 1). Nonetheless, the cellular, biochemical, and physiological mechanisms by which HBOT achieves beneficial results in chronic wounds are not fully understood, and there remains skepticism regarding its efficacy. This review provides a comprehensive overview of HBOT and discusses the developmental history of HBOT, its mechanisms of action, and recent findings regarding its efficacy as a treatment option for chronic wounds. This article digs deep into the roots of controversy surrounding the effectiveness of this treatment modality and offers future directions to address existing challenges.

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METHODS

The data outlined in this article have been extracted from Systematic Reviews published in English from January 1, 2000 to July 1, 2019, extracted from The National Library of Medicine's MEDLINE database, using the search terms "Hyperbaric," "Hyperbaric Oxygen," "Hyperbaric Oxygen Therapy," and "Chronic Wound."

Historical Notes

HBOT is not a novel concept, as the first reports of its use date back to 1662 when the British physician Henshaw first utilized compressed air for hyperbaric therapy in a chamber called a "Domicilium" (Fig. 2).[13] In 1789, toxic effects of oxygen were first reported, thereby increasing a reluctance to use HBOT.[13]

A wide-spread use of HBOT was not adopted until the 20th century. In 1928, a Kansas City physician, Cunningham, built a large hyperbaric chamber spanning 5 stories, which was capable of accommodating up to 40 patients at a time (Fig. 3).[13] Ite Boerema, recognized as the father of modern hyperbaric medicine, published the first clinical paper on HBOT in 1956 at the University of Amsterdam, describing the intraoperative use of hyperbaric oxygen to prolong safe operating times during cardiac surgery (Fig. 4). Boerema later reported on HBOT's beneficial effects as a treatment for necrotizing infections and ischemic leg ulcers.[14]

Kulonen first reported use of HBOT in chronic wounds in 1968. As research has begun to elucidate the oxygen-dependent cellular processes involved with tissue repair, such as collagen production by fibroblasts and the microbicidal activity of macrophages, the utilization of HBOT in the treatment of chronic wounds has become commonplace. This was followed by the decision by the Centers for Medicare & Medicaid Services to initiate reimbursement for HBOT for the treatment of diabetic foot ulcer (DFU) in 2002.

Overview and Description of the Technology

HBOT entails full body exposure and breathing of 100% oxygen while inside a hyperbaric chamber pressurized to greater than sea level ("sea level" is defined as 1 atmosphere absolute [ATA]).[15,16] Typically, treatments involve pressurization to between 2.0 and 2.5 ATA, which would be equivalent to ~250 kPa/inch^2, approximately the pressure at a depth of ~15 m of water. Treatment duration varies from 45 to 300 minutes depending upon the indication for which HBOT has been prescribed, with most treatment sessions lasting from 90 to 120 minutes.[17] Therapy for acute indications may require only 1 or 2 treatment sessions, whereas chronic medical conditions may warrant up to 30 or more treatment sessions. Patients may receive up to 3 treatment sessions per day depending on the medical indication. Chambers are either single-occupant (mono-place) or multiple-occupant (multi-place).[18]

Mechanisms of Action

Most therapeutic benefits of HBOT can be attributed to the relationships between gas concentration, volume, and pressure. We know from Henry's law that the amount of an ideal gas dissolved in a solution is directly proportional to its partial pressure (Fig. 5). Therefore, increasing partial pressure of oxygen in arterial blood during HBOT would improve the cellular delivery and supply of oxygen. This is the primary principle behind the effectiveness of HBOT in treating conditions in which oxygen delivery has been compromised, such as carbon monoxide poisoning and ischemia.

Another major effect of HBOT can be explained by Boyle's law, which indicates that the volume of a gas bubble is inversely related to the pressure exerted upon it (Fig. 6); this is the central concept underlying the beneficial properties of HBOT in management of conditions such as decompression illness and intravascular embolism.[18]

Several other therapeutic mechanisms of HBOT have been described in recent literature. It has been demonstrated that HBOT enhances neovascularization, and plays a role in improving the immune response, activating fibroblasts, downregulating inflammation, upregulating synthesis of growth factors, potentiating antibiotics and antibacterial processes, enhancing antioxidant response, and ameliorating ischemia-reperfusion injury.[2,9,18–22]

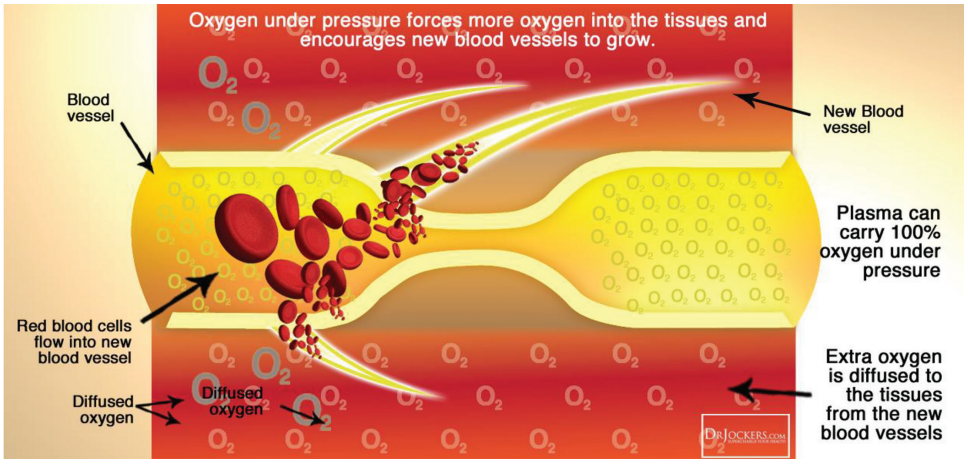

Fig. 1. Pathology of chronic wounds. Chronic wounds are characterized by hypoxia, impaired angiogenesis, and prolonged inflammation.

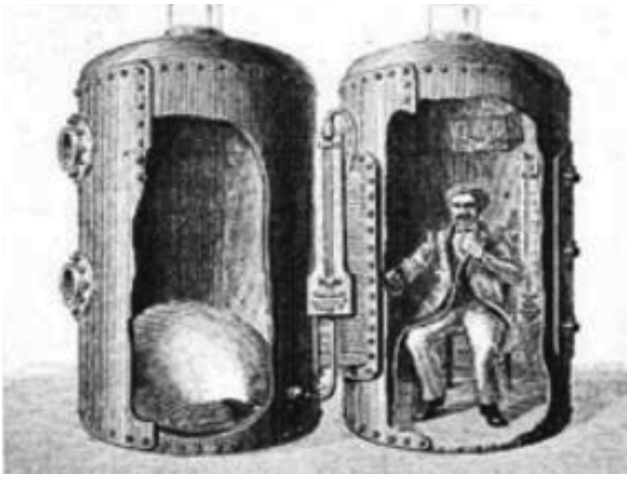

Fig. 2. 1662: Henshaw's Domicilium.

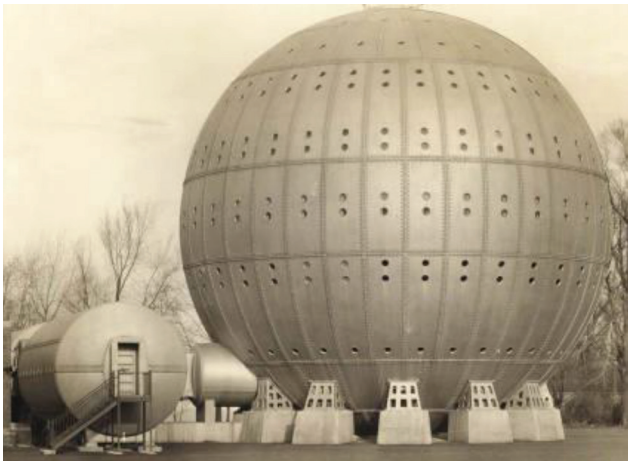

Fig. 3. 1928: Cunningham's steel ball hospital.

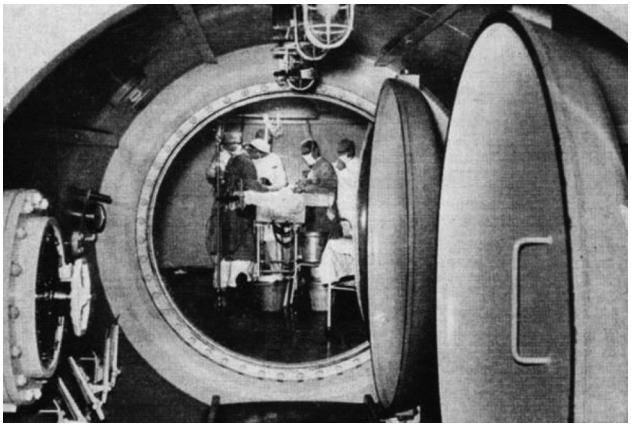

Fig. 4. Ite Boerema operating in pure oxygen.

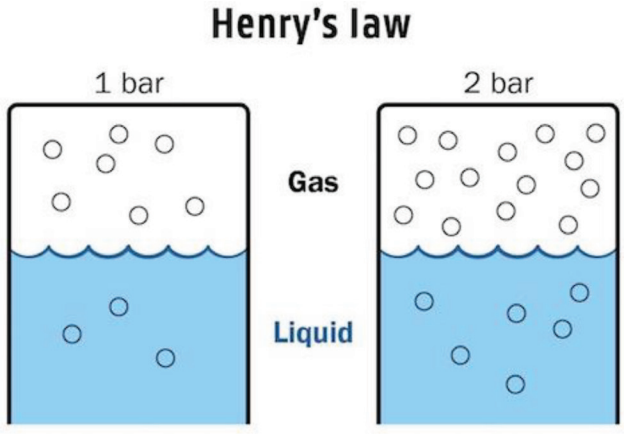

Fig. 5. Henry's Law: The concentration of a dissolved gas equals the pressure times the solubility coefficient of that gas.

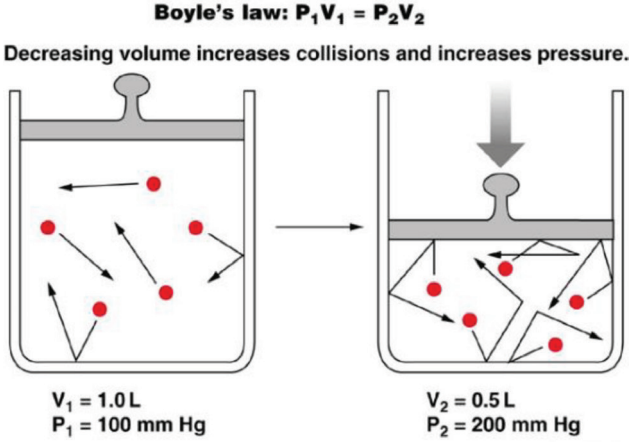

Fig. 6. Boyle's Law: Elevating hydrostatic pressure increases partial pressure of gases and causes a reduction in the volume of gas-filled spaces.

Contraindications and Adverse Effects

Although hyperbaric oxygen therapy remains relatively safe, several adverse side effects have been observed. Reversible myopia has occurred as a direct result of oxygen's effects on the eye's lens, whereas others have experienced barotrauma in the ears and sinuses and in rare cases, the teeth, and lungs.[23] Middle ear barotrauma is among the most common side effects of HBOT, affecting up to 2% of the patients undergoing therapy. This can be prevented and managed by autoinflation techniques and inserting tympanostomy tubes, respectively. Other observed side effects include chest tightness, coughing, fatigue, headaches, vomiting, and a burning sensation in the chest.[2,24] Although undesirable, these effects are reversible and nonfatal, leaving HBO therapy as a safe adjunctive treatment method for approved morbidities.

Oxygen toxicity is among the more serious complications associated with HBOT and can be associated with neurologic (eg, convulsions and psychological changes) and/or pulmonary (eg, pulmonary edema and respiratory failure) symptoms. Decompression sickness may occur in patients breathing compressed air that contains nitrogen. Fire hazard is considered the most common fatal complication of HBOT.[9,18,21,25,26]

HBOT may not be suitable for some individuals due to their current health or treatment regimen. "Absolute" contraindications for HBOT include untreated pneumothorax

and concomitant use of certain chemotherapeutics such as doxorubicin or cisplatin. Additionally, there are several "relative" contraindications that warrant extreme caution; these include poorly controlled seizure disorder, hyperthyroidism, congestive heart failure with ejection fraction less than 30% (it is important to note that oxygen is a vasoconstrictor, and as a result HBOT may increase cardiac afterload), severe chronic obstructive pulmonary disease, asymptomatic pulmonary blebs, or bullae incidentally found on chest radiograph, active upper respiratory or sinus infections, recent ear or thoracic surgery, history of pneumothorax, uncontrolled fever, claustrophobia, and inability to equalize pressure in the middle ear.[18,21]

Indications and Clinical Use

HBOT serves as a "primary" therapy for a number of medical conditions. There exists an indisputable level of evidence that supports HBOT as the standard of care for the potentially fatal conditions of carbon monoxide poisoning, decompression illness, and arterial and venous gas embolisms.[1–3] As such, HBOT has been approved by the Undersea and Hyperbaric Medical Society (UHMS) for 13 illnesses, including decompression sickness and arterial gas embolisms, though others propose it as a treatment for conditions outside of this list.[27] (Please see Tables 1 and 2 for the full list of HBOT indications currently approved by "Undersea & Hyperbaric Medical Society" and "Centers for Medicare & Medicaid Services", respectively.)

Albeit not as strong as the available evidence for its "primary" use, research has shown HBOT to be beneficial as an "adjunctive" therapy in the case of a diverse range of other pathologies including but not limited to those of neurology, oncology, orthopedic, rheumatology, cardiovascular, genitourinary, gastrointestinal, and hepatobiliary origin, as well as acute and chronic wounds. Moreover, some studies have displayed HBOTs favorable impact on radiation-induced injuries where fibrotic deposition, diminished vascularity, and tissue hypoxia play role in the disease pathogenesis.[18,28–32] Although there appears to be a correlation between the use of HBOT and an improved outcome, causation has yet to be definitively established. Conditions such as diabetic foot ulcers, ischemic stroke, sports injuries, and multiple sclerosis are common diseases that are treated with HBOT but a lack of strong support from peer-reviewed research, with many studies being underpowered. As such, HBOT has been described as "a therapy in search of disease."[27,33] Further studies need to be performed that are properly randomized, controlled, and conducted so that its proper uses may be identified.

Over the past decade, Cochrane Reviews has assessed potential "adjunctive" indications for HBOT. The results of these Systematic Reviews are summarized in Table 3. It is important to point out that the authors have unanimously taken note of the fact that the majority of the trials included in these Systematic Reviews suffered from small sample sizes, methodological deficiencies, and/or poor reporting outcomes, concluding that the results should be interpreted "cautiously." The one common consensus in these Systematic Reviews was that "appropriately Powered trials of high methodological rigor is required to define which patients, if any, can be expected to benefit most from HBOT."[4,34–47]

Table 1. Indications for Hyperbaric Oxygen Therapy per Undersea and Hyperbaric Medical Society

Indications for HBOT per Undersea and Hyperbaric Medical Society
Air or gas embolism
Carbon monoxide poisoning
Cyanide poisoning
Clostridial myositis and myonecrosis (gas gangrene)
Crush injury, compartment syndrome, and other acute traumatic ischemias
Decompression sickness
Arterial inefficiencies: central retinal artery occlusion
Arterial inefficiencies: enhancement of healing in selected problem wounds
Severe anemia
Intracranial abscess
Necrotizing soft–tissue infections
Osteomyelitis (refractory)
Delayed radiation injury (soft tissue and bony necrosis)
Compromised grafts and flaps
Acute thermal burn injury
Idiopathic sudden sensorineural hearing loss

Table 2. Indications for Hyperbaric Oxygen Therapy per Centers for Medicare and Medicaid Services

Indications for HBOT per Centers for Medicare and Medicaid Services
Acute carbon monoxide intoxication
Decompression illness
Gas embolism
Gas gangrene
Acute traumatic peripheral ischemia
Crush injuries and suturing of severed limbs
Acute peripheral arterial insufficiency
Progressive necrotizing infections
Preparation and preservation of compromised skin grafts
Chronic refractory osteomyelitis
Osteoradionecrosis
Soft-tissue radionecrosis
Cyanide poisoning
Actinomycosis
Diabetic wounds of the lower extremity with type 1 or 2 diabetes, a Wagner Grade 3 or higher ulcer, and failure of adequate course of standard wound therapy

Financial Cost

Cost-effectiveness is a central issue in modern healthcare. The cost of a full course of HBO treatment for diabetic foot ulcers varies by location and depends upon several factors, such as setup costs and ongoing costs, reimbursement systems, and the number of patients treated per center. Costs also differ geographically. In the United States, charges are typically between $200 and $1,250 per treatment session, with a full course of treatment averaging 50–60 hours in the HBO chamber and costing from $50,000 (Medicare) to $200,000 (private pay).[21,48] In 2011, a full HBO treatment in the Netherlands was about €6,920 (equaled $7,762), displaying the cost differential outside the United States.[49]

According to market research, the global HBOT devices market size was estimated at USD 2.21 billion in 2016.[50] A rising number of university and private companies funded clinical trials indicates an ongoing adoption of the technique and contributes to propel growth of

Table 3. Cochrane Review Results on Potential Indications for Hyperbaric Oxygen Therapy

Cochrane Study Title	Publication Year	Authors' Conclusions
HBOT for chronic wounds[4]	2015	In diabetic foot ulcers, HBOT significantly improved healing in the short term, but not in the long term.
HBOT for chronic wounds[34]	2004	In diabetic foot ulcers, HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. The routine management of chronic wounds associated with other pathologies with HBOT is not justified
HBOT for late radiation tissue injury[35]	2016	For LRTI affecting tissues of the head, neck, anus, and rectum, HBOT is associated with improved outcome. HBOT appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field. No evidence of important clinical effect on neurological tissues.
HBOT for autism spectrum disorder[36]	2016	No evidence that HBOT improves symptoms of ASD
HBOT for necrotizing fasciitis[37]	2015	Failed to support or refute the effectiveness of HBOT
HBOT for acute coronary syndrome[38]	2015	There is some evidence from small trials to suggest that HBOT is associated with a reduction in the risk of death, the volume of damaged muscle, the risk of major adverse cardiac events, and time to relief from ischemic pain. The routine application of HBOT cannot be justified.
HBOT for migraine and cluster headache[39]	2015	There was some evidence that HBOT was effective for the termination of acute migraine in an unselected population
HBOT for acute ischemic stroke[40]	2014	No good evidence to show that HBOT improves clinical outcomes, but the possibility of clinical benefit has not been excluded
HBOT for malignant otitis externa[41]	2013	No clear evidence to demonstrate the efficacy of HBOT when compared with antibiotics and/or surgery
HBOT for acute surgical and traumatic wounds[42]	2013	No high-quality evidence. Although 2 small trials suggested that HBOT may improve the outcomes of skin grafting and trauma, these trials were at risk of bias.
HBOT for bony fractures[43]	2012	No evidence to support or refute the effectiveness of HBOT for the management of delayed or nonunion bony fractures
HBOT for idiopathic sudden sensorineural hearing loss and tinnitus[44]	2012	For people with acute ISSHL, the application of HBOT significantly improved hearing, but the clinical significance remains unclear. No evidence of a beneficial effect of HBOT on chronic ISSHL or tinnitus
HBOT for traumatic brain injury[45]	2012	Although the addition of HBOT may reduce the risk of death and improve the final GCS, there is little evidence that the survivors have a good outcome. The routine application of HBOT to these patients cannot be justified.
HBOT for vascular dementia[46]	2012	Insufficient evidence to support HBOT as an effective treatment

CCS, Glasgow Coma Scale; ISSHL, Idiopathic Sudden Sensorineural Hearing Loss; LRTI, late radiation tissue injury.

the HBOT market. Additionally, technological development in the field of hyperbaric oxygen therapy devices is expected to push/increase the demand over the next years and further impel their growth. As HBO can be used to treat several conditions noninvasively, market research found that nearly 90% (1800 out of 2000) of hospitals and 71% (500 out of 700) of clinics are already offering hyperbaric oxygen therapies for many of the diseases previously detailed, including chronic wounds.

Efficacy in Chronic Wounds

HBOT has been used as an "adjunctive" therapy for chronic wounds since the mid 1960s. The mechanisms by which HBOT may augment healing in chronic wounds are not fully understood, though several rationales have been proposed throughout years. It has been demonstrated that HBOT can modulate the local and systemic effects witnessed in both acute and chronic injuries. In general, the common denominators in chronic wounds are hypoxia, prolonged inflammation, and impaired angiogenesis, all of which may potentially be ameliorated by HBOT.[18,51]

The data on efficacy of HBOT in chronic wounds are often inconsistent and inconclusive.[51–56] Among various etiologies involved in the development of chronic wounds, the highest number of studies and the bulk of HBOT literature have been devoted to the subject of DFUs. A 2004 Cochrane Review evaluated the role of HBOT in chronic wounds, concluding that HBOT may reduce the risk of major amputation in DFU patients and may improve healing at 1 year. Unfortunately, many of the studies reviewed suffered from limited sample sizes and methodological flaws. The same study evaluated the role of HBOT in chronic wounds of venous, arterial, and pressure etiology, and concluded that the routine utilization of HBOT for these indications was not justified based on the evidence (Table 3).[34]

In 2015, an updated Cochrane Review was conducted. The evidence from this study revealed that HBOT may improve the healing rate of DFU in the short term (ie, 6 wks), but not the long term (ie, 1 y). The authors further found no significant difference in major amputation rate in DFU population, while once again emphasizing the various flaws in the study design and reporting outcomes of the trials included (Table 3).[4] Löndahl et al[57] conducted a randomized, double-blinded, placebo-controlled clinical trial in 2010 evaluating 94 patients with Wagner Grade 2, 3, or 4 DFUs. They concluded that adjunctive HBOT facilitates healing in selected patients.[57] A 2017 report by Lam et al demonstrated that HBOT may improve healing and decrease amputation in "ischemic" DFUs; however, there was limited evidence on its effect on nonischemic DFUs and nondiabetic arterial ulcers.[51]

Zhao et al[58] conducted a meta-analysis on DFUs in 2017 studying 9 randomized clinical trials. They found that although HBOT was associated with a greater reduction in the wound size compared with the standard therapy, no

differences existed with respect to the rate of complete healing, amputation risk, and adverse events.[58] The following year, in 2018, Ennis et al[53] conducted a retrospective study of over 600,000 Wagner Grades 3 and 4 DFUs concluding that HBOT may be of benefit in the case of "advanced" ulcers. Most recently, in 2019, Golledge and Singh[59] carried out a systematic review and meta-analysis of 9 clinical trials in the field of DFUs. Authors concluded that HBOT improves the healing of DFUs and reduces the amputation rate.[59]

In contrast, 2 recent studies by Fedorko et al[52] and Santema et al[55] found that HBOT did not offer any significant advantages toward complete wound healing in DFUs associated with lower-limb ischemia. However, these studies too have been subject to criticism due to several methodological errors.[60–62]

While definitive proof for HBOT as a therapeutic has yet to be established, it appears that by and large, among the potential indications for HBOT in the field of chronic wounds, the strongest favorable evidence exists for ischemic, infected (ie, Wagner Grade 3 or worse) DFUs.[51–56]

Why the Controversy?

As we have highlighted in this article, much controversy exists with regard to the adjunctive therapeutic effects of HBOT on chronic wounds. There are several culprits for the existing discord. First and foremost, a comprehensive mechanistic understanding of the technology is lacking. HBOT acts through diverse and not-fully-understood mechanisms to promote angiogenesis and decrease inflammation. Moreover, many of the initial HBOT studies that demonstrate favorable outcomes were performed in the inpatient/hospital setting, which ensured proper patient, physician, and staff compliance; it is not completely unexpected to see that these results have not fully translated to the reality of the outpatient/clinic setting. Also, there are inherent impediments to an ideal study design investigating HBOT; as an example, the unique environment of hyperbaric chambers generates significant challenges to ideal blinding of both patients as well as investigators.[7] Finally, trials investigating HBOT are faced with the same challenges such as "procedural variations" and others that are almost impractical to account for, which have plagued clinical studies in this particular field for decades.[63–66]

To make the matter even worse, similar to the efficacy trials, there have been contradictory reports on economics and cost-effectiveness of HBOT in the field of chronic wounds. The cost of diabetic foot disease in the United States in 2007 was $30 billion, of which $19 billion was due to foot ulceration and $11 billion to amputations. It was estimated in 2007 that effective diabetic foot ulcer and amputation prevention could realistically save the US healthcare system up to $21.8 billion annually.[67] Unfortunately, studies have failed to prove unanimously that HBOT has the potential to lower the costs of care for DFUs. The 2008 Study by Canadian Agency for Drugs and Technologies in Health reported that adjunctive HBOT for DFUs is cost-effective compared with standard care alone.[68] The more recent study conducted in 2017 by Health Quality Ontario indicated that adjunctive HBOT for DFUs may lower costs due to reduced amputation rate, but overall authors concluded that "there is uncertainty" regarding cost-effectiveness.[69]

This overall environment of uncertainty has inevitably led to discrepancies between "accepted," "covered," and "off-label" indications for HBOT. This has brought several stakeholders with differing motivations into play, paving the way for the utilization of HBOT for unregulated and unwarranted indications, whereby little to no supportive evidence exist.[70] Not surprisingly, the skepticism ensued has made it even more challenging to vindicate this potential therapy or to see its merits.

CONCLUSIONS

Compressed air and hyperbaric oxygen have been utilized in medicine for centuries. HBOT is now considered the mainstay of treatment for a number of life-threatening conditions such as carbon monoxide poisoning, decompression illness, and gas embolism.[1–3,71] Moreover, HBOT has the distinctive ability to remedy tissue hypoxia, reduce inflammation, and alleviate ischemia-reperfusion injury.[7] The current evidence in the field of chronic wounds suggests that HBOT may have favorable effects on ischemic, infected (ie, Wagner Grade 3 or worse) DFUs.[51–56] Despite many studies highlighting the potential benefits of HBOT, much controversy remains with regard to its efficacy in wound healing.[15] The paucity of high-quality randomized controlled trials makes it difficult to properly assess the efficacy of HBOT. To accurately validate the potential benefits of HBOT, more vigorous investigations with adequately powered sample sizes are warranted.

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