Point: Hyperbaric Oxygen Is Beneficial for Diabetic Foot Wounds

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(See the counterpoint by Berendt on pages 193–8)

Diabetic foot ulcers occur in 1.9% of adults with diabetes annually [1], resulting in amputation in 15%–20% of patients within 5 years [2]. Direct medical costs for diabetic ulcer care represent the majority of the estimated $4.6–$13.7 billion US annual expenditure for diabetic peripheral neuropathy [3]. Even modest improvements in the prevention and therapy of diabetic foot ulcers have the potential to substantially impact such costs, largely because of the avoidance of major amputation.

The physiology that results in ulceration in the diabetic foot has been extensively reviewed [4]. Loss of nociceptive and autonomic nerves results in a dry, hyperkeratotic surface that is subject to mechanical cracking, infection, and tissue destruction. Local ischemia, age, and tissue reinjury result in chronic, nonhealing wounds that remain a portal of entry for deep-tissue infection. Such infections are a common cause of hospital admission for diabetic patients and are the most common reason for infectious diseases consultation in this population. Evidence-based guidelines for treatment of the infected diabetic foot have emphasized conventional mechanical and antimicrobial therapies [5]. Of the adjunctive therapies available for treatment, only the use of granulocyte colony-stimulating factor in actively infected ulcers and the use of hyperbaric oxygen therapy in refractory ulcers were considered to

be supported in those guidelines. Both were cited as having moderate evidence (Infectious Diseases Society of America–US Public Health Service grade B-I) to support their use in wounds unresponsive to surgery and conventional therapy [5]. This report will briefly review the evidence supporting the use of adjunctive hyperbaric oxygen therapy in selected, nonhealing diabetic lower-extremity wounds.

STANDARD TREATMENT OF DIABETIC FOOT ULCERS

Generally accepted care for diabetic foot ulcers includes (1) optimized nutritional support and glycemic control; (2) off-loading of the site of injury; (3) debridement of nonviable tissue; (4) provision of a clean, moist environment for support of nascent granulation tissue and epithelialization; (5) correction of remediable vascular impairment; and (6) treatment to resolve infection [5–7]. Of these commonly employed methods, clinical trials have shown clear-cut efficacy only for off-loading [5]. In wounds without obvious infection or underlying osteomyelitis, antimicrobial use has not been shown to be of value. In spite of studies of bacterial concentration in burn wounds showing inhibition of healing and risk for systemic infection when bacterial concentrations exceed 10^5 per gram of tissue, the only placebo-controlled trial of antibiotics in diabetic foot ulcer treatment [6] failed to show clearly enhanced healing in the treated subjects. Although control of soft-tissue and bone infection may be necessary to allow healing of diabetic foot ulcers, antimicrobial therapy and standard wound care alone is often insufficient to result in healing.

The majority of "nonhealing" wounds will heal with rigorous application of commonly accepted methods. Only after the failure of conventional care is the nonhealing wound appropriate for adjunctive therapies,

such as engineered biological coverings, topical growth factors, and hyperbaric oxygen therapy.

PHYSIOLOGIC RATIONALE AND OTHER USES

The physiological pathways of normal wound healing remain incompletely defined. After initial injury and an inflammatory phase in which inflammatory cells migrate to the area, hypoxia and elevated lactate in the wound center stimulate fibroblast replication, collagen production, and endothelial cell growth [8]. This stimulation and ingrowth of tissue from the wound edges is optimal in the presence of a steep oxygen gradient from the periphery to the hypoxic center [9]. The high concentration of dissolved oxygen during hyperbaric oxygen treatment optimizes this concentration gradient and facilitates wound repair.

During the period of high oxygen concentration, there is stimulation of phagocyte oxidative killing and enhanced collagen posttranslational modification [8]. Hyperbaric oxygen therapy directly enhances fibroblast replication, osteoclast activation, and upregulation of vascular endothelial growth factor and platelet-derived growth factors [10]. A persistent effect following administration of hyperbaric oxygen appears to be stimulation of capillary growth. In studies of radiation-damaged hypovascular bone, Marx et al. [11] demonstrated that, after a series of intermittent hyperbaric oxygen treatments, capillary density increased to 80% of normal tissue. This observation is considered to be the primary physiologic mechanism underlying the reduction in postsurgical osteoradionecrosis when hyperbaric oxygen therapy is used prior to surgery on radiation-damaged hypovascular tissue. Similarly, hyperbaric oxygen therapy promotes angiogenesis in the nonhealing wound [9]. By stimulating capillary ingrowth in the periphery of the nonhealing wound, nutrient deficiencies—including hypoxia—can be corrected.

HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy is the intermittent administration of inhaled 100% oxygen while the subject is at an ambient pressure >1 atmosphere absolute (atm abs; 1 atm abs = 101.3 kpascals). With regard to infectious diseases, hyperbaric oxygen therapy is generally recognized to be a primary modality of care in addition to surgery and antibiotics in the treatment of clostridial myonecrosis. Other life-threatening infections that may benefit from adjunctive hyperbaric oxygen therapy include necrotizing soft-tissue infections, chronic refractory osteomyelitis, and certain cases of intracranial abscess.

In the United States, hyperbaric oxygen treatment of nonhealing wounds usually consists of intermittently inhaling 100% oxygen for 60–90 min at a pressure of 2.0–2.4 atm abs. This can result in partial pressure of oxygen within the arterial circulation of 1200 mm Hg. At this high concentration of dissolved plasma oxygen, the diffusion distance of oxygen into tissues from the end-arteriole is increased from 60 microns to 250 microns [12]. Even with the increased diffusion of oxygen into tissues, however, insufficient local arteriolar and capillary availability can prevent sufficient oxygen diffusion to hypoxic cells.

Oxygen tension in the area near the nonhealing wound can be measured using a polarographic electrode in an ionic solution separated from the epidermis by an oxygen-permeable membrane. Oxygen diffusing from the capillary bed beneath the electrode is reduced at the cathode to produce a measurable current corresponding to the oxygen concentration. Transcutaneous oxygen concentration ($TcPO_2$) measured in this manner provides an objective parameter that can be used with modest predictive ability in the initial and subsequent evaluation of the patient [12–14]. In general, distal nonhealing diabetic wounds with a local $TcPO_2$ >35 mm Hg are likely to heal without adjunctive hyperbaric oxygen therapy, whereas a local $TcPO_2$ <20 mm Hg increases the risk for nonhealing by 39-fold [15]. Although there is no absolute discriminatory value of $TcPO_2$ in predicting failure of hyperbaric oxygen therapy, patients able to attain a periwound $TcPO_2$ of ≥200 mm Hg breathing 100% oxygen at 2.5 atm abs are likely to heal [13, 14].

In a retrospective evaluation, Fife et al. [16] measured $TcPO_2$ and used hyperbaric oxygen therapy only in those patients with periwound hypoxia. Consistent with this patient selection, there was a dose-response effect noted, with response rates diminishing as the Wagner classification increased from grade I to grade V. The overall response rate for treated patients with Wagner grade III wounds was 77%; for Wagner grade IV, 64%; and for Wagner grade V, 30%. The healing rate for patients with Wagner grade I and II wounds was 83%, in contrast with 47% in trials using topical recombinant human platelet-derived growth factor BB (becaplermin; Regranex, Ortho-McNeil), which excluded hypoxic wounds ($TcPO_2$, <30 mm Hg) and Wagner grade III, IV, and V wounds [17].

CLINICAL TRIALS OF ADJUNCTIVE HYPERBARIC OXYGEN THERAPY

Outcome measure 1: wound healing. The first controlled trial of hyperbaric oxygen therapy in diabetic lower extremity wounds was published nearly 30 years ago [18]. Since then, there have been several prospective, randomized, controlled trials of hyperbaric oxygen therapy in nonhealing diabetic lower extremity wounds. Kessler et al. [19] hospitalized 28 diabetic patients with chronic nonhealing wounds. Macrovascular disease was excluded in all patients. All patients received a regimen of glycemic control, off-loading, and wound care and were randomized to hyperbaric oxygen therapy or control. Hyperbaric oxygen-treated patients received conventional treatments twice daily for 10 days during a 2-week hospitalization. Fol-

lowing the 2-week hospitalization, patients were observed as outpatients for an additional 2 weeks. Patients receiving hyperbaric oxygen therapy had twice the rate of wound healing during hyperbaric oxygen therapy than did the control group. However, healing rates became comparable in treatment and control groups after the cessation of hyperbaric treatments, with no significant difference in wound area at 4 weeks between groups. During this short trial, 2 patients in the hyperbaric oxygen group but none in the control group healed completely. The short follow-up period and small size of the study limit the conclusions that can be drawn; however, the treatment and control arms received standard care that was uniform.

Abidia et al. [20] randomized 18 diabetic subjects with ischemic ulcers to receive 100% oxygen or air to breathe at 2.4 atm abs pressure for 90 min daily for 30 treatments. Complete healing 1 year after therapy occurred in 5 of 8 patients in the hyperbaric oxygen therapy group and in 1 of 8 patients in the control group. The relative risk of nonhealing in the control group was 2.3 (95% CI, 1.1–4.7) [21]. There was a significant decrease in the wound area in the treated group compared with the control group.

The effect of hyperbaric oxygen therapy on wound healing has been shown to be durable, with >90% of wounds remaining closed after an average follow-up period exceeding 4 years [22]. In the study by Kalani et al. [23], 76% of patients treated with hyperbaric oxygen therapy had intact skin at the 3-year follow-up, compared with 48% of control patients. In addition, there was a 20% reduction of amputation in the treated group.

Outcome measure 2: amputation. The outcome variable most commonly reported by prospective trials of hyperbaric oxygen therapy in diabetic lower extremity ulcers has been the rate of major (above-ankle) amputation (table 1) [20, 23–25].

Faglia et al. [25] prospectively studied 68 diabetic subjects with nonhealing lower extremity wounds. All patients received specialty clinic standard care, with macrovascular evaluation and optimization prior to enrollment. The 35 subjects randomized to receive hyperbaric oxygen therapy received an average of 38.8 treatments. Major amputations, performed by a surgical team blinded to the treatment, occurred in 3 (8.6%) of 35 subjects in the hyperbaric group and in 11 (33%) of 33

subjects in the control group. The relative risk for the treated group was 0.26 (95% CI, 0.08–0.84; $P = .016$). The difference in outcomes for major amputation remained significant in a multivariate analysis, which also showed low ankle-brachial index and high Wagner grade to be negative prognostic determinants.

A meta-analysis of the Faglia et al. study [25] and 2 other prospective, controlled, randomized trials with high homogeneity was reported by Kranke et al. [21]. The trials analyzed included 118 patients. The authors found a relative risk for major amputation of 0.31 (95% CI, 0.13–0.71). Their analysis showed that 4 patients would need to receive hyperbaric oxygen therapy (number needed to treat, 4) to avoid 1 amputation (95% CI, 3–11).

PATIENT SELECTION AND MONITORING

Before referral for adjunctive hyperbaric oxygen therapy, a patient should have demonstrated no progress toward healing while receiving standard care. Failure to recognize correctable arterial insufficiency will result in a poor or nondurable response to hyperbaric oxygen therapy. Optimally, each patient referred for hyperbaric oxygen therapy should have a comprehensive vascular surgery consultation, including regional arterial perfusion indices, toe-brachial indices, and measurements of the periwound $TcPO_2$ level. Similarly, wounds that exhibit normal levels of tissue oxygenation usually fail to heal only when not appropriately off-loaded.

The dose-response relationship for hyperbaric oxygen treatment has been largely derived using animal models to study a variety of pathological conditions and in human studies of radiation-injured tissues. These studies suggest that a treatment effect can first be observed after 2 weeks of daily treatments. $TcPO_2$ level can be used to monitor improvement in tissue oxygenation during therapy, with increasing $TcPO_2$ levels occurring in the wound periphery as angiogenesis proceeds [25]. Treatment that demonstrates enhanced healing is usually continued for at least 30 days, at which time Center for Medicare and Medicaid Services regulations require that progress toward healing be documented. A logistic regression model of hyper-

Table 1. Rate of major amputations in prospective, randomized, controlled trials of hyperbaric oxygen (HBO$_2$) therapy for nonhealing, diabetic lower extremity ulcers.

Study	Year	No. of subjects	Study type	Amputation rate, %	
				HBO$_2$	No HBO$_2$
Doctor et al. [24]	1992	30	Prospective, randomized, controlled	13	47
Faglia et al. [25]	1996	68	Prospective, randomized, controlled	9	33
Kalani et al. [23]	2002	38	Prospective, randomized, controlled	12	33
Abidida et al. [20]	2003	18	Prospective, randomized, controlled, blinded	12	12

baric oxygen therapy in diabetic wound healing showed $TcPO_2$ near the wound and a history of having smoked >10 pack-years of cigarettes to be independent predictors of the need for increased numbers of hyperbaric treatments for wound healing to occur [26]. The requirement to observe objective measurement of enhanced healing within 30 days, which usually means 20–30 hyperbaric treatments, may not be realistic for patients with marginal $TcPO_2$ and a history of smoking.

COSTS AND COST-EFFECTIVENESS

Treatment costs for hyperbaric oxygen therapy are high. The acquisition cost for a hyperbaric chamber capable of treating one patient at a time ("monoplace") and associated facility remodeling is ~$400,000. "Multiplace" facilities (figure 1) may have initial capital costs of millions of dollars. Operational costs of hyperbaric chambers depend on the design of the facility and required staffing. All chambers require at a minimum a medical attendant and an on-site supervising physician. The cost in the United States for 30 hyperbaric oxygen treatments using conventional wound healing protocols is ~$20,000. Guo et al. [27] calculated the incremental cost of adjunctive hyperbaric oxygen therapy for a nonhealing diabetic wound to be $5166 per quality-adjusted life-year at 5 years after treatment. Because of the high direct medical costs associated with a major amputation and rehabilitation, hyperbaric oxygen therapy may actually lower the cost of care for diabetic nonhealing wounds in the first year of therapy [28].

ADVERSE EFFECTS OF HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy is generally well tolerated. The pressure and duration of oxygen exposure used in hyperbaric oxygen therapy are chosen to minimize the likelihood of adverse effects and may be modified for patients with a history of seizure or obstructive lung disease, to further reduce the risk of treatment morbidity.

Adverse effects of pressurization and depressurization result from expansion of gases in enclosed anatomic compartments. Otic barotrauma may result from the inability of the patient to equalize pressure across the tympanic membrane. This may occur in 2%–4% of patients and may require temporary tympanostomy or pressure equalization tubes in some. Sinus barotrauma is less frequent, usually occurring in the presence of a concurrent upper respiratory infection, and it rarely requires permanent discontinuation of hyperbaric oxygen therapy. Pulmonary obstructive disease may rarely lead to lung overpressurization during decompression. The incidence of pneumothorax during routine hyperbaric therapy is estimated to be <1 in 1,000,000 exposures.

Adverse effects associated with high inspired oxygen concentrations are usually noted in the CNS, eyes, or lungs. Hy-

Figure 1. Interior view of a modern multiplace hyperbaric oxygen therapy chamber.

peroxia can induce generalized seizures. At the pressures used to administer hyperbaric oxygen therapy for diabetic wounds, this occurs 0.03% of patients [29]. An oxygen-induced seizure is treated with immediate cessation of 100% inhaled oxygen and is not a contraindication to continued hyperbaric oxygen therapy, because it is an idiosyncratic reaction.

Although the mechanism of action is unclear, transient myopia may occur in <10% of patients during hyperbaric oxygen therapy. The incidence of this increases if the number of treatments is extended beyond the 40–60 usually used in the United States. This visual change resolves over weeks to months after the conclusion of therapy [29].

Protracted exposure of the lung to high inspired concentration of oxygen can produce direct pulmonary toxicity. The level and duration of oxygen exposure in patients receiving <60 treatments of 90 min at 2.4 atm abs is unlikely to produce lasting changes in pulmonary function [30].

The stimulation of angiogenesis provided by hyperbaric oxygen might, in theory, enhance vascular growth within malignancies. Current evidence, however, does not suggest that hyperbaric oxygen therapy enhances the growth rate of neoplastic tissue [31].

Hyperbaric oxygen treatment is increasingly available in the United States. The Undersea and Hyperbaric Medical Society (UHMS) lists >350 military and civilian hyperbaric chambers in the U.S. [32]. The UHMS publishes evidence-based guidelines for indications for the use of hyperbaric oxygen therapy every 4 years. The UHMS provides a program of facility certification based on adherence to recognized treatment protocols, facility safety, and operational methodology. In addition, board certification in Undersea and Hyperbaric Medicine is available through the American Board of Emergency Medicine and the American Board of Preventive Medicine.

FUTURE NEEDS

The numerous clinical parameters that may affect wound healing in the diabetic lower extremity ulcer make large, multicenter, prospective, randomized, controlled trials imperative to establish reliable selection criteria for use of adjunctive hyperbaric oxygen therapy. The same is true for validation of many of the accepted standard therapies for treatment of diabetic lower-extremity ulcers. It is unfortunate that federal research funding has been absent in supporting clinical trials in this area of great public health importance. Fortunately, the generation and widespread dissemination of professional society guidelines for prevention and treatment of diabetic lower-extremity ulcers and their complications may reduce the proportion of diabetic patients who undergo amputation [33].

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