HYPERBARIC OXYGEN THERAPY FOR DIABETIC WOUNDS

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Impairment of wound healing and decreased resistance to infection in diabetic patients with long-standing disease or inadequately controlled blood sugar have long been recognized. They have resulted in major health problems for diabetics, including diabetic foot disease. In addition to wound healing problems directly attributed to diabetes, tissue hypoxia secondary to ischemia further impairs wound healing. Hyperbaric oxygen (HBO) therapy has been shown to elevate tissue oxygen levels even in patients with significant peripheral vascular disease, thereby enhancing white cell function to fight infection and improving the capacity of injured tissue to heal.[6, 42]

HBO therapy is the use of intermittent inhalation of 100% oxygen under pressure greater than 1 atm,[17] which necessitates that the entire patient be enclosed in a chamber capable of tolerating increased pressure; it must be differentiated from topical administration of oxygen, which consists of encasing a limb in a container, with oxygen applied exogenously. Topical oxygen has no physiologic or pharmacologic similarities to HBO.

This article reviews the current literature concerning the use of HBO in nonhealing lower extremity wounds of diabetics. Physiologic principles and pertinent clinical studies are critically evaluated, and recommendations for clinical use are provided.

PHYSICS AND PHYSIOLOGY

HBO therapy is based on two physical factors derived from the ideal gas laws: mechanical compression of bubbles (Boyle's law) and

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high-dose oxygen (Henry's law). Boyle's law states that at a constant temperature, a given volume of gas is inversely proportional to its pressure[44]; therefore, if the pressure is doubled, the volume of the gas is halved. This principle is important in the treatment of decompression sickness and air embolism. Henry's law is crucial to the effectiveness of HBO in wound healing. It states that the amount of gas (oxygen) that will dissolve in a given volume of solvent (plasma) at a given temperature (37°C) is proportional to the pressure of the gas with which the solvent is in equilibrium and the solubility coefficient of the gas in the solvent.[27, 44] Therefore, when the patient breathes oxygen while atmospheric pressure increases during hyperbaric compression, more oxygen is dissolved in the plasma.

Hemoglobin is the principal source of oxygen transport at sea level, or 1 atm absolute (1 ATA) pressure.[28] The normal concentration of hemoglobin is approximately 15 g per 100 mL blood. One gram of hemoglobin can carry 1.34 mL oxygen.[5] Thus, when hemoglobin is 100% saturated, 100 mL blood can transport 20 mL oxygen (20 vol%). In the normal, healthy subject at sea level, hemoglobin is approximately 97% saturated and has an oxygen content of 19.4 vol%.[9] With increasing oxygen concentration at sea level, hemoglobin will be 100% saturated, with an arterial oxygen pressure (P_{O_2}) between 100 and 200 mm Hg.[28] Increasing alveolar P_{O_2} above this level does not increase the amount of oxygen transported by hemoglobin.

Plasma is a secondary carrier of oxygen to the tissue. At 1 ATA and an arterial P_{O_2} of 95 mmHg, 0.29 mL oxygen is dissolved in each 100 mL blood.[9] Unlike hemoglobin saturation, which has an S-shaped curve, the amount of dissolved oxygen in plasma is linearly related to the oxygen partial pressure (Fig. 1). Thus, if the inspired oxygen pressure is increased, the amount of dissolved oxygen increases rapidly and linearly. At 3 ATA, the amount of oxygen dissolved in plasma exceeds 6 vol%.[28] This dissolved oxygen content is equivalent to a sea-level oxygen capacity of 4.5 g oxyhemoglobin per 100 mL blood and can meet the metabolic demands of all but the most metabolically active tissues, such as myocardium and brain. With normal peripheral perfusion, wounds extract only about 1 vol%, or 1 mL oxygen from each 100 mL blood.[8] As a consequence, under hyperbaric conditions, wound oxygen demands can be met entirely from the dissolved oxygen content of the plasma.

ANTIBACTERIAL EFFECTS

There are many intrinsic problems with white cell function in diabetics. The primary problem concerns leukocytes obtaining adequate oxygen to produce intracellular high-energy oxygen radicals, which are necessary for killing wound pathogens.

White blood cells phagocytose bacteria in a variety of environments, which can range from normoxic (P_{O_2} equivalent to that found in air at 1 ATA) to almost anoxic. The energy requirements for particle ingestion
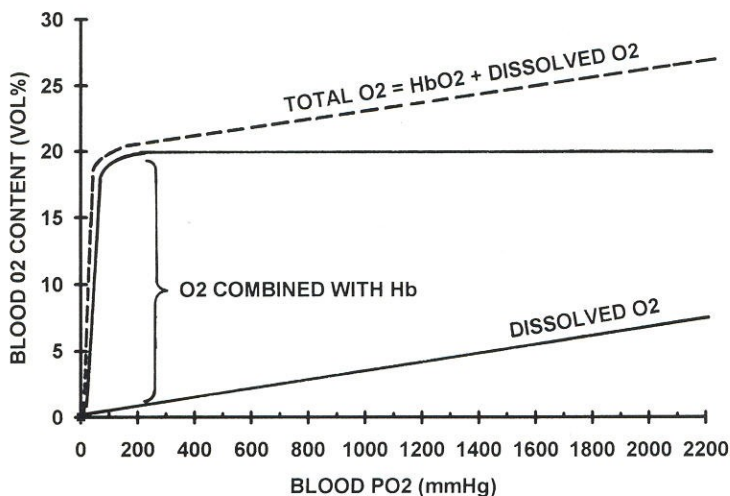
Figure 1. Extension of oxygen-hemoglobin dissociation curve. Note that increased blood oxygen content (vol%) at high levels of blood oxygen tension is accomplished by increased dissolved oxygen (solubility of O_2 0.003 vol% per mm Hg PaO_2 or 2.3 vol% per ATA PaO_2). (*Adapted from* Lambertsen CJ: Physiological effects of oxygen inhalation at high partial pressures. *In* Fundamentals of Hyperbaric Medicine, Washington DC, National Academy of Sciences, National Research Council, 1966, pp 12–20.[26] Reprinted with permission from FUNDAMENTALS OF HYPERBARIC MEDICINE. Copyright 1966 by the National Academy of Sciences. Courtesy of the National Academy Press, Washington, DC.)

and degranulation are met primarily by anaerobic glycolysis. In hypoxic environments, ingestion occurs normally with glycogen consumption and lactic acid production,[12] so leukocytes would appear to be well equipped to function in low-oxygen states.

Leukocytes are able to kill ingested bacteria with oxygen-independent systems and/or an oxygen-dependent antimicrobial system.[31] The oxygen-independent systems that are well studied include acid, lactoferrin, lysozyme, and granular cationic proteins. The oxygen-dependent antimicrobial system uses reduced oxygen moieties (free radicals) to attack organisms directly. The components of this system consist of superoxide anion, hydroxyl radicals, singlet oxygen, halide ions, hydrogen peroxide, and myeloperoxidase.

The importance of the oxygen-dependent system can be seen in patients with chronic granulomatous disease (CGD), in which leukocytes are deficient in the oxygen-dependent antimicrobial system and other components that are dependent on oxidative metabolism.[14, 41] As a consequence, antimicrobial efficacy is severely impaired. Patients with CGD generally suffer from repeated infections; death generally occurs during adolescence.

After phagocytosis in normal subjects, a number of metabolic changes occur in the leukocyte. A marked increase in oxygen consumption, or oxidative burst, occurs within seconds after particle ingestion.

This increase has been measured at 15 to 20 times the basal rate.[3] Studies with oxidative-pathway inhibitors such as cyanide or hypoxic environments demonstrated no inhibition of phagocytosis but greatly impaired killing of phagocytosed bacteria.[11, 22] In 1974, Mandell[31] showed that oxygen was essential for killing certain species of phagocytosed bacteria, such as *Staphylococcus aureus, Salmonella typhimurium, Proteus vulgaris, Escherichia coli,* and *Klebsiella pneumoniae.*

Mader et al[30] reported that in vitro leukocyte killing of *Staphylococcus aureus* was markedly decreased at an oxygen tension of 23 mm Hg but improved at 45, 109, and 150 mm Hg, with greatest efficiency at 150 mm Hg (Fig. 2). Hohn et al[13] also demonstrated that the killing efficiency of cultured leukocytes increased as PO_2 was increased to 150 mm Hg. Knighton et al[24] found that modification of inspired oxygen concentrations from 12% to 45% had a significant effect on bacterial counts in experimental wounds infected with *Pseudomonas aeruginosa.* They found that lesion size and necrosis at higher inspired oxygen concentrations for the first 3 hours after bacteria injection were comparable to those obtained with administration of antibiotic at the time of bacteria injection. The conclusion was that the difference in lesion size was due to a difference in oxygen-dependent leukocyte bacterial killing efficiency.

Oxygen, in addition to its effect on leukocytes, augments the bactericidal action of various antibiotics. Aminoglycoside antibacterial action is much less efficient under low oxygen tensions.[45] Adams and co-workers[1, 2] demonstrated that elevation of oxygen tensions above hypoxic levels restored tobramycin's killing effects on *Pseudomonas aeruginosa.* Keck et al[19] showed that HBO increased the effectiveness of sulfonamides. Vancomycin also does not kill microorganisms well under low oxygen tensions, and theoretically, an improved oxygen tension may improve its bactericidal effect.[29]

In addition to improving leukocyte bacterial killing, HBO has directly lethal effects on anaerobic and microaerophilic aerobic organisms.[33] The action of HBO on anaerobes is based on the intracellular formation of oxygen free radicals. Anaerobic organisms are extremely sensitive to those oxygen radicals because of the lack of superoxide dismutase and catalase (which break down oxygen free radicals).[32] Anaerobic bacteria are present in a significant percentage of diabetic foot infections.

WOUND HEALING EFFECTS

In 1969, Silver[43] elegantly demonstrated the oxygen gradient in wounds, in which PO_2 values were normoxic at the wound edge but declined to less than 3 mm Hg in the wound's dead space.[43] Hypoxia and lactate production are known to be necessary stimulants for fibroblast replication, collagen production, and angiogenesis; however, wound healing is a dynamic process, and adequate oxygen tensions are mandatory for the healing process to continue. Diabetic wounds have impaired
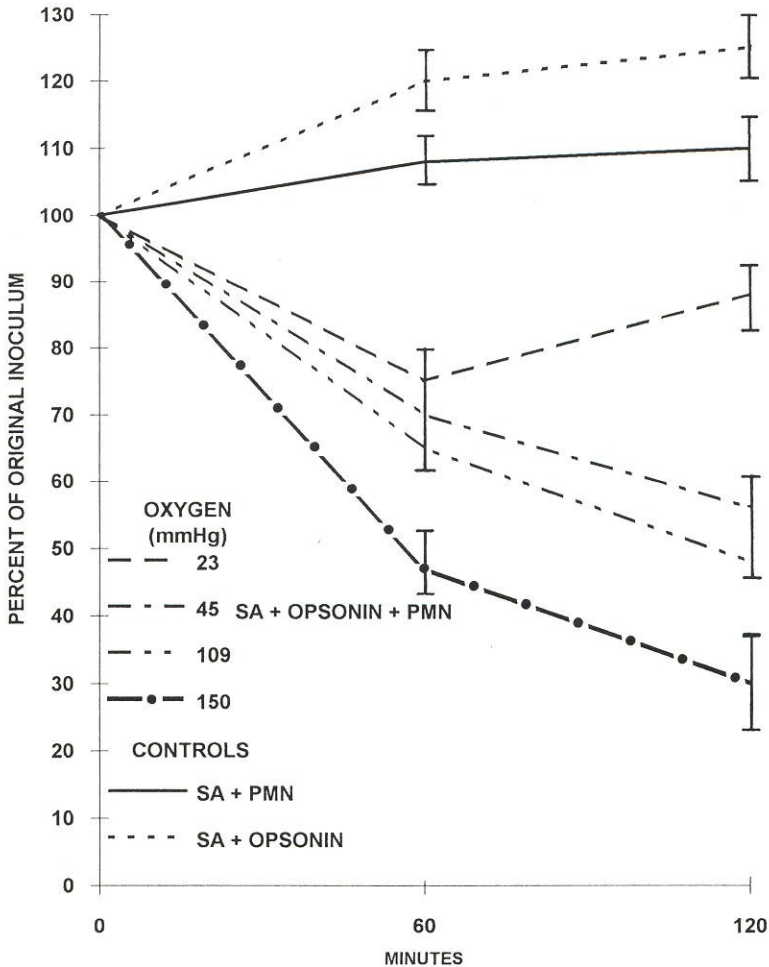
Figure 2. Mean phagocytic killing of *Staphylococcus aureus* (SA) under different oxygen tensions. SA, rabbit peritoneal leukocytes (PMN), and opsonin were mixed at 37°C and removed after 60 or 120 minutes when the number of CFU of initial inoculum of SA was counted. (*Adapted from* Mader JT, Brown GL, Gockian JC, et al: A mechanism for amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 142:915–922, 1980; with permission.)

connective-tissue regenerative systems for wound healing,[34] and in many patients this problem is exacerbated by ischemia secondary to peripheral vascular disease.

During the past 20 years, the relationship of hypoxia and high lactate concentrations, separately and together, have been elucidated as independent variables.[15] Hunt and Pai,[16] in 1972, demonstrated that collagen synthesis and deposition are functions of the oxygen supply.

As arterial oxygen tension increases from 40 to 200 mm Hg, the amount of hydroxyproline more than doubles. Niinikoski,[36] using subcutaneous cellular sponge implants in rats, showed that twice as much hydroxyproline was produced in an environment of 70% oxygen than in an environment of 18% oxygen (Fig. 3). In an environment of 12% oxygen, hydroxyproline production was significantly inhibited. In the same study, Niinikoski noted that the RNA:DNA ratio in wound cells was significantly increased with increased oxygen as long as the tissue lactate levels remained high. More recently, Mehm et al[35] suggested that optimal fibroblast proliferation and hydroxylation of proline occurs at a tissue P_{O_2} of 80 mm Hg. It appears that fibroblasts can replicate in hypoxic environments but require oxygen to produce collagen. The optimal tissue P_{O_2} for collagen synthesis and fibroblast proliferation is approximately 80 to 200 mm Hg.

In severely hypoxic wounds, angiogenesis has been noted to be accelerated under HBO conditions.[20] The angiogenic effect is stimulated by an angiogenesis factor that is released by hypoxic macrophages.[25] These new capillaries spread into the new collagen matrix of the healing wound, increasing surrounding tissue oxygen tension and stimulating new collagen production. In this circumstance, enhanced angiogenesis seems to be an indirect effect of elevation of surrounding tissue oxygen levels to normal levels.
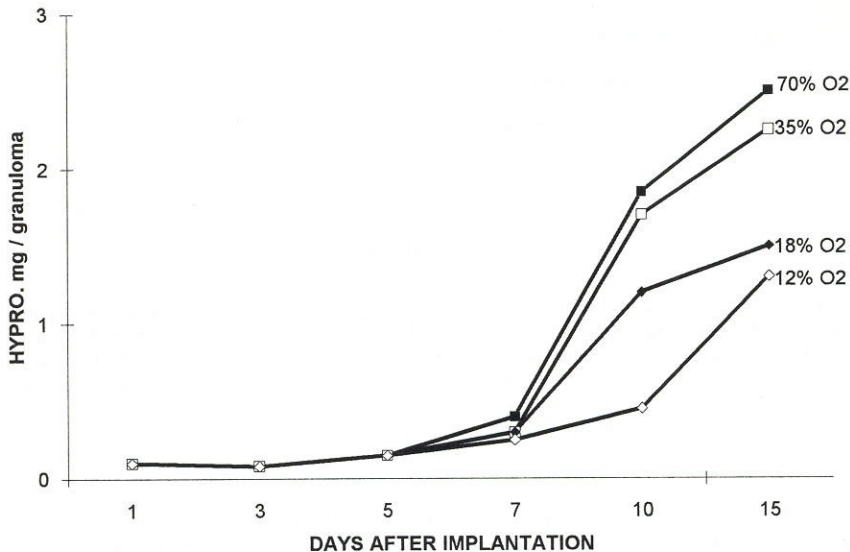

Figure 3. Effect of different ambient oxygen tensions on production of collagen hydroxyproline in subcutaneous cellulose sponge implants in rats. (*Adapted from* Niinikoski J: Effect of oxygen supply on wound healing and formation of experimental granulation tissue. Acta Physiol Scand Suppl 334:1, 1969; with permission.)

A number of investigations have documented that oxygen enhances epithelialization in open wounds. It appears that epithelial cells can easily live in anaerobic environments but use oxygen when it is available.[18] In both normal and ischemic wounds, epithelial spread is increased when oxygen tension is elevated.[21, 38]

CLINICAL EXPERIENCE

HBO has been used for a number of years in the treatment of diabetic wounds. The rationale for treatment can briefly be summarized as follows: Diabetic wounds are polymicrobial with a high incidence of anaerobic organisms. Infection can potentiate pedal ischemia and consequently decrease tissue oxygen levels. HBO increases tissue oxygen levels, increases host antimicrobial defense, promotes wound healing, and is directly toxic to anaerobic organisms.

A number of anecdotal and retrospective studies have supported the finding that HBO is an effective adjunct in the surgical management of these wounds. Hart et al,[10] Pedesini et al[39] and Perrins and Barr[40] have shown positive outcomes for diabetic wounds treated with HBO. Davis,[7] in a clinical series of 168 patients, obtained a 70% success rate by using adjunctive HBO therapy. Oriani et al,[37] treating Wagner class 3 and class 4 diabetic feet, reported a 5% amputation rate in the HBO-treatment group (n = 62) and a 33% amputation rate in the non–HBO-treatment group (n = 18). Wattel et al[46] retrospectively reviewed 59 diabetic patients treated with HBO, finding that 13% required amputation and 87% completely healed.

Similarly positive results were obtained by Baroni and associates[4] in 1987 in a prospective, controlled clinical trial in which diabetic foot wounds were adjunctively treated with HBO. Twenty-eight patients with Wagner class 3 and class 4 lesions were divided into an HBO-treatment group (n = 18) and a non–HBO-treatment group (n = 10). Control of diabetes was similar, and the surgeons were blinded as to HBO treatments. In the HBO-treatment group, 16 patients healed, and 2 required amputations. In the non–HBO-treatment group, 1 healed, 4 required amputations, and 5 remained unchanged.

The preponderance of physiologic studies and clinical trials support the use of HBO in diabetic foot disease. The literature supports the conclusion that HBO treatments benefit a select portion of diabetic patients with foot wounds. Further well-controlled, prospective studies on outcome, patient-selection parameters, oxygen dose, and duration of treatments are warranted.

PATIENT SELECTION

Use of HBO to treat diabetic wounds is generally sought after days or weeks of local wound care, surgical débridements, and antibiotics

DIABETIC FOOT WOUND ASSESSMENT

WOUND GRADING

KNIGHTON WOUND GRADE 3, 4, 5, 6

DIABETES CONTROL
I.V. ANTIBIOTICS
WOUND CARE
NUTRITION
OFF LOADING

DIMINISHED PEDAL PULSES AND/OR TROPHIC CHANGES

DEBRIDEMENT AND/OR MINIMAL AMPUTATION

HEAL

DIABETIC FOOT EDUCATION
FOOT STRUCTURE EVAL
PREVENTIVE ORTHOTICS
REGULAR FOOT CARE

CONSIDER:
RE-EVAL. FOR OSTEO
RE-EVAL. NUTRITION
VASCULAR CONSULT
PLASTIC SURGERY CONSULT
WHGF

HYPOXIA

$TCPO_2$
(IF NOT PREVIOUSLY ACCOMPLISHED)

HBO TREATMENT
DEBRIDEMENT AND/OR MINIMAL AMPUTATION
DAILY WOUND CARE

HEAL

HIGHER LEVEL AMPUTATION

REHABILITATION

VASCULAR RECONSTRUCTION AND/OR MINIMAL AMPUTATION

LARGE VESSEL DISEASE

ARTERIOGRAM (IF INDICATED)

EVIDENCE OF LARGE VESSEL DISEASE — YES

$TCPO_2$, MAPPING

VASCULAR CONSULTATION

KNIGHTON WOUND GRADE 1, 2

OSTEOMYELITIS PRESENT

DIMINISHED PEDAL PULSES AND/OR TROPHIC CHANGES

DIABETES CONTROL
ANTIBIOTICS
WOUND CARE
NUTRITION
OFF LOADING

DEBRIDEMENT OR MINIMAL AMPUTATION

HEAL

DIABETIC FOOT EDUCATION
FOOT STRUCTURE EVAL
PREVENTIVE ORTHOTICS
REGULAR FOOT CARE

CONSIDER:
RE-EVAL. FOR OSTEO
RE-EVAL. NUTRITION
$TCPO_2$, MAPPING
VASCULAR SURGERY CONSULT
PLASTIC SURGERY CONSULT
WHGF

HYPOXIA

$TCPO_2$
(IF NOT PREVIOUSLY ACCOMPLISHED)

HBO TREATMENT
DAILY WOUND CARE

Figure 4. See legend on opposite page.

have been used unsuccessfully. More recently, surgeons have been using HBO perioperatively for amputations to minimize risk of further tissue loss. It is clear that many patients benefit from HBO, but some questions still remain to be answered. What diabetic wounds should be considered for HBO treatment? Where in the treatment regimen of diabetic wounds should HBO be considered? What are the selection criteria?

Prior to referral of the patient for HBO treatments, control of diabetes and infection, along with vascular evaluation, if indicated, should be well under way. Of primary importance for the patient is the adequacy of peripheral perfusion. Noninvasive vascular evaluation, including capillary filling time, Doppler pulse waveform analysis, Doppler blood pressure index, and transcutaneous oximetry are all useful in predicting wound healing with or without HBO treatment. Angiographic studies should be performed if large-vessel disease is suspected. Vascular reconstruction is highly recommended if angiograms confirm an occlusive process and vasculature reconstruction is surgically possible.

Once medical management of the diabetic wound has been maximized and vascular evaluation is accomplished, experience shows that transcutaneous oxygen mapping is the most useful test for prediction of wound healing outcomes. White and Klein[47] reviewed the literature and found that transcutaneous oxygen pressures ($TcPO_2$) values above 40 mm Hg were required for successful wound healing after amputation (without HBO treatment). Wyss et al[48] found in a series of 188 diabetic patients with peripheral vascular disease that patients with leg or foot $TcPO_2$ values below 20 mm Hg were significantly more likely to have ulcers, rest pain, and amputation than were those with $TcPO_2$ values above 20 mm Hg. Campagnoli et al[6] found that $TcPO_2$ levels greater than 400 mm Hg during HBO exposure resulted in predictable healing. Also, they noted that the faster the rise of the tissue oxygen level when initially exposed to HBO, the greater the likelihood of a favorable outcome.

The Jefferson C. Davis Wound Care and Hyperbaric Medicine Center uses the diabetic foot wound algorithm in Figure 4. As can be seen on the algorithm, transcutaneous oxygen mapping of the affected extremity is integral in the acceptance or rejection of patients for HBO therapy. During the past 5 years, we have used the $TcPO_2$ values in Table 1 as part of our selection criteria. $TcPO_2$ levels greater than 40 mm Hg should result in healing of diabetic wounds with standard medical and surgical interventions. Using HBO, we have achieved wound healing in patients with $TcPO_2$ values as low as 10 to 20 mm Hg on room air at 1 ATA. $TcPO_2$ values less than 10 mm Hg while air is breathed are not a good prognostic sign, and even with HBO, the wound has little chance of healing.

Figure 4. Diabetic foot wound assessment and treatment algorithm. Knighton wound grading scale used in initial assessment.[23] WHGF = Wound healing growth factors; HBO = hyperbaric oxygen therapy; $TcPO_2$ = transcutaneous oxygen tension

Table 1. TcPO$_2$ ASSESSMENT IN DIABETIC CANDIDATES FOR HBO THERAPY*

TcPO$_2$ on Air†	TcPO$_2$ on Oxygen‡	Select for HBO
>40	NA	No
10–40	Significant rise§	Yes
<20	No rise	No

*Selection criteria used at the Jefferson C. Davis Wound Care and Hyperbaric Medicine Center, San Antonio, Texas.
†TcPO$_2$ value in the region of the wound as the patient breathes room air at 1 ATA.
‡TcPO$_2$ value in the region of the wound as the patient breathes 100% oxygen at 1 ATA.
§A 50% rise in TcPO$_2$ constitutes a significant rise.

CONTRAINDICATIONS

The only absolute contraindication to HBO treatment is untreated pneumothorax; however, a number of other air-trapping conditions may preclude a patient from receiving HBO treatments. Any air-trapping lesions in the lungs, such as cysts or bullae, need to be evaluated carefully, with HBO treatments delivered by slow changes in pressure if used. Patients with active asthma in which airway obstruction occurs should not be treated until all wheezing has resolved, and pressure changes should be made at a slow rate. Certain types of ear surgery involving the ossicles may preclude future HBO treatment, because the trauma of equalization of pressure in the middle ear or performance of a Frenzel maneuver might damage the surgically repaired ossicles. Chronic sinusitis and upper respiratory tract infection make ventilation of the middle ear and sinuses difficult and thus preclude HBO treatment until the infection is resolved.

Many patients who are candidates for HBO are elderly, so the cardiovascular system must also be considered. When high-dose oxygen is given under hyperbaric conditions, vasoconstriction occurs, increasing the total peripheral resistance and cardiac work. As a consequence, patients with congestive heart failure can experience acute worsening of heart failure and must be treated with caution.

A number of hyperbaric medicine centers have noted decreased insulin requirements as their diabetic patients undergo a course of treatment. Pretreatment blood glucose levels should be measured, and no insulin-dependent diabetic should be allowed in the chamber with a blood glucose level below 100 mg/dL. Our experience shows that these patients have a high risk for cerebral oxygen toxicity reactions in the chamber. Although cerebral oxygen-toxicity seizures have no sequelae if properly treated, the experience can be disconcerting to the patient.

CONCLUSION

The ideal tissue oxygen tension for wound healing remains to be determined, but a TcPO$_2$ of at least 40 mm Hg has been generally accepted as offering wounds the best opportunity to heal. Whether these

oxygen tensions can be achieved by breathing 100% oxygen at 1 ATA, or at 2.4 ATA in a hyperbaric chamber, depends on the severity of the patient's peripheral perfusion. At present, transcutaneous oxygen mapping offers the best method to determine the extent of tissue hypoxia and whether it is correctable with hyperbaric oxygen therapy.

The correction of tissue hypoxia is essential for the salvaging of hypoperfused diabetic foot wounds. Although HBO therapy can provide intermittent correction of wound hypoxia, it is useful only as part of a total medical and surgical approach to the patient. With careful attention to diabetes control, meticulous wound care, culture-specific antibiotics, and maximized peripheral perfusion, the use of HBO can improve outcome.

As evidenced by the current literature, HBO improves outcome in selected diabetic foot patients. The role of oxygen in the physiology of wound healing is well established. What remain to be determined are well-defined patient selection criteria and treatment protocols. Further outcome studies are also warranted to support the use of this treatment modality.

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