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Hyperbaric oxygen and wound healing

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Nonhealing wounds are a major health problem worldwide. Managing difficult wounds often involves prolonged hospitalizations, numerous surgical interventions, and medical wound management, all of which frequently lead to exuberant costs, morbidity, and even mortality. A thorough understanding of basic wound healing, diagnosis, and principles of hyperbaric oxygen (HBO) as an adjuvant therapy can facilitate healing a problem wound.

Wound healing

Phases of wound healing

A wound heals by primary or secondary intention. A laceration or incision, which is reapproximated, is an example of wound healing by primary intention. Most chronic wounds heal by secondary intention via formation of granulation tissue, contraction, and central migration of the peripheral epithelium.

The three phases of wound healing are inflammation, repair, and maturation, all of which superimpose to effectively repair a wound. The inflammation phase involves vascular and cellular responses. Arterioles constrict, and then dilate. Fibrin congregates, platelets aggregate, and the coagulation cascade is initiated. Neutrophils and macrophages invade the

wound, removing tissue debris and bacteria. Macrophages attract the fibroblast to the injured site, stimulating fibroblast proliferation and angiogenesis. Resolution of the inflammation phase initiates the repair phase, in which collagen synthesis from fibroblast proliferation occurs. During maturation, collagenase is present, promoting breakdown and repair of existing collagen cross-links, and thus contributing to the wound strength.

Impaired wound healing

Problem wounds are those that fail to heal in response to standard medical and surgical therapy. These wounds are frequently found in patients who have multiple local and systemic factors inhibiting tissue healing. Advanced age, nutritional deficits, vascular insufficiency, diabetes, infection, tobacco use, hypoxia, and immunosuppression are among some of the important risk factors that interfere with wound healing. Among these, hypoxia and infection adversely affect wound healing most frequently. The consequence of many of these risk factors results in low oxygen tensions, which adversely effect neutrophil, macrophage, and fibroblast functions.

The role of oxygen

The neutrophil, macrophage, and fibroblast require oxygen to function during inflammation and repair phases. Both, oxygen-dependent and oxygen-independent systems are required in order for neutrophils and macrophages to kill microorganisms.

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Oxygen radicals derived from molecular oxygen are important in bacterial killing. Leukocytes contain an enzyme—NADPH-linked oxygenase—that is activated, resulting in oxidants. After activation, an oxidative burst allows molecular oxygen to be reduced to superoxide radicals, thus killing bacteria by oxidizing cell membranes. The superoxide radicals are reduced to oxygen and peroxide by superoxide dismutase. Myeloperoxidase combines with peroxide and chloride or iodide to form hypochlorite or hypoiodite. Intracellularly, excess peroxide is reduced to oxygen by a catalase. If iron is present, the reaction occurs extracellularly, producing OH^- , a harmful oxygen radical. This oxygen radical kills bacteria effectively, but also harms surrounding cells. If cells are hypoxic, the oxygen-dependent pathway is severely incapacitated, leading to increasing rates of infection [1].

Collagen synthesis from fibroblasts also requires oxygen. Fibroblasts follow the macrophages into the wound environment. Nonhelical procollagen is created by protein synthesis involving proline, lysine, and glycine. Oxygen is an important cofactor re-

quired during hydroxylation of proline and lysine during formation of procollagen. Next, propeptides are cleaved off of procollagen to form tropocollagen via lysyl oxidase. Glycosaminoglycans provide a matrix for cross-linking and aggregation of collagen molecules to form collagen mature fibers. Mature collagen synthesis requires prolyl-hydroxylase and lysyl-hydroxylase, which are enzymes dependent on oxygen for function. Energy metabolism of the cell is first priority, occurring through oxidative phosphorylation, which then allows enzymes to use molecular oxygen. If the tissue is hypoxic, procollagen hydroxylation suffers and mature collagen cannot be formed [2].

The problem wound environment is hypoxic, acidotic, and contains high levels of lactate. This environment forms a concentration gradient, largely responsible for the inward movement of wound healing cells [3]. Hypoxia is the result of the initial vascular damage, coagulation, and vasoconstriction. Furthermore, leukocytes increase oxygen consumption, causing a lower oxygen tension in the wound [2]. Acidosis results from an increase in oxygen



Fig. 1. Monoplace hyperbaric oxygen chamber. (Courtesy of Sunrise Hospital and Medical Center, Las Vegas, NV.)

demand in the face of a decreased oxygen supply. In wounds, lactate accumulates due to hypoxia. Lactate accumulation is also caused by leukocytes, fibroblasts, and endothelial cells. These cells have few mitochondria and therefore rely on glycolysis, even in the presence of oxygen, resulting in high levels of lactate. Furthermore, lactate stimulates collagen secretion and angiogenesis.

Angiogenesis occurs rapidly in wounds across a gradient of low lactate and high oxygen tension to areas of high lactate and low oxygen levels [3]. Although profound hypoxia inhibits all wound-healing processes, moderate low oxygen tensions initiates angiogenic growth factor production in vitro and upregulates vascular endothelial growth factor [2]. Recent data supports lactate as the agent responsible for initiating these growth factors [3], but the intricate details of this pathway remain to be elucidated.

Wound diagnosis

To determine the etiology of a nonhealing wound, an accurate diagnosis must be made. As with any medical problem, the evaluation begins with an adequate history and physical examination. Information regarding the duration, wound environment (dressings, topical treatments), surgery (debridements, grafts), and presence of comorbidities (diabetes, vascular disease, malnutrition, and so forth) are important components. Examination of the wound will provide information such as wound size, location, depth, and infection. Peripheral vascular disease can be diagnosed by the presence of skin changes and diminished pulses. Venous stasis can also be determined. Examination of the granulation tissue will also provide clues as to the etiology of the wound. If the granulation tissue is beefy red in appearance, the wound environment is healthy. If the granulation tissue is pale, friable, or nonexistent, the wound is likely hypoxic.

The foundation of treating a problem wound is the identification and correction of the underlying etiologic and risk factors that may hinder the healing process. An angiogram should be obtained, if indicated, to determine the presence of vascular abnormalities amenable to surgical intervention. Furthermore, noninvasive evaluation, consisting of evaluation of tissue oxygenation and perfusion of the wound, is essential. Arteriole Doppler studies, consisting of both segmental and toe pressures, should be obtained to evaluate perfusion. Transcutaneous oximetry (TcPO₂) is used to assess oxygenation of the wound. If both of

these values are normal, a wound should heal spontaneously. If they are abnormal, adjunctive therapy may be needed to aid in healing the wound.

HBO as a therapy

The management of problem wounds should always include correction of perfusion and oxygenation deficiencies, debridement, infection control, aggressive wound care, and surgical closure. In problem wounds, adjunctive care may also be necessary. When a deficiency in oxygenation of the wound is found, in the face of nonreconstructable vascular disease, HBO as an adjunctive therapy should be considered.

Definition

HBO is defined as a treatment in which 100% oxygen is delivered to a patient at greater than two times the normal atmospheric pressure at sea level. The goal is to increase oxygen delivery to tissues by increasing the partial pressure of oxygen in plasma. This is based on Henry's law, which states that the



Fig. 2. Multiplace hyperbaric oxygen chamber (inside). (Courtesy of Kindred Hospital, Las Vegas, NV.)



Fig. 3. Multiplace hyperbaric oxygen chamber (outside). (Courtesy of Kindred Hospital, Las Vegas, NV.)

concentration of a gas dissolved in fluid is directly proportional to the pressure exerted on the gas. In other words, HBO therapy results in “hyperoxic plasma,” because arteriole PO_2 levels can reach greater than 2000 mm Hg and tissue PO_2 levels can reach levels greater than 600 mm Hg.

HBO therapy is accomplished via a monoplace or multiplace chamber. A monoplace chamber is a hollow sphere designed to deliver HBO to one patient without the use of an oxygen mask (Fig. 1). Respirator-dependant patients can be supported on ventilators that are specially designed for the monoplace chamber. Pertinent vital signs and transcutaneous oxygen levels can be monitored while the patient is in the monoplace chamber. Multiplace chambers can accommodate more than one person (Figs. 2, 3). Because compressed air is used for pressurization, patients must wear tight-sealing oxygen masks, or hoods, that deliver 100% oxygen. Chambers must also have vacuum reducers to conduct exhaled carbon dioxide out of the tank. The advantages of a multiplace chamber are in treating more than one patient at a time and direct care for patients, including defibrillation, suctioning, and chest tube insertion. In contrast, if patients are in a monoplace chamber, they must be decompressed before direct patient care can



Fig. 4. Tc PO_2 machine.

be administered. In addition, there are less claustrophobic events in multiplace chambers when compared with monoplace chambers.

An increase in tissue oxygen tension by HBO therapy enhances wound healing by a number of mechanisms. It increases neutrophil bactericidal

capacity, kills some anaerobic bacteria, inhibits toxin formation in some anaerobes, encourages fibroblast activity, and promotes angiogenesis [4]. Classically, oxygen delivery depends on the amount of oxygen carried by hemoglobin, rather than on arterial oxygen content. In wounds, how-

Transcutaneous Oximetry Monitoring

Date: _____ Time: _____

Patient Name: _____ Diagnosis: _____

Physician: _____ Technician: _____ Cal: _____ mm Hg

Reference site: (2nd intercostal space) Air _____ mm Hg - 100%O₂ _____ mm Hg

Site #1	Site #2	Site #3
Room Air _____ mm Hg	Room Air _____ mm Hg	Room Air _____ mm Hg
100%O ₂ _____ mm Hg	100%O ₂ _____ mm Hg	100%O ₂ _____ mm Hg
1 min. _____ mm Hg	1 min. _____ mm Hg	1 min. _____ mm Hg
2 min. _____ mm Hg	2 min. _____ mm Hg	2 min. _____ mm Hg
3 min. _____ mm Hg	3 min. _____ mm Hg	3 min. _____ mm Hg
4 min. _____ mm Hg	4 min. _____ mm Hg	4 min. _____ mm Hg
5 min. _____ mm Hg	5 min. _____ mm Hg	5 min. _____ mm Hg
10 min. _____ mm Hg	10 min. _____ mm Hg	10 min. _____ mm Hg

Fig. 5. TcPO₂ evaluation form.



Fig. 6. Initial evaluation of a 58-year-old insulin-dependent diabetic patient with a limb-threatening foot wound. The patient had a normal perfusion pressure and a low transcutaneous oxygen measurement.

ever, this is not true. Intercapillary distances are large and oxygen consumption is relatively low in wounds. Furthermore, microvasculature damage and peripheral vasoconstriction increase diffusion distances. Partial pressure is the driving force of diffusion. A higher PO_2 level is needed to force oxygen into injured and healing tissues [5,6]. Therefore, HBO creates a steep tissue oxygenation gradient, providing an even more powerful stimulus than lactate or moderate hypoxia, to initiate and propel wound healing [5,6].

Supporting data

The effects of HBO on wound healing have been shown in several clinical trials. Conditions such as osteomyelitis, necrotizing infections, ischemia reperfusion, and thermal injuries have been studied with promising results [7–9]. Perhaps the most informative studies have been in diabetic lower extremity wounds. Overall, several studies have shown decreased wound size [10–12], decreased rates of amputation [10, 13–16], and increased numbers of

healed wounds [15, 17, 18] among patients receiving HBO therapy as an adjunctive treatment.

Baroni et al [10] conducted a nonrandomized study of 18 hospitalized diabetics and 10 diabetic control patients. They reported that a significant number of subjects who received HBO went on to heal their wound when compared with subjects who had not received HBO. In a continuation of this study [16], a significant decrease in amputations was found among patients who underwent HBO, when compared with the control group. The same researchers published a third study [17] that involved 151 diabetic patients with wounds of the lower extremity (there was no control group in this study). One hundred and thirty of the patients completely healed their wounds with adjunctive HBO. Furthermore, the authors of a prospective randomized trial [14] involving 35 subjects who received HBO and 33 patients who were controls reported a significantly lower incidence of major amputations among Wagner grade IV ulcers. Wattel et al [18] conducted a noncontrolled study consisting of 59 diabetic patients with wounds. Fifty-two patients who received HBO went on to heal their wounds. Doctor et al [13] showed a significant decrease in amputation rate in 30 patients who were



Fig. 7. Wound after surgical debridement.



Fig. 8. Wound after 15 hyperbaric treatments.

subjected to HBO when compared with the control group during a prospective randomized study. Hamerlund et al [11] found a significant reduction in wound size among nondiabetic patients who received HBO in a prospective randomized study. Zamboni et al [12] followed nonhealing diabetic ulcers in a prospective nonrandomized study, and found a significant reduction in wound size for HBO patients when compared with non-HBO patients. Kalani et al [15] followed chronic diabetic foot wounds for 3 years in a prospective randomized study. When compared with conventionally treated wounds, HBO patients had an accelerated rate of healing, reduced rate of amputation, and an increased rate of completely healed wounds on a long-term basis.

Many factors play an important role in wound healing. Diabetic control, circulatory problems, presence of infection, and wound size or depth may adversely affect wound healing. Many of these studies failed to compare these variables during analysis of their data. Nonetheless, the results are promising and should serve as a stimulus for the development of double-blinded prospective randomized studies in the future.

Patient evaluation

Proper patient selection for HBO therapy is crucial. The etiology of the problem wound ensures successful management. A vascular surgery consultation is the first priority, to determine if a reconstructible lesion exists. If the patient has nonreconstructable vascular disease, HBO therapy may be indicated. Tissue oxygenation and perfusion must be evaluated in each wound. Noninvasive arteriole Doppler studies, consisting of segmental and toe pressures, are used to evaluate perfusion, whereas TcPO₂ is used to evaluate oxygenation.

Currently, TcPO₂ is the best tool available to evaluate tissue hypoxia, wound-healing potential, and patient selection for HBO therapy, and to monitor progress during therapy (Figs. 4, 5) [19]. A transcutaneous oxygen tension greater than 50 mm Hg indicates that the wound should heal spontaneously. Values between 30 and 50 mm Hg are marginal, and values below 30 mm Hg indicate that the wound will not heal without adjunctive therapy. HBO therapy will accelerate tissue repair in hypoxic wounds in which oxygen tension can be elevated to therapeutic levels [19]. Therefore, if a patient has been found to have TcPO₂ levels below 40 mm Hg,



Fig. 9. Wound after 30 hyperbaric treatments and prior to successful skin graft.

and these levels have been shown to increase to greater than 100 mm Hg while breathing 100% oxygen or to greater than 200 mm Hg at 2.5 atmospheres absolute, the patient may be a candidate for HBO. Repeated TcPO₂ with the patient breathing room air for at least 12 hours after an HBO treatment is documented on a weekly basis. Importantly, there is often a 2-week period in which there is no improvement in wound appearance, despite HBO. These patients may eventually respond to HBO, and therefore amputation should be delayed. When healthy granulation tissue is present—which usually occurs after 15 to 30 treatments—TcPO₂ should be measured at room air. If TcPO₂ levels are above 40 mm Hg, HBO should be discontinued and proper wound care should be continued until the wound heals.

The diabetic patient poses a challenge during evaluation of tissue perfusion and oxygenation. Diabetic patients may have normal or falsely elevated noninvasive Doppler studies and low TcPO₂ levels, implying satisfactory perfusion and inadequate oxygenation of the wound. Many factors unique to diabetes may contribute to decreased oxygen delivery to the wound, such as red blood cell membrane stiffness and glycosylated hemoglobin. In general, a diabetic patient with normal noninvasive Doppler and low TcPO₂ level responds best to HBO (Figs. 6–9).

Presently, the use of HBO therapy is necessary in only 15% to 20% of patients [19]. HBO therapy in compromised diabetic wounds is usually reserved for wounds with tendon or bone exposed, as well as those wounds with impending gangrene that do not respond to traditional management of debridement, antibiotics, and general wound care, including vascular reconstruction. HBO therapy increases wound oxygen tension, enhancing host antibacterial mechanisms and promoting wound healing [19]. Overall, HBO is reserved for wounds in which hypoxia and infection are the etiology. Rarely, HBO is indicated for other wounds such as venous ulceration or decubitus ulcers [7].

HBO treatment protocols

Protocols for administering HBO vary depending on the wound severity and chamber type. Oxygen pressure, duration, periodicity, and total number of sessions may vary from center to center. Typically, treatments are delivered at 2.0 to 2.4 atmospheres for 90 to 120 minutes once or twice daily in multiplace chambers [7]. Treatments in monoplace chambers are typically performed at 2.0 atmospheres [7]. When serious infections are present, patients are typically

hospitalized, and given both IV antibiotics and hyperbaric treatments twice daily. HBO is an adjuvant treatment; therefore, diabetic control, debridement, and aggressive wound treatment are given first priority. When the wound bed has adequate granulation tissue, application of grafts can shorten morbidity, hospital stay, and health care costs.

Summary

Problem wounds, which fail to respond to traditional medical and surgical therapy, can be challenging to the plastic surgeon. Surgical, outpatient, and inpatient wound care costs can be exorbitant. Indirect costs, such as those related to patient productivity, disability, and premature death, can also be significant. The underlying problem in failure of a wound to heal is usually hypoxia and infection. HBO treatments in selected patients can facilitate healing by increasing tissue oxygen tension, thus providing the wound with a more favorable environment for repair. Therefore, HBO therapy can be an important component to any comprehensive wound care program.

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