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Correction of Hypoxia, a Critical Element for Wound Bed Preparation Guidelines: TIMEO$_2$ Principle of Wound Bed Preparation

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Abstract

Wound bed preparation is an organized approach to create an optimal environment for wound healing by the use of the most cost-effective therapeutic options. It has become an essential part of wound management and seeks to use the latest findings from molecular and cellular research to maximize the benefits of today's advanced wound care products. The international advisory panel on wound bed preparation met in 2002 to develop a systemic approach to wound management. These principles of this approach are referred to by the mnemonic TIME, which stands for the management of nonviable or deficient tissue (T), infection or inflammation (I), prolonged moisture imbalance (M), and nonadvancing or undermined epidermal edge (E). One critical element of pathophysiology, understanding of the hypoxic nature of the wound and correction of hypoxia as a critical element of wound bed preparation, is not covered. This article proposes to add correction of hypoxia to the TIME principle (TIMEO$_2$ principle) based on the evidence. The evidence that will support the reason and the need for modification of the wound bed preparation protocol is discussed.

keywords: Chronic wounds, Hyperbaric oxygen therapy, Hypoxia, TIMEO$_2$ principle, Wound bed preparation

Introduction

Normal wound healing proceeds through an orderly sequence of steps involving control of contamination and infection, resolution of inflammation, regeneration of the connective tissue matrix, angiogenesis, and resurfacing. Several of these steps are critically dependent on adequate perfusion and oxygen availability. Chronic wounds are wounds that have failed to proceed through this orderly sequence of events and have failed to establish a sustained anatomic and functional result.[1,2] This failure of wound healing is usually the result of 1 or more local wound or systemic host factors inhibiting the normal tissue response to injury. These factors include persistent infection, malperfusion and hypoxia, cellular failure, and unrelieved pressure or recurrent trauma.[3] The concept of wound bed preparation allows us to break down into individual components the critical steps involved in optimizing the clinical aspects and the microenvironment of chronic wounds.[4-8] This review discusses wound bed preparation with an emphasis on the principle that correction of hypoxia is critical in the wound repair process. It expands on the TIME principle of wound bed preparation[5] and includes the important role of correction of hypoxia for wound bed preparation. With growing evidence of the importance of the correction of hypoxia, the TIMEO$_2$ principle (Figure 1) will, I hope, become the standard of care for wound bed preparation.

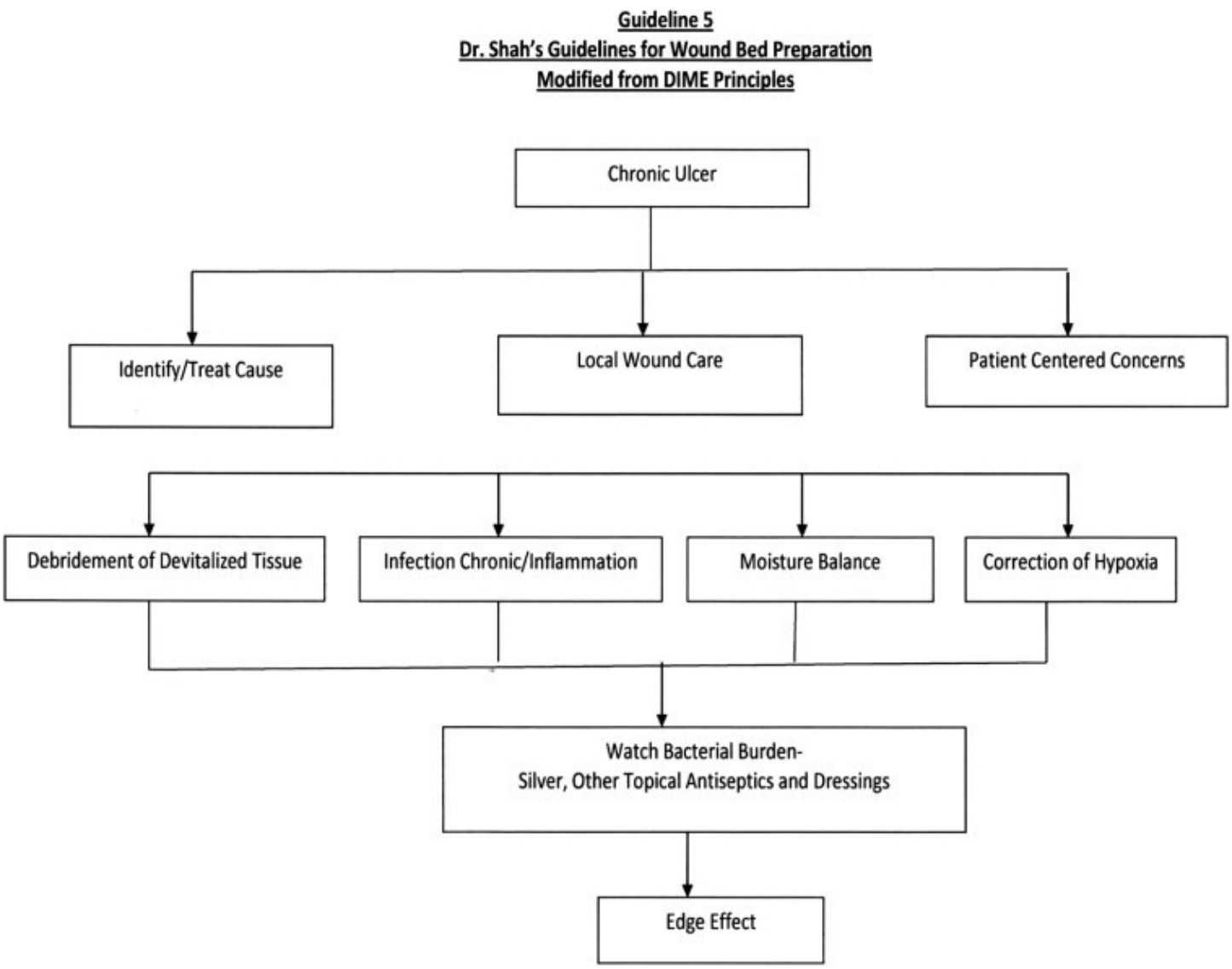

Figure1

Suggested Updated Guidelines for Wound Bed Preparation Modified From DIME Principles.53,76

Overview of Wound Bed Preparation

Wound bed preparation can be defined as the global management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures. It is a systematic approach to correcting molecular and cellular abnormalities, which is critical to promoting healing of chronic wounds. Wound bed preparation includes basic wound care, along with the foundational aspects of wound care and advanced wound technology.7-9 Chronic wounds do not heal, because of multiple factors: (1) psychosocial issues, (2) excess bacteria, (3) excess exudate production, (4) alkaline pH, (5) prolonged inflammation, (6) devitalized tissue, (7) low volume of growth factors, (8) cell senescence, (9) concurrent illness, (10) excessive proteases, (11) poor local vascular supply, and (12) hypoxia.

The main goal for wound bed preparation is to create a well-vascularized, stable wound bed with minimal exudate.

The modified wound bed preparation score10 as proposed by Falanga et al includes the categories of (1) healing edges, (2) black eschar, (3) greatest wound depth or granulation tissue, (4) exudate amount, (5) edema, (6) periwound dermatitis, (7) periwound callus or fibrosis, (8) pink wound bed, and (9) wound duration prior to treatment.

The wound bed preparation score decreases if there is an increase in necrotic tissue and a decrease in granulation tissue, and clinically hypoxic wounds are slow to develop granulation tissue and angiogenesis.6,11 Correction of hypoxia (Figure 2) is a good additional step for wound bed preparation as it helps with (1) enhancement of white blood cell killing, (2) inhibition of toxin formation, (3) inactivation of toxins (*Clostridium perfringens*), (4) bacteriostasis, (5) antibiotic transport across the cell wall,12-15 (6) collagen cross-linking,16 and (7) angiogenesis.

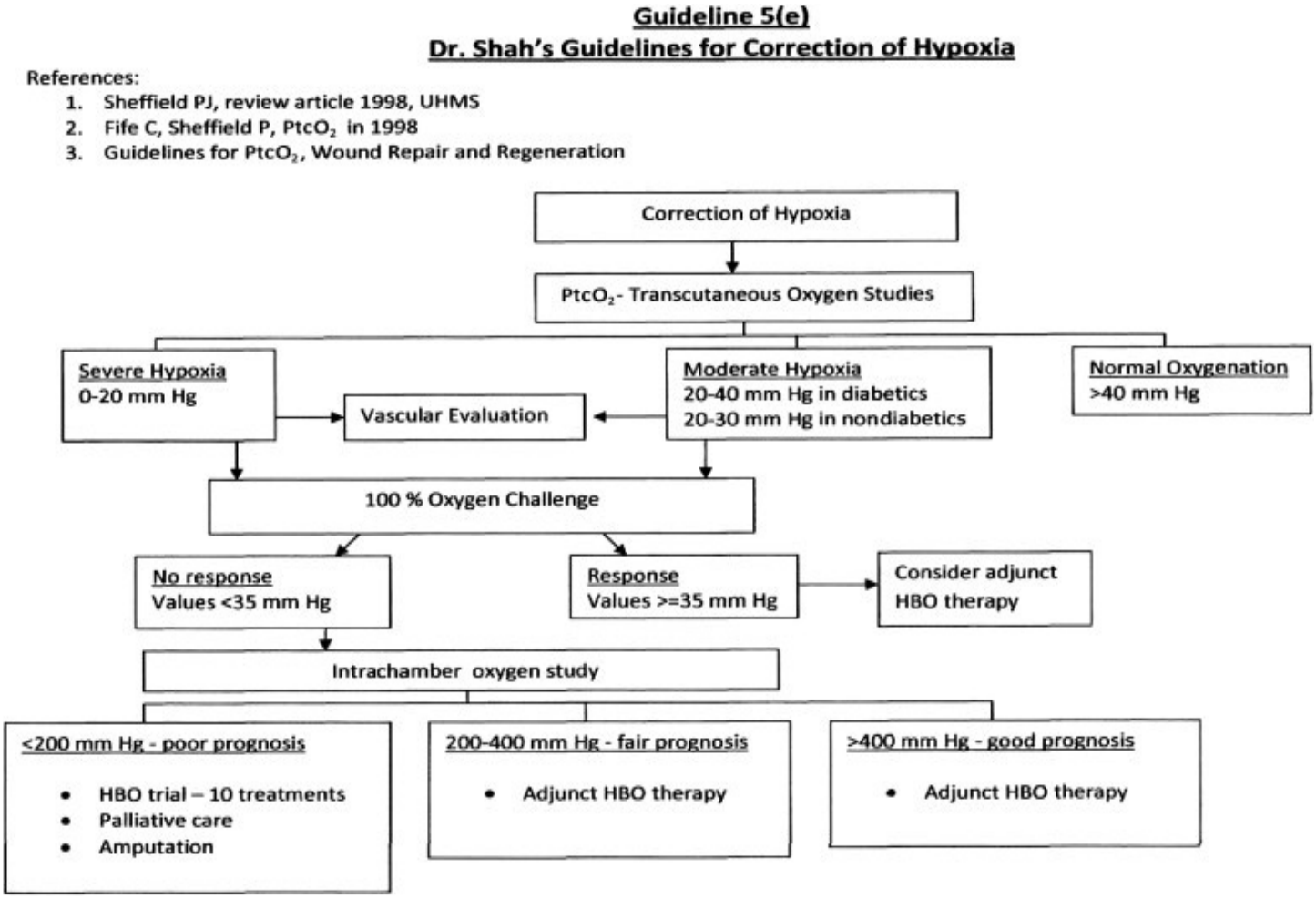

Figure2

Suggested Updated Protocol for Correction of Hypoxia.29,30,53,55,56,69,76

The $TIMEO_2$ paradigm (modified here to include correction of hypoxia) (Figure 2) includes the following components:

- 1. Tissue
- 2. Infection or chronic inflammation
- 3. Moisture balance
- 4. Edge effect

- 5. Correction of hypoxia

This article focuses on the correction of hypoxia (Figure 2) as a critical step in wound bed preparation.

Hypoxic Nature of Wounds

The hypoxic nature of wounds has been demonstrated,17 and the hypoxia, when increased, correlates with impaired wound healing18 and increased rates of wound infection.19 Local oxygen tensions in the vicinity of the wound are approximately half the values observed in normal, nonwounded tissue.20-22 The rate at which normal wounds heal has been shown to be oxygen dependent. Fibroblast replication, collagen deposition,16 angiogenesis,23-26 resistance to infection,27-29 and intracellular leucocyte bacterial killing30,31 are oxygen-sensitive responses essential to normal wound healing.

Hypoxia has been defined in consensus statements from the 2007 Undersea and Hyperbaric Medical Society workshop on transcutaneous oximetry ($PtcO_2$) in clinical practice as follows32:

- 1. Hypoxia is defined as $PtcO_2$ < 40 mm Hg (respiring air).
- 2. Normal extremities reach $PtcO_2$ > 100 mm Hg (respiring O_2).
- 3. Critical limb ischemia usually has $PtcO_2$ < 30 mm Hg.
- 4. Amputation healing is unlikely at $PtcO_2$ < 40 mm Hg or if $PtcO_2$ rise on O_2 is < 10 mm Hg.
- 5. After revascularization, healing usually occurs if $PtcO_2$ increases to > 40 mm Hg (increase might be delayed).
- 6. $PtcO_2$ obtained while breathing normobaric air can identify patients who will not heal spontaneously.

The laboratory evidence for hypoxia's playing a major role in wound healing failure is not in dispute. Clinical studies identifying the risks of failure of wound or amputation flap healing define periwound hypoxia as a primary reason for failure of future healing. When periwound $PtcO_2$ values were below 20 mm Hg, they were associated with a 39-fold increased risk of primary healing failure.33 Hyperbaric physicians routinely measure for wound hypoxia before treatment decisions as clinically hypoxic wounds are slow to develop new vessels (granulation tissue).

$PtcO_2$ values measured at sea level can help predict healing failure (Figure 3) but have no value in predicting benefit with subsequent hyperbaric oxygen (HBO) treatment; however, they help in predicting failure to heal without HBO treatment.34

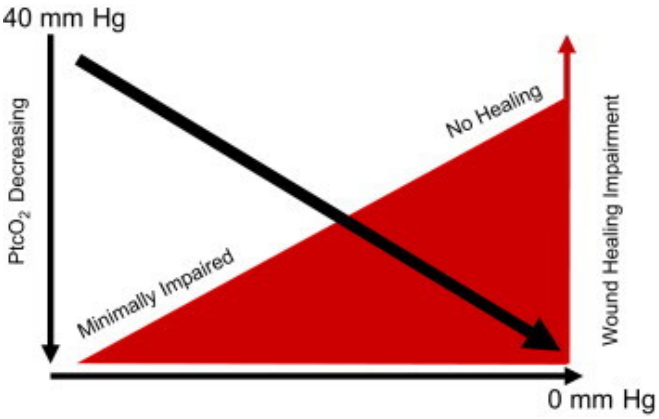

Figure 3

Wound Healing Impairment With Decreasing Transcutaneous Oximetry ($PtcO_2$).

Measurement of Wound Hypoxia

$PtcO_2$ is a commonly used, noninvasive assessment tool to measure the local tissue oxygen tension in tissue fluids below the skin, and it is derived from local capillary (nutritive) blood perfusion.[35-38] Originally, the technique was developed for use in neonatology,[39] but it is now commonly used in pediatric intensive care units,[40] plastic surgery,[41] vascular surgery,[42] anesthesiology,[43] orthopedics,[44] and hyperbaric medicine.[45] Tissue oxygenation and perfusion data are collected to identify the presence of tissue hypoxia, responders to hyperoxia, and adequacy of perfusion.[35,46]

Although several tests intended to identify significant wound hypoxia have been used, including ankle brachial index, skin perfusion pressure, and laser Doppler flow, transcutaneous oxygen is the most useful[43] for predicting the failure of a wound to heal, for predicting healing of planned amputation, for predicting response to HBO treatment, as well as for evaluating success of revascularization.

Two evidence-based reviews support $PtcO_2$ as a screening tool for a wound population at high risk for vascular disease.[32,47] When clinically indicated, $PtcO_2$ should be used to validate referral for vascular status and be used in conjunction with HBO therapy intervention.[48]

Correction of Hypoxia (Role of Hyperbaric Oxygenation of Wounds)

Regardless of the primary etiology of problem wounds, hypoxia is a critical element as a cause for nonhealing. A large body of evidence demonstrates that intermittent oxygenation of hypoperfused wound beds only achieved by exposing them to HBO therapy mitigates many of these impediments and sets into motion a cascade of events that leads to wound healing.[11]

Increasing the chamber pressure while breathing oxygen (1) increases alveolar Po_2, (2) increases blood oxygen transport, (3) increases tissue Po_2, and (4) aids healing of hypoxic wounds by daily bringing tissue Po_2 to a normal level.

Correction of hypoxia (Figure 2) (HBO therapy) is achieved by intermittent administration of oxygen under increased atmospheric pressure of at least 1.4 atmosphere absolute (ATA) and above. Oxygen is transported by 2 mechanisms: (1) chemical binding to hemoglobin and (2) physical dissolution in plasma. Once hemoglobin is saturated, increases in Po_2 can affect only the plasma-dissolved oxygen fraction. As the Po_2 increases, the amount of O_2 physically dissolved in plasma increases in a linear fashion.[49] Physiologically, this HBO produces a directly proportional increase in plasma volume fraction of transported oxygen that is readily available for cellular metabolism (Figure 4).

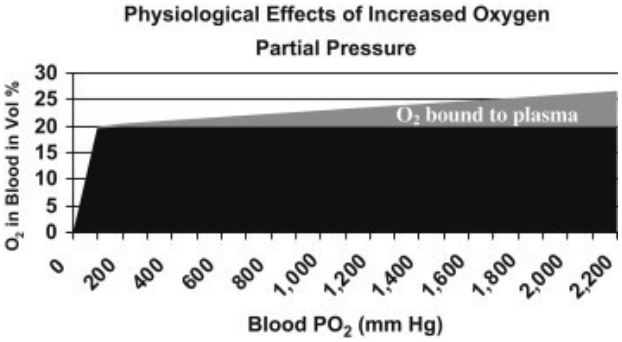

Figure 4

Physiological Effects of Increased Po_2.

Under hyperbaric conditions, dissolved oxygen in plasma is a major benefit. Plasma transports 2.1 vol% per atm Po_2 at 1 ATA, 4.4 vol% at 2 ATA, 5.3 vol% at 2.36 ATA, and 6.8 vol% at 3 ATA (Figure 4). As inspired Po_2 increases, tissue Po_2 increases in the skin and wound.[11,31,36] HBO therapy also increases diffusion distance, corrects local tissue hypoxia, and brings Po_2 up to normal in selected wounds[11,36]; multiple HBO treatments increase Po_2 in the wound, indicating improved vascularity. HBO benefits ischemic and hypoxic wounds by bringing the oxygen tension up to a normal level daily.

A key factor in HBO therapy's enhancement of the hypoxic wound environment is its ability to establish adequate oxygen availability within the vascularized connective tissue compartment that surrounds the wound. To carry out their specific inflammatory or repair functions, neutrophils, fibroblasts, macrophages, and osteoclasts are all dependent on an environment in which oxygen is not deficient. Improved leukocyte function of bacterial killing[11,50,51] and synergistic effects with antibiotics[12,13] have been demonstrated. Supression of synthesis of many bacterial toxins[12] occurs when tissue Po_2 values are sufficiently elevated during treatment. Blunting of systemic inflammatory responses[13] and prevention of leukocyte activation and adhesion after ischemic reperfusion[52-54] are effects that may persist even after completion of HBO therapy.

Significant stimulation of tissue growth factors supporting wound healing has also been demonstrated by a variety of mechanisms. First, release of vascular endothelial growth factor is stimulated.[48] Second, platelet-derived growth factor receptor appearance is also induced.[55-57] Third, a persistent increase in nitric oxide in wound fluid was demonstrated in wound fluid of diabetic ulcers that was associated with increased granulation tissue formation and wound closure in patients receiving HBO therapy.[58] Finally, increased release of stem, or progenitor, cells from bone marrow through a nitric oxide–dependent mechanism was also demonstrated in patients receiving HBO therapy.[59]

Oxidation appears to be among the most important signals that control the healing process, and this may be another mechanism for the benefits of HBO therapy in hypoxic wounds.

Arterial Po_2 elevations to 1,500 mm Hg or greater are achieved with 2 to 2.5 ATA. This significant level of hyperoxygenation allows for the reversal of localized tissue hypoxia, which may be secondary to ischemia or to other local factors within the compromised tissue (eg, edema and inflammation).

Sheffield et al in their review article discussed the use of oximetry to assess wound healing potential and select HBO candidates.[36] Every wound should trigger these 4 questions:

- 1. Is wound healing complicated by severe hypoxia?[32]

  Hypoxia exists if baseline air value < 40 mm Hg for diabetics or < 30 mm Hg for nondiabetics (Table).

  Table

  Suggested Classification System for Degree of Ischemia and Hypoxia Based on $PtcO_2$ Data[12,14,55,56]

	Diabetics	Nondiabetics
Adequate for healing	> 40 mm Hg	> 30 mm Hg
Moderate hypoxia	21-40 mm Hg	21-30 mm Hg
Severe hypoxia	0-20 mm Hg	0-20 mm Hg

- 2. Does the patient's wound respond to 100% oxygen challenge?
- 3. Does the patient's wound site respond to HBO?

  HBO values should rise above normobaric oxygen values and should achieve > 200 mm Hg (some hyperbaric physicians use > 100 mm Hg).

- 4. Is the patient's wound at the point where it will heal without further HBO treatment?

Fife et al[34] looked at the relationship between in-chamber $PtcO_2$ and HBO therapy success and reported that 75.6% of patients improved after HBO when intrachamber $PtcO_2$ during HBO treatment was > 200 mm Hg. Furthermore, correction of hypoxia (Figure 2) with increased oxygenation with $PtcO_2$ during HBO > 200 mm Hg was found to be the single best discriminator of success or failure (Figure 5). As in-chamber $PtcO_2$ increases, likelihood of success from HBO therapy increases.[34]

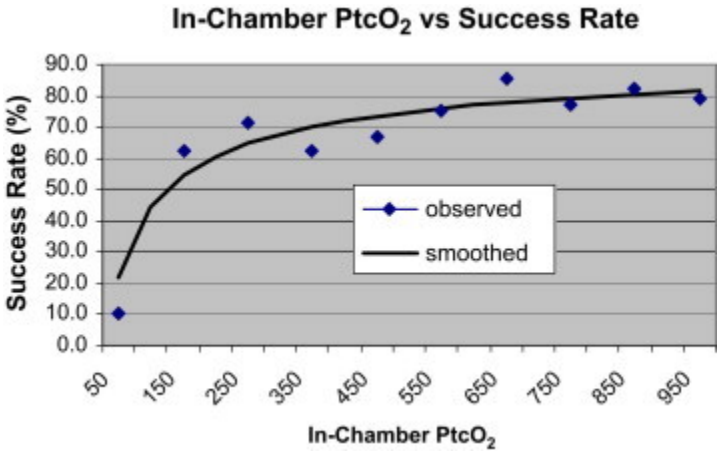

Figure 5

Relationship Between In-Chamber $PtcO_2$ and HBO Therapy Success (Fife: summary of findings).

This evidence-based review of the literature has shown the importance of correction of hypoxia (Figure 2) as an important intervention for wound bed preparation and healing in salvage of diabetic wounds.[32,33,48,54,60] While the majority of the wounds are possibly hypoxic and could potentially benefit from HBO therapy for wound bed preparation, at the present time most of the accumulated evidence suggests hypoxic diabetic lower extremity wounds and radiation wounds benefit from correction of hypoxia (Figure 2) (HBO therapy). Marx has demonstrated the enhanced vascularity and cellularity in heavily irradiated tissues after HBO therapy by comparing histologic specimens from patients pre and post HBO[61] and also demonstrated the serial improvement in transcutaneous oxygen measurements in patients receiving HBO as an indirect measure of vascular improvement.[62] Recently, Goldman showed a 3-fold reduction in risk of major amputation when HBO was included in the therapy of diabetic wounds.[54] Löndahl et al showed complete healing in 52% of patients in an HBO group, compared with 29% with placebo.[55]

Multiple consensus statements recommend HBO therapy as a reasonable modality to salvage diabetic limbs. In April 1999, the Consensus Development Conference on Diabetic Foot Wound Care sponsored by the American Diabetes Association[56] concluded that "it is reasonable to use this modality [HBO] to treat severe and limb or life threatening wounds that have not responded to other treatments, particularly if ischemia that cannot be corrected by vascular procedures is present."[56] The Wound Healing Society in 2006 in its guidelines also recommended HBO as having level-1 evidence and suggested that "HBO may be of benefit in reducing the amputation rate in patients with ischemic diabetic foot ulcer.[63] In 2010, *Wound and Ostomy Wound Management* published a Consensus Recommendation on Advancing the Standard of Care for Treating

Neuropathic Foot Ulcers in Patients With Diabetes[48] and found that there is sufficient evidence for the use and applicability of HBO therapy in persistently ischemic or infected diabetic foot ulcers. But HBO therapy "should be used in combination with optimization of perfusion, aggressive local wound care and systemic antibiotic therapy when indicated," and evidence also indicates that HBO therapy "has been shown to reduce amputation rates in prospective, randomized controlled clinical trials when compared to standard therapy that included aggressive revascularization, debridement, treatment of infection, and glycemic control."[48]

Guidance on When to Use Advanced Therapy With HBO

There is enough evidence to support use of advanced therapy if conventional therapy has not been successful within 4 weeks, and alternative therapies should be considered.[57-59] The initial rate of healing during the first 4 weeks can predict whether ulcers are likely to heal by 24 weeks.[58,59] If initial healing rates are < 0.1 cm/week at the 4-week interval, then advanced therapy should be considered.[58] Ulcers with a poor prognosis should be treated with a more advanced therapy.[57,58,64-68] Rapid identification of patients who are unlikely to respond to conventional care will allow for earlier interventions with advanced therapies.[57,69-74] I propose the timely use of HBO therapy in wound bed preparation for wounds that have a poor prognosis and wounds that have not shown significant signs of healing in the first 4 weeks of standard wound care.[6,75,76]

Conclusion

In chronic wounds, the orderly sequence of events seen in acute wounds becomes disrupted or "stuck" at 1 or more of the different stages of wound healing. For the normal repair process to resume, the barrier to healing must be identified and removed through application of the correct techniques. It is important, therefore, to understand the molecular events that are involved in the wound healing process in order to select the most appropriate intervention. Wound bed preparation is the management of a wound in order to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures. Correction of hypoxia (Figure 2) is an important intervention to be done in the chronic wound as a part of wound bed preparation principles.

Conflict of interest: The author reports no conflicts of interest.

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