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Arterial Inefficiencies: Enhancement of Healing In Selected Problem Wounds, Hypoxia And Wound Healing Failure

Problem wounds represent a significant and growing challenge to our healthcare system. The incidence and prevalence of these wounds are increasing in the population resulting in growing utilization of healthcare resources and dollars expended. Venous leg ulcers represent the most common lower extremity wound seen in ambulatory wound care centers with recurrences frequent and outcomes often less than satisfactory. Pressure ulcers are common in patients in long term institutional care settings adding significant increases in cost, disability, and liability. Foot ulcers in patients with diabetes contribute to over half of lower extremity amputations in the United States in a group at risk representing only 3 per cent of the population.(1) In response to this challenge specialized programs have emerged designed to identify and manage these patients using standardized protocols and a variety of new technologies to improve outcomes. Hyperbaric oxygen treatment (HBO2T) has been increasingly utilized in an adjunctive role in many of these patients coinciding with optimized patient and local wound care.

Although the underlying physiology and basic science support the contention that HBO2T is likely to be useful in a variety of problem wounds, the best evidence exists for treatment of ischemic, infected (Wagner Grade III or worse) diabetic foot ulcers. This review will therefore focus on these areas, along with suggesting appropriate areas for further research. As more studies are completed in other types of wounds, for example in ischemic, non-diabetic foot ulcers, the recommendations in this review will be updated.

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 upon adequate perfusion and oxygen availability. The end result of this process is sustained restoration of anatomical continuity and functional integrity. Problem or 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.(2) This failure of wound healing is usually the result of one 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 hypoxic nature of all wounds has been demonstrated,(4) and the hypoxia, when pathologically increased, correlates with impaired wound healing(5) and increased rates of wound infection.(6) Local oxygen tensions in the vicinity of the wound are approximately half the values observed in normal, non-wounded tissue.(7,8,9) The rate at which normal wounds heal has been shown to be oxygen dependent. Fibroblast replication, collagen deposition,(10) angiogenesis,(11,12,13,14) resistance to infection,(15,16,17) and intracellular leukocyte bacterial killing(18,19) are oxygen sensitive responses essential to normal wound healing. However, if the periwound tissue is normally perfused, steep oxygen gradients from the periphery to the hypoxic wound center support a normal wound healing response.(20,21)

Peripheral arterial occlusive disease (PAOD) is common and progressive. It often results in critical limb ischemia, non-healing ulcers, and amputation. PAOD is a common co-morbidity that frequently complicates the management of both venous leg ulcers and diabetic foot ulcers.(95)

Measurement Of Wound Hypoxia

Transcutaneous oxygen tension (PtcO2) measurements provide a direct, quantitative assessment of oxygen availability to the periwound skin and an indirect measurement of periwound microcirculatory blood flow. The application of PtcO2 measurement in the assessment of peripheral vascular disease has been well described by Scheffler(22) and its application to wound healing problems by Sheffield.(23) This technology allows objective determination of the presence and degree of local, periwound hypoxia serving as a screening tool to identify patients at risk for failure of primary wound or amputation flap healing. It can also be used during assessment of patients with lower extremity wounds as a screening tool for occult peripheral arterial occlusive disease.

PtcO2 measurements are made by applying a Clark polarographic electrode on the prepared surface of the skin. A constant voltage is applied to the cathode that reduces oxygen molecules that have diffused from the superficial dermal capillary plexus through the epidermis, stratum corneum, and electrode membrane generating a current that can be measured and converted to a value representing the partial pressure of oxygen in mmHg. The electrode heats the surface of the skin to 43 to 45o C to increase cutaneous blood flow, skin permeability, and oxygen diffusion. The electrode is typically about 0.3mm from the capillary network in normal skin.(24) PtcO2 is non-linear with respect to blood flow, exhibiting a hyperbolic response to changes in blood flow that is more pronounced as flow rates decrease. PtcO2 is a more accurate reflection of changes in perfusion than is measurement of ankle brachial index.(25)

Although several tests intended to identify significant wound hypoxia and / or ischemia have been used, including ankle brachial index, skin perfusion pressure, and laser Doppler flow, transcutaneous oximetry (PtcO2 or TCOM) is generally accepted as most useful(26) for predicting failure to heal a wound without intervention, failure to heal a planned amputation, and failure to respond to HBO2T, as well as evaluating the success of revascularization.

There is some variability in PtcO2 values obtained based upon the type of electrode and temperature used, in general, values below 25-40 mmHg have been associated with poor healing of wound and amputation flaps with the lower the value the greater the degree of healing impairment. Multiple studies(27,28,29,30,31,32,33,34,35) have demonstrated that PtcO2 values are a better predictor of flap healing success or failure following amputation or revascularization procedures than arterial Doppler studies or clinical assessment, particularly in patients with diabetic foot ulcers.(36,37) The addition of provocative testing with lower extremity elevation or dependency(38,39) or following occlusion induced ischemia and recovery(40) or with 100% oxygen breathing(41) may increase the sensitivity of the test as a screening tool for detecting occult lower extremity arterial insufficiency.

The laboratory evidence for hypoxia playing a major role in wound healing failure is not in dispute. Clinical studies identifying the risks of wound or amputation flap healing failure define periwound hypoxia as a primary determinant of future healing failure. Pecoraro(42) reported that when periwound PtcO2 values were below 20 mmHg they were associated with a 39 fold increased risk of primary healing failure. In clinical practice, hyperbaric medicine physicians routinely measure transcutaneous PO2 and use the information obtained to make patient selection and treatment decisions. Unfortunately, however, the clinical trials and case series described below have not used measured periwound hypoxia as a specific patient selection criterion.

Identifying wounds most likely to benefit is paramount for cost effective application of HBO2T. Patients with wounds that fall within a category defined as potentially appropriate for adjunctive HBO2T should be evaluated for likelihood of benefit. Hypoxia (i.e. wound PO2 < 40 mmHg) generally best defines wounds appropriate for HBO2T—or rather, lack of hypoxia (i.e. wound PO2 >40-50 mmHg) defines wounds potentially not appropriate for HBO2T. Breathing 100% oxygen at 1 ATA or under hyperbaric conditions can improve the accuracy of PtcO2 measurement in predicting successful healing with adjunctive hyperbaric oxygen treatment. The following conclusions were drawn from a study of 1144 diabetic foot ulcer patients who underwent adjunctive hyperbaric oxygen treatment in support of wound healing or limb salvage.(43) PtcO2 measured on air at sea level defines the degree of periwound hypoxia but has almost no value in predicting benefit with subsequent hyperbaric oxygen treatment. These measurements are more useful in predicting who will fail to heal without hyperbaric oxygen treatment. PtcO2 values below 35 mmHg obtained while breathing 100% oxygen at sea level are associated with a 41% failure rate of subsequent hyperbaric oxygen treatment while values obtained greater than 35 mmHg were associated with a 69% likelihood of a beneficial response. PtcO2 values measured during hyperbaric oxygen treatment exceeding a cutoff value of 200 mmHg were 74% reliable in predicting wound healing improvement or limb salvage as the result of a therapeutic course of hyperbaric oxygen. This positive predictive value is consistent with those reported by others in both arterial insufficiency and diabetic lower extremity wounds.(44,45,46) Lack of an increase in PtcO2 to >100 mmHg appears to be an appropriate cut-off for predicting failure to heal, at least in ischemic diabetic foot ulcers. This requirement for achieving supraphysiologic wound oxygen concentration lends support to the argument that restoration of wound normoxia is not the primary mechanism of action of HBO2T in healing hypoxic wounds. The failure rate for <100 mmHg is not 100%, however, so that it is not unreasonable to give a trial of HBO2T (10-15 treatments) to such patients for whom the alternative is amputation.

It is notable that PtcO2 is a better predictor of failure than success. While aggressive distal lower extremity bypass grafting and lower extremity angioplasty have contributed to increased wound healing and limb salvage rates, technical grafting success does not necessarily equate with limb salvage. Hyperbaric oxygen treatment offers an intriguing opportunity to maximize oxygen delivery and ultimately to increase wound blood flow via neovascularization in the setting of minimal or insufficiently corrected blood flow.

This underlines the central role of oxygen in wound healing. That is, there is a level of oxygen below which a wound does not have the capacity to heal. Wounds with a PO2 higher than that level, however, are not guaranteed to heal, because there are a variety of non-oxygen related impediments to healing that may prevent the normal progression of repair in the presence of adequate tissue oxygen.

Unfortunately there is a lack of prospective clinical trial data linking periwound hypoxia as a selection criterion for hyperbaric oxygen and demonstrating the contribution of hyperbaric oxygen treatment to improved outcome in these circumstances. Independent evidenced-based reviews of hyperbaric oxygen treatment in problem wounds(47,48) have been unable to define a "hypoxic wound” as a specific wound category. Instead these reviews have endorsed treatment of specific wound types such as diabetic foot ulcers, acute traumatic ischemic injuries, radiation tissue injury, and compromised grafts and flaps, among others.

Physiology Of Hyperbaric Oxygenation Of Wounds

Regardless of the primary etiology of problem wounds, a basic pathway to non-healing is the interplay between tissue hypoperfusion, resulting hypoxia, and infection. A large body of evidence exists which demonstrates that intermittent oxygenation of hypo-perfused wound beds, a process only achievable in selected patients by exposing them to hyperbaric oxygen treatment, mitigates many of these impediments and sets into motion a cascade of events that leads to wound healing.(49) Hyperbaric oxygenation is achieved when a patient breathes 100% oxygen at an elevated atmospheric pressure. Physiologically, this produces a directly proportional increase in the plasma volume fraction of transported oxygen that is readily available for cellular metabolism. Availability of substrate for oxygen dependent enzymatic reactions critical to repair and resistance to infection is even more important than normalization of metabolic rate. Furthermore, oxidants appear to be among the most important signals that control the healing process, and this may be another mechanism for the benefits of HBO2T in hypoxic wounds. Arterial PO2 elevations to 1500 mmHg or greater are achieved with 2 to 2.5 atm abs with soft tissue and muscle PO2 levels elevated correspondingly. Oxygen diffusion varies in a direct linear relationship to the increased partial pressure of oxygen present in the circulating plasma caused by hyperbaric oxygen therapy. 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).

In the hypoxic wound, hyperbaric oxygen therapy acutely corrects the pathophysiology related to oxygen deficiency and impaired wound healing. A key factor in hyperbaric oxygen 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. Proper oxygenation of the vascularized connective tissue compartment is crucial to the efficient initiation of the wound repair process and becomes an important rate-limiting factor for the cellular functions associated with several aspects of wound healing.

Neutrophils, fibroblasts, macrophages, and osteoclasts are all dependent upon an environment in which oxygen is not deficient in order to carry out their specific inflammatory or repair functions. Improved leukocyte function of bacterial killing(50,51,52) and antibiotic potentiation,(53,54) have been demonstrated. Suppression of synthesis of many bacterial toxins(55) occurs when tissue PO2 values are sufficiently elevated during treatment. Blunting of systemic inflammatory responses(56) and prevention of leukocyte activation and adhesion following ischemic reperfusion(57,58,59) are effects that may persist even after completion of hyperbaric oxygen treatment.

Stimulation of tissue growth supporting wound healing has also been demonstrated by a variety of mechanisms: 1) Vascular endothelial growth factor (VEGF) release is stimulated(60) and platelet derived growth factor (PDGF) receptor appearance(61,62,63) is also induced. 2) Boykin(64) has recently demonstrated persistent increases in nitric oxide in wound fluid in diabetic ulcers associated with increased granulation tissue formation and wound closure when patients are exposed to 20 hyperbaric oxygen treatments at 2.O ATA for 90 minutes 3) Thom(65) has shown that stem/progenitor cell release from bone marrow through a nitric oxide dependent mechanism occurs in patients receiving hyperbaric oxygen treatment for soft tissue and osteoradionecrosis. The population of CD34 cells in peripheral circulation doubled in response to single HBO treatment (2 ATA, 120 mins). Over course of 20 treatments circulating CD34 cells increased 8 fold, total WBC count unchanged

The net result of serial hyperbaric oxygen exposures is improved local host immune response, clearance of infection, enhanced tissue growth and angiogenesis leading to progressive improvement in local tissue oxygenation and healing of hypoxic wounds.