



**OXYGEN, AND ITS ROLE
IN WOUND HEALING: A
LITERATURE REVIEW**

PROF. PAUL DAVIS, JOHN WILKINS

BACKGROUND

The role of oxygen in wound healing has been contentious, but the evidence for its positive impact is mounting and the understanding of its mode of action is becoming clearer. The dispute is now resolving, for when all the evidence is set out, and the arguments made, it is surprising that there should ever have been any doubt at all about the central importance of oxygen to the process of healing. The debate should not be so much about whether oxygen is beneficial, as about the manner of its delivery to a wound (profile, duration, timing, accessory agents etc.).

There is much to be said about oxygen, for it is essential to most cellular processes; not just those responsible for wound healing and repair. Even at the most basic level, it is self evident that oxygen is needed to release the energy needed for the whole repair and recovery process, through oxidative respiration. Energy metabolism in the absence of oxygen is inefficient and leads to an unhelpful metabolic acidosis in the tissue and, paradoxically, oxidative stress.

While there is a strong body of evidence for the positive effects of oxygen on wound healing, there is also an increasing awareness that a lack of oxygen in wounds is detrimental to the healing process.

Many of the effects of oxygen on wound healing are predictable and may even seem obvious (e.g. all cells need oxygen to survive and to be active), but there are many particular effects that are special to wounds, such as the production of key cell signalling molecules from white blood cells. This wound-healing role is multifaceted, for oxygen is crucial to all of the main processes involved. In particular, the following are identified as especially important:

- Metabolic Support
- Matrix Repair
- Antisepsis & Infection control
- Signalling & Control

Although acute wounds, from e.g. surgery or trauma, differ from chronic wounds, both types have been found to benefit from extra oxygen, and both are adversely affected by a lack of oxygen.

The complex wound healing process demands large amounts of energy. If a wound becomes infected, then there is an even bigger energy demand, which in turn means that there is an even greater demand for oxygen.

EVIDENCE FROM THE LITERATURE

Oxygen is essential for all the body's cellular metabolic functions. It also plays a key, multifaceted role in wound healing, through:

Metabolic Support - sustaining cellular processes

Matrix Repair - supporting tissue regeneration (e.g. collagen synthesis, re epithelialisation and neovascularisation)

Antisepsis and Infection Control - inhibition of anaerobic bacteria plus assistance of the body's natural defences by supporting polymorphonuclear cell function

Signalling & Control - activating the body's repair systems by e.g., inducing VEGF production and enabling nitric oxide production

Oxygen is required to release the additional energy used in wound repair (*Trabold 2003 and Hopf 2001*). Continuous supply of oxygen to the tissue through microcirculation is vital for the healing process and for resistance to infection. It is a fundamental clinical observation that wounds do not heal in tissue that does not bleed, and they almost always heal in tissue that bleeds extensively (*Gottrup 2004*).

During wound healing the structural interconnectedness and functionality of the damaged tissue are re-established. This is only possible through the restoration of the microcirculation and thereby the delivery of nutrients to the regenerating tissue. A key component of the nutrition is oxygen, which is critically important for healing a wound by production of granulation tissue and for ensuring resistance against infection (*Gottrup 2004*).

Ischemia is also a global enemy of healing. Modern growth factor therapies cannot accelerate repair processes that are lacking oxygen (*Robson 1998*). Generally, a periwound oxygen pressure (PO₂) of <30mmHg implies that there may be insufficient oxygen for healing; below 10mmHg, oxygen is deficient, and growth factors have little chance of directing healing mechanisms for cells in these wounds (*Mustoe 1994*).

Ischemia/hypoxia can directly inhibit wound healing processes such as angiogenesis, collagen synthesis and epithelialization. It also impedes the ability of leukocytes to kill bacteria. As bacteria multiply, more leukocytes are recruited to the wound site, further increasing oxygen consumption (*Falanga 2001*).

METABOLIC SUPPORT

A healing wound undertakes a great deal of metabolic activity. In order for a wound to heal, it must have sufficient energy and nutrients to drive the healing process. Oxygen is essential in these metabolic processes:

Energy - Delivering/releasing the energy required for the cellular processes of healing.

Tissue regeneration - Supporting metabolic activity for cell proliferation and overall matrix synthesis, including synthesis of growth factors, enzymes, etc.

MATRIX REPAIR

- Formation of granulation tissue
- Epithelialisation
- Contraction
- Re-modelling

All these are involved in tissue regeneration and healing. The healing process requires the proliferation of cells of various types, as matrix is built-up, new blood vessels are formed and epithelium is replaced. Such cellular activity depends on oxygen availability to allow unhindered respiration.

The biosynthetic pathways needed to build all the bio-polymers (e.g. proteoglycans, structural proteins) are all dependent on oxygen to satisfy the underlying energy requirements. Various enzymes are required, including the matrix metallo-proteinases, and these, too, are costly in terms of energy, and hence oxygen, requirements.

Collagen synthesis is a fundamental part of these processes. The deposition of collagen is crucial for rebuilding of connective tissue and as part of the process of angiogenesis. Oxygen is a co-factor required in the hydroxylation of proline and lysine during the formation of pro-collagen. Mature collagen synthesis requires prolyl-hydroxylase and lysyl-hydroxylase enzymes, both of which are dependent on oxygen for their function (*Jonsson 2000*).

Neovascularization/Angiogenesis is essential for complete healing. This must be triggered by an appropriate signal. In high oxygen environments, macrophage leukocytes can trigger this signal, leading to an orchestrated, complex series of events involving tissue degradation followed by collagen formation and organisation, endothelial cell migration/colonisation and vessel formation.

ANTISEPSIS & INFECTION CONTROL

When a wound is created the body's natural defences are activated: neutrophils gather at the wound site shortly after trauma and release bactericidal reactive oxygen species (ROS) and hydrogen peroxide (H₂O₂) to kill bacteria and prevent infection. Macrophages arrive at the wound in response to environmental stimuli, phagocytose foreign particles, and release vascular endothelial growth factor (VEGF), an angiogenic factor crucial for wound healing (Cho 2001). Oxygen has a key role in these events:

Polymorphonuclear Cell Function Support – This is important for the first line defence against micro-organisms.

Potentiating the respiratory burst activity of leukocytes - One of the main microbial killing mechanisms of macrophages and neutrophil leukocytes is the "respiratory burst" – a natural activity by which these cells kill microbes. Individuals with defects in their respiratory burst process fall victim to bacterial infections. Leukocytes need oxygen to deliver the respiratory burst effect, and enhanced oxygen levels can boost its potency.

Enhancing phagocytic activity of leukocytes - These leukocytes also have other bacterial killing mechanisms, triggered when they swallow-up the microbes (phagocytosis). This is an oxygen-dependent process, as it involves substantial energy expenditure, so it does not work well in an oxygen-deprived environment. It works best in an oxygen-enriched situation.

Direct Antimicrobial Action - Oxygen is also lethal to anaerobic bacteria and is important in the effective functioning of some antibiotics.

SIGNALLING & CONTROL

The understanding of the role of molecular oxygen as a signalling and control agent has undergone a major evolution from its long-recognized importance as an essential factor for oxidative metabolism. It is now recognised as an important cell signal interacting with growth factors and other (e.g. redox) signals to regulate signal transduction pathways (Hunt 2004).

Over the past decade, research in the field of wound healing has provided new insight into the mechanism of action of hypoxia and hyperoxia as modifiers of the normal time-course of wound healing (Tandara 2004). The molecular signal released by macrophages to trigger angiogenesis is "Vascular Endothelial Growth Factor" (VEGF). High oxygen levels can cause macrophage leukocytes to release VEGF (paradoxically,

low levels – hypoxia - can do this too, via another factor called "Hypoxia Induced Factor", or HIF). The genes for a number of other important factors and enzymes are induced by high oxygen levels.

The production of nitric oxide (NO) is also recognised as a pivotal signalling and control event in wound healing. NO is made by the enzyme nitric oxide synthase (NOS), and in the early stages of wound healing the inducible form of the enzyme (iNOS) is up-regulated. However, it can only function if arginine AND oxygen are in plentiful supply, to enable production of NO at the appropriate rate (Boykin 2000).

Oxygen also has a direct role in signalling (stimulating) the process of epithelialisation, a key later-stage healing event in which new epithelial cells proliferate, organise themselves and differentiate into structured epithelium.

CURRENT OXYGEN THERAPIES

There are several current wound therapies which seek to augment the injured body's compromised oxygen levels, on a local or systemic basis:

HYPERBARIC OXYGEN (HBO) THERAPY

Though there remains some controversy over the use of systemic HBO therapy (perhaps because of its poorly discriminated use), there are many reports of its positive effects on wound healing (Abidia 2003, Gordillo 2003, Greif 2000, Hammarlund 1994, Sheikh 2000, Hopf 1997, Allen 1997, Knighton 1986).

However, the apparent advantages of HBO therapy are tempered by its inconvenience and expense, and by the potentially harmful effects of prolonged hyperoxia.

TOPICAL OXYGEN THERAPIES

Topical oxygen therapy in wound care has thus far received less attention than HBO therapy. The advantages of topical oxygen therapy include low cost, lack of systemic oxygen toxicity, and the ability to receive treatment at home, making the potential benefits of oxygen therapy available to a much larger population of patients. In a study with surgical patients, topical oxygen had no detrimental effects on wounds and showed beneficial indications in promoting wound healing (Kalliainen 2000).

The wound healing efficacy of an oxygen generating dressing (which contained hydrogen peroxide) on an infected wound animal system was investigated (Wright

2003), and accelerated healing was observed.

OXYZYME™

Oxyzyme™ is Archimed's new concept in wound care. Its basis is the oxygenation of the wound environment through the action of a new patented Oxyzyme™ dressing technology. This oxygenation of the wound environment provides an oxygen rich environment, much like hyperbaric and topical oxygen delivery devices. Through this oxygenation the wound and the healing process will derive the proven benefits of oxygen.

CONCLUSIONS

The importance of adequate levels of oxygen during the healing process is universally acknowledged. Oxygen is involved in many of the mechanisms of the natural healing process. It has a key role in metabolic support, matrix repair, antiseptis/infection control and signalling and control of cell responses. Wounds which receive adequate oxygen generally heal at an increased rate compared to those which don't have an adequate oxygenation (Knighton 1986, Hammarlund 1994, Hopf 1997, Allen 1997, Greif 2000, Kalliainen 2000, Sheikh 2000, Abidia 2003, Gordillo 2003, Wright 2003).

ANNOTATED BIBLIOGRAPHY

Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, et al., "The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial", *Eur. J. Vasc. Endovasc. Surg.*, 2003; 25(6):513-8.

"Ischaemic lower-extremity ulcers in the diabetic population are a source of major concern because of the associated high risk of limb-threatening complications. The aim of this study was to evaluate the role of hyperbaric oxygen in the management of these ulcers. Eighteen diabetic patients with ischaemic, non-healing lower-extremity ulcers were recruited in a double-blind study. Patients were randomly assigned either to receive 100% oxygen (treatment group) or air (control group), at 2.4 atmospheres of absolute pressure for 90 min daily (total of 30 treatments). **Healing with complete epithelialisation was achieved in five out of eight ulcers in the treatment group compared to one out of eight ulcers in the control group.** The median decrease of the wound areas in the treatment group was 100% and in the control group was 52% (p=0.027). Cost-effectiveness analysis has shown that despite the extra cost involved in using hyperbaric oxygen, there was a potential saving in the total cost of treatment for each patient during the study.

Hyperbaric oxygen enhanced the healing of ischaemic, non-healing diabetic leg ulcers and may be used as a valuable adjunct to conventional therapy when reconstructive surgery is not possible."

Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H et al., "Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms.", *Arch. Surg.*, 1997; 132(9):991-996.

"Respiratory burst activity, ie, O₂-production, is dependent on PO₂, temperature, pH, and glucose concentrations within the physiologic range. To determine whether environmental conditions characteristic of wounds may limit human neutrophil respiratory burst metabolism and to clarify the degree to which bactericidal oxidant production depends on local PO₂. Human blood and wound neutrophils were stimulated with phorbol myristate acetate. Oxygen consumption and superoxide production were measured

over a range of 30 to 300 mm Hg PO₂, 0 to 40 mmol/L glucose, pH 6.0 to 8.0, and 30 degrees C to 37 degrees C. The apparent Michaelis Menten constant for oxidant production with respect to PO₂ was calculated. Oxygen consumption and O₂-production were dependent on PO₂ throughout the range tested. Half-maximal oxidant production occurred in the range of 45 to 80 mm Hg PO₂ and maximal at PO₂ higher than 300 mm Hg. These data agree with the highest previous estimates. Oxidant generation was also dependent on pH, temperature, and glucose concentration, but to a lesser extent.

Leukocyte bacterial killing capacity as measured by oxygen consumption and superoxide production are substantially impaired at the low oxygen tensions often found in wounds. Changes in pH, temperature, and glucose concentration have lesser but nonetheless significant consequences. **The data provide a plausible mechanism for the vulnerability of some wounds to infection and for the previous finding that increasing oxygen tension at wound sites enhances bactericidal function. Thus, the data serve as a basis for future studies on prevention of wound infection."**

Boykin JV, "The nitric oxide connection: hyperbaric oxygen therapy, becaplermin, and diabetic ulcer management", *Adv. Skin Wound Care*, 2000;13(4 Pt 1):169-174.

"Clinical experience with adjunctive hyperbaric oxygen therapy in the treatment of diabetic ulcers has shown that wound hyperoxia increases wound granulation tissue formation and accelerates wound contraction and secondary closure. In addition to wound hyperoxia, increased wound nitric oxide production caused by hyperbaric oxygen therapy also appears to be important for successful diabetic wound repair. The results of a preliminary retrospective study suggest that nitric oxide production is reduced in the nonhealing diabetic wound, and that topical becaplermin therapy is effective only when wound nitric oxide production deficiency is corrected. In addition, the data suggest that below a critical level of endogenous nitric oxide production, diabetic ulcer repair may not be achieved. Under this hypothesis, diabetic patients with chronic, nonhealing ulcers that respond to becaplermin should have substantially increased endogenous nitric oxide production compared with those

ulcers that do not respond to becaplermin. The results of a preliminary clinical study support the use of combined therapy using topical becaplermin and hyperbaric oxygen therapy as a means of successfully treating the chronic diabetic ulcer patient with deficient nitric oxide production and local wound hypoxia."

Cho M, Hunt TK, Hussain MZ, "Hydrogen peroxide stimulates macrophage vascular endothelial growth factor release.", *Am. J. Physiol. Heart Circ. Physiol.*, 2001, 280: H2357-H2363.

"Neutrophils gather at the wound site shortly after trauma and release bactericidal reactive oxygen species (ROS) and H₂O₂ to kill bacteria and prevent infection. Macrophages arrive at the wound in response to environmental stimuli, phagocytose foreign particles, and release vascular endothelial growth factor (VEGF), an angiogenic factor crucial for wound healing. Because oxidants are released early in inflammation and have been found to regulate transcription factors, we investigated a possible role of H₂O₂ in VEGF stimulation. Human U937 macrophages exposed to H₂O₂ and allowed to recover in H₂O₂-free medium rapidly showed an increase in VEGF mRNA. The H₂O₂-mediated mRNA increase was dose dependent, blocked by catalase, and associated with elevated VEGF in conditioned media. The increase in VEGF was also found in primary rat peritoneal macrophages and the RAW 264.7 murine macrophage cell line. Transcriptional inhibition with actinomycin D revealed no significant difference in mRNA half-life. Transient transfections with a 1.6-kb VEGF promoter-luciferase construct (Shima DT, Kuroki M, Deutsch U, Ng YS, Adamis AP, and D'Amore PA, *J. Biol. Chem.* 271: 3877-3883, 1996) showed a ninefold stimulation of VEGF gene promoter activity. **We concluded that H₂O₂ increases macrophage VEGF through an oxidant induction of VEGF promoter. This oxidant stimulation can be mediated by activated neutrophils."**

Falanga V (ed.), "Caveats to consider with Growth Factor Therapy.", *Cutaneous Wound Healing*, 2001, publ. Martin Dunitz. Ch 25, p381.

"Ischemia is also a global enemy of healing and growth factor therapies cannot influence repair processes that require oxygen but do not have it (Robson 1998). Generally, a

periwound oxygen pressure (PO₂) <30mmHg implies that there may be insufficient oxygen for healing; below 10mmHg, oxygen is deficient, and growth factors have little chance of directing healing mechanisms for cells in these wounds (Mustoe 1994). Ischemia/hypoxia can directly inhibit wound healing processes such as angiogenesis, collagen synthesis and epithelialisation. It also inhibits the ability of leukocytes to kill bacteria. As bacteria multiply, more leukocytes are recruited to the wound site, further increasing oxygen consumption. If attempts are not made to increase the blood and oxygen supply to oxygen deficient wounds, growth factors may appear to fail to enhance healing when the real cause was an oxygen deficiency.”

Gordillo GM, Sen CK, “Revisiting the essential role of oxygen in wound healing.”, *Am. J. Surg.* 2003; 186(3): 259-263.

“Hypoxemia, caused by disrupted vasculature, is a key factor that limits wound healing. Correcting hypoxemia through the administration of supplemental oxygen (O₂) can have significant beneficial impact on wound healing in the perioperative and outpatient settings. Beyond its role as a nutrient and antibiotic, O₂ may support vital processes such as angiogenesis, cell motility, and extracellular matrix formation. Recent discoveries highlight a novel aspect, addressing the role of O₂ in wound healing via the production of reactive oxygen species (ROS). Almost all wound-related cells possess specialized enzymes that generate ROS (including free radicals and H₂O₂) from O₂. Defect in these enzymes is associated with impaired healing. Low wound pO₂ is expected to compromise the function of these enzymes. At low concentrations, ROS serve as cellular messengers to support wound healing. The use of systemic hyperbaric O₂ therapy presents potential advantages, as well as risks. There is evidence to suspect that the use of pressure and systemic pure O₂ may not be essential in wound care. Elimination of these factors by using sub-pure systemic O₂ under normobaric conditions may significantly minimize the risk of O₂ toxicity. Furthermore, opportunities to treat dermal wounds using topical O₂ therapy warrant further investigation. Given that many growth factors require ROS for their function, it is reasonable to assume that approaches to correct wound pO₂ will

serve as an effective adjunct in treating chronic wounds.”

Gotttrup F, “Oxygen, Wound Healing and the Development of Infection. Present Status.”, *World J. Surg.* 2004; 28(3): 312-5.

“It is a fundamental clinical observation that wounds do not heal in tissue that does not bleed, and they almost always heal in tissue that bleeds extensively. Continuous supply of oxygen to the tissue through microcirculation is vital for the healing process and for resistance to infection. Evaluation of tissue perfusion and oxygenation is important in all types of wound patients. Monitoring systems should measure the hemodynamic situation and the ability of the cardiovascular system to deliver an adequate volume of oxygen to meet the metabolic demands of the peripheral tissue. Oxygen therapy is important in relation to both healing and resistance to infections. External factors have been shown to significantly decrease the peripheral oxygen supply, and supplementary perioperative oxygen to reduce the surgical wound infection rate by one-half in patients undergoing colorectal resection. Hyperbaric oxygen therapy may be beneficial in situations where the nutritive flow and oxygen supply to the healing tissue are compromised by local injury, and particularly if anaerobic infection is present. However, the definitive proof for the effect and indications of this therapy in wound healing still has to be established. It can be concluded that adequate delivery of oxygen to the wound tissue is vital for optimal healing and resistance to infection. Assessment of perfusion and oxygenation is essential for the wound patient, as well as the treating personnel. The indication for hyperbaric oxygen treatment still needs to be defined. During wound healing the continuity and function of the damaged tissue are re-established. This is only possible through a restoration of the microcirculation and thereby the nutrition to the tissue. The main component of the nutrition is oxygen, which is critically important for healing a wound by production of granulation tissue and for ensuring resistance against infection. This has been shown experimentally, but recently a short period of supplementary oxygen has been shown to decrease wound complications in clinical practice as well.”

Greif R, Akça O, Horn E-P, Kurz A, Sessler DI, “Supplemental Perioperative Oxygen to Reduce the Incidence of Surgical-Wound Infection.”, *N. Engl. J. Med.*, 2000; 342:1613-1614.

“Destruction by oxidation, or oxidative killing, is the most important defense against surgical pathogens and depends on the partial pressure of oxygen in contaminated tissue. An easy method of improving oxygen tension in adequately perfused tissue is to increase the concentration of inspired oxygen. We therefore tested the hypothesis that the supplemental administration of oxygen during the perioperative period decreases the incidence of wound infection. We randomly assigned 500 patients undergoing colorectal resection to receive 30 percent or 80 percent inspired oxygen during the operation and for two hours afterward. Anesthetic treatment was standardized, and all patients received prophylactic antibiotic therapy. With use of a double-blind protocol, wounds were evaluated daily until the patient was discharged and then at a clinic visit two weeks after surgery. We considered wounds with culture-positive pus to be infected. The timing of suture removal and the date of discharge were determined by the surgeon, who did not know the patient’s treatment-group assignment. Arterial oxygen saturation was normal in both groups; however, the arterial and subcutaneous partial pressure of oxygen was significantly higher in the patients given 80 percent oxygen than in those given 30 percent oxygen. Among the 250 patients who received 80 percent oxygen, 13 (5.2 percent; 95 percent confidence interval, 2.4 to 8.0 percent) had surgical-wound infections, as compared with 28 of the 250 patients given 30 percent oxygen (11.2 percent; 95 percent confidence interval, 7.3 to 15.1 percent; P=0.01). The absolute difference between groups was 6.0 percent (95 percent confidence interval, 1.2 to 10.8 percent). The duration of hospitalization was similar in the two groups.

The perioperative administration of supplemental oxygen is a practical method of reducing the incidence of surgical-wound infections.”

Hammarlund C, Sundberg T, “Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study”, *Plas. Reconst. Surg.* 1994; 93:829-833.

“To evaluate the effect of hyperbaric oxygen therapy on chronic wound healing,

16 otherwise healthy patients who had nondiabetic, chronic leg ulcers with no large vessel disease were included in a double-blind study. Patients were grouped according to age and then randomly assigned to two groups breathing either air or oxygen at 2.5 atmospheres of absolute pressure for 90 minutes 5 days per week for a total of 30 treatments. The wound area was copied onto transparent film covering the wound and then measured using only one matching wound from each patient. The mean decrease of the wound areas at weeks 2, 4, and 6 in the oxygen group were 6 percent (SD±14), 22 percent (SD±13), and 35.7 percent (SD±17), respectively, and in the air group, 2.8 percent (SD±11), 3.7 percent (SD±11), and 2.7 percent (SD±11), respectively, giving a p value less than 0.05 at week 4, and a p value less than 0.001 at week 6 between the groups using the Mann-Whitney U test. These data indicate that hyperbaric oxygen therapy may be used as a valuable adjunct to conventional therapies when nondiabetic wounds do not heal.”

Harding KG, Morris HL, Patel GK, “Science, medicine and the future: healing chronic wounds.”, *B.M.J.*, 2002; 19;324(7330):160-163.

“Greater interest in wound healing is needed to ensure higher standards of basic care. Precise identification of the systemic, local, and molecular factors underlying the wound healing problem in individual patients should allow better tailored treatment. Allogeneic skin grafting and bioengineered skin equivalents are being used successfully in patients with venous leg ulcers and diabetic patients with foot ulcers.”

Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH, III, Jensen JA, et al., “Wound tissue oxygen tension predicts the risk of wound infection in surgical patients.”, *Arch. Surg.* 1997; 132(9):997-1004.

“OBJECTIVE: To test the hypothesis that subcutaneous wound oxygen tension (PsqO₂) has a predictive relation to the development of wound infection in surgical patients. DESIGN: A noninterventional, prospective study. SETTING: A university department of surgery. PATIENTS: One hundred thirty operative general surgical patients at notable risk of infection as predicted by an anticipated Study on the Effect of Nosocomial Infection Control (SENIC) score of 1 or greater.

OUTCOME MEASURES: PsqO₂ was measured perioperatively. Its relation to the subsequent incidence of surgical wound infection was then determined and compared with the SENIC score as a criterion standard. RESULTS: Although the SENIC score and PsqO₂ are inversely correlated, PsqO₂ is the stronger predictor of infection. Low PsqO₂ identified patients at risk and concentrated them in a cohort that was about half the size of that identified by the SENIC score.

CONCLUSIONS: Subcutaneous perfusion and oxygenation are important components of immunity to wound infections. The SENIC score identifies systemic physiological variables that are important to the development of wound infection. Nevertheless, PsqO₂ is the more powerful predictor of wound infection. Moreover, PsqO₂ can be manipulated by available clinical means, and thus may direct interventions to prevent infection.”

Hopf HW, Humphrey LM, Puzifferri N, West JM, Attinger CE, Hunt TK, “Adjuncts to preparing wounds for closure: hyperbaric oxygen, growth factors, skin substitutes, negative pressure wound therapy (vacuum-assisted closure)”, *Foot Ankle Clin* 2001; 6(4):661-682.

“Achieving closure in a chronic wound requires provision of adequate oxygen delivery to the tissue, adequate protein and other nutritional factors, a moist environment, an appropriate inflammatory milieu, debridement, and correction of contributing medical diagnoses. In some patients, these conditions are achieved easily, whereas in others, greater effort is required. Adjunctive treatments, including HBO₂, growth factors, skin substitutes, and negative-pressure wound therapy (e.g., VAC) can provide the proper conditions for healing in appropriately selected patients.”

Hunt TK, Hopf H, Hussain Z, “Physiology of wound healing.”, *Adv. Skin Wound Care*, 2000, 13(2):6-11.

“Wound healing is a complicated process that recruits at least 4 distinct cell types. Though the process is continuous, it is commonly referred to as occurring in “phases.” The main phases of wound healing include coagulation, which begins immediately after injury; inflammation, which initiates shortly thereafter; a migratory and proliferative

process, which begins within days and includes the major processes of healing; and a remodeling process, which may last for up to a year and is responsible for scar tissue formation and development of new skin. Wound healing is affected by several factors. These include local factors (growth factors, edema and ischemia, low oxygen tension, and infection), regional factors (arterial insufficiency, venous insufficiency, and neuropathy), systemic factors (inadequate perfusion and metabolic disease), and other miscellaneous factors, such as nutritional state, preexisting illnesses, exposure to radiation therapy, and smoking. In general, chronic wounds may be managed by preventing or medically treating infections through debridement and occlusive dressings. For wounds that are unresponsive to such interventions, the use of skin replacements is becoming a viable option. In this regard, a product such as Graftskin (APLIGRAF, Organogenesis Inc, Canton, MA, and Novartis Pharmaceuticals Corporation, East Hanover, NJ), a bilayered living skin construct with allogeneic dermis and epidermis, is a positive development.”

Hunt TK, Ellison EC, Sen CK, “World Progress in Surgery : Oxygen: At the Foundation of Wound Healing – Introduction.”, *World Journal of Surgery* 2004; 28(3):291-293.

“Wound Healing: Oxygen & Emerging Therapeutics” Columbus, Ohio, September 12-15, 2002. Sponsored by the National Institutes of Health (R13 AR 049171), International Union of Biochemistry & Molecular Biology and UNESCO-Global Network of Molecular & Cell Biology. Conference co-chairs: Chandan K. Sen, the Ohio State University Medical Center and Thomas K. Hunt, University of California-San Francisco. This congress was conceived for two reasons: to consolidate what is known about oxygen in the repair process and to stimulate discussion about new developments of control of healing by redox regulated signaling processes. A historical and evolutionary perspective on the role of oxygen in wound healing - from the classical physiology of oxygen in the wound to the refined concept of redox signaling - is presented.”

Jonsson K, Jensen JA, Goodson WH, III, Scheuenstuhl H, West J, Hopf HW et al., "Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients.", *Ann Surg* 1991; 214(5):605-613.

"Oxygen tension and collagen deposition were measured in standardized, subcutaneous wounds in 33 postoperative surgical patients. Pertinent clinical and wound parameters were analyzed by Pearson's correlation test and sequential linear regression analysis. Collagen deposition was directly and significantly proportional to wound oxygen tension and measures of perfusion. There were no significant correlations with hematocrit, estimated blood loss, length of operation, smoking, age, weight, sex, or urine output. This study in humans confirms animal experiments showing that collagen deposition and tensile strength in wounds are limited by perfusion and tissue oxygen tension. It appears unnecessary to maintain hemoglobin at normal levels to support repair, provided that peripheral perfusion can be maintained at a high level in compensation for anemia. These circumstances reflect the fact that although oxygen is essential to many aspects of healing, and must be delivered at adequate partial pressures, reparative tissue consumes relatively little of it."

Kalliainen LK, Gordillo GM, Schlanger R, Sen CK, "Topical oxygen as an adjunct to wound healing: a clinical case series.", *Pathophysiology* 2003; 9(2):81-87.

"BACKGROUND: Disrupted vasculature and high energy-demand to support processing and regeneration of wounded tissue are typical characteristics of a wound site. Oxygen delivery is a critical element for the healing of wounds. Clinical experience with adjunctive hyperbaric oxygen therapy in the treatment of chronic wounds have shown that wound hyperoxia increases wound granulation tissue formation and accelerates wound contraction and secondary closure. Nevertheless, the physiologic basis for this modality remains largely unknown. Also, systemic hyperbaric oxygen therapy is associated with risks related to oxygen toxicity. Topical oxygen therapy represents a less explored modality in wound care. The advantages of topical oxygen therapy include low cost, lack of systemic oxygen toxicity, and the ability to receive treatment at home, making the benefits of oxygen therapy available to a much larger population of patients. MATERIALS AND METHODS: Over 9 months, seven

surgeons treated 58 wounds in 32 patients with topical oxygen with follow-up ranging from 1 to 8 months. The data presented herein is a retrospective analysis of the results we have achieved using topical oxygen on complex wounds. RESULTS: Thirty-eight wounds in 15 patients healed while on topical oxygen. An additional five wounds in five patients had preoperative oxygen therapy; all wounds initially healed postoperatively. In two patients, wounds recurred post-healing. In ten wounds, topical oxygen had no effect; and two of those patients went on to require limb amputation. There were no complications attributable to topical oxygen. Three patients died during therapy and one died in the first postoperative month from underlying medical problems. Two patients were lost to follow-up. CONCLUSIONS: **In this case series, topical oxygen had no detrimental effects on wounds and showed beneficial indications in promoting wound healing.**"

Knighon DR, Halliday B, Hunt TK, "Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance.", *Arch. Surg.*, 1986; 121(2):191-195.

"Since prophylactic antibiotics and changes in tissue partial pressure of oxygen may affect bacterial clearance by different mechanisms, we tested the effects of hypoxia, hyperoxia, and normoxia with and without antibiotic administration on bacterial clearance. We found that improving tissue oxygenation by administration of normobaric oxygen decreased infectious necrosis as effectively as prophylactic antibiotic administration and that improved tissue oxygenation and antibiotic administration had an additive effect. **We believe that a fraction of inspired oxygen of 45% should be added to prophylactic antibiotics as standard perioperative and postoperative care.**"

Mustoe TA, Ahn ST, Tarpley JE et al., "Role of hypoxia in growth factor responses: differential effects of basic fibroblast growth factor in an ischemic wound model.", *Wound Rep. Regen.* 1994; 2:277-283.

"Both recombinant basic fibroblast growth factor and platelet-derived growth factor-BB homodimer are potent inducers of new tissue generation in models of normal dermal repair. However, their therapeutic targets include chronic wounds, which

are frequently characterized by local tissue hypoxia. To explore the potential of recombinant basic fibroblast growth factor and platelet-derived growth factor-BB homodimer to stimulate more clinically relevant repair, we created an ischemic dermal wound on the rabbit ear by ligating two of the arteries which feed the ear. Both recombinant basic fibroblast growth factor and platelet-derived growth factor-BB homodimer stimulated marked neovascularization of the wound ($p < 0.0001$), but only recombinant platelet-derived growth factor-BB homodimer accelerated and augmented granulation tissue formation ($p = 0.01$) and reepithelialization. This study is the first demonstration of a direct angiogenic effect of recombinant platelet-derived growth factor-BB homodimer in vivo. India ink perfusion coupled with endothelial cell-specific histochemistry showed that nearly all the neovessels in all wounds were functional, indicating rapid capillary morphogenesis. In the nonischemic (normal) rabbit ear, recombinant basic fibroblast growth factor and platelet-derived growth factor-BB homodimer accelerated healing comparably, as expected. Higher doses of recombinant basic fibroblast growth factor also failed to elicit stimulatory effects in ischemic wounds. **These results indicate that differential responsiveness to growth factors is related to local tissue hypoxia, angiogenesis alone is an insufficient stimulus for repair. These data also suggest new therapeutic approaches for the treatment of chronic wounds.**"

Muth CM and Mutschler W, "Einfluss von hyperbarem Sauerstoff (HBO) auf die Wundheilung (Value of hyperbaric oxygen in wound healing).", *Trauma und Berufskrankheit (Trauma & Occupational Disease)*, 2004; 6(1): 16-20.

"Hyperbaric oxygenation is achieved when a patient breathes 100 percent oxygen in an environment of elevated atmospheric pressure. Physiologically, this produces a directly proportional increase in the plasma volume fraction of transported oxygen which is readily available for cellular metabolism. **A number of beneficial biochemical, cellular and physiologic effects result which account for the use of hyperbaric oxygen as an adjunctive therapy in the treatment of clostridial myonecrosis, crush injuries, compromised flaps, osteoradionecrosis and chronic problem wounds. Indications, modes**

of treatment, contraindications, side effects, costs and experimental and clinical results are presented. Overall, these data demonstrate that hyperbaric oxygen is no longer "a therapy in search of diseases". However, more randomized controlled clinical trials are necessary to demonstrate its efficacy."

Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, et al., "Wound bed preparation: a systematic approach to wound management", *Wound Rep. Regen.*, March 2003; 11: 1-28.

"The healing process in acute wounds has been extensively studied and the knowledge derived from these studies has often been extrapolated to the care of chronic wounds, on the assumption that nonhealing chronic wounds were simply aberrations of the normal tissue repair process. However, this approach is less than satisfactory, as the chronic wound healing process differs in many important respects from that seen in acute wounds. In chronic wounds, the orderly sequence of events seen in acute wounds becomes disrupted or "stuck" at one 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. Experts in wound management consider that wound bed preparation is an important concept with significant potential as an educational tool in wound management.

This article was developed after a meeting of wound healing experts in June 2002 and is intended to provide an overview of the current status, role, and key elements of wound bed preparation. Readers will be able to examine the following issues;

- the current status of wound bed preparation;
- an analysis of the acute and chronic wound environments;
- how wound healing can take place in these environments;
- the role of wound bed preparation in the clinic;
- the clinical and cellular components of

the wound bed preparation concept;

- a detailed analysis of the components of wound bed preparation."

Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK, "Effect of hyperoxia on vascular endothelial growth factor levels in a wound model.", *Arch. Surg.* 2000; 135(11):1293-1297.

"HYPOTHESIS: **Hyperbaric oxygen (HBO) therapy increases vascular endothelial growth factor (VEGF) levels in wounds.** DESIGN: Wounds were monitored for oxygen delivery during HBO treatment, and wound fluids were analyzed for VEGF and lactate on days 2, 5, and 10 following wounding. SETTING: Experimental animal model. INTERVENTIONS: Rats were randomized to HBO therapy and control groups. The HBO therapy was administered for 90 minutes, twice daily with 100% oxygen at 2.1 atmospheres absolute. Treatment was administered for 7 days following wounding. MAIN OUTCOME MEASURES: Vascular endothelial growth factor, PO₂, and lactate levels in wound fluid were measured on days 2, 5, and 10. RESULTS: Wound oxygen rises with HBO from nearly 0 mm Hg to as high as 600 mm Hg. The peak level occurs at the end of the 90-minute treatment, and hyperoxia of lessening degree persists for approximately 1 hour. The VEGF levels significantly increase with HBO by approximately 40% 5 days following wounding and decrease to control levels 3 days after exposures are stopped. Wound lactate levels remain unchanged with HBO treatment (range, 2.0-10.5 mmol/L). CONCLUSIONS: **Increased VEGF production seems to explain in part the angiogenic action of HBO. This supports other data that hypoxia is not necessarily a requirement for wound VEGF production.**"

Sibbald RG, "An approach to leg and foot ulcers: a brief overview.", *Ostomy Wound Manage.*, 1998; 44(9):28-32, 34-5.

"Legs and feet are susceptible to ulcer formation. Three main types of lower extremity ulcers are venous, arterial, and neurotropic. Ulcer care should include treatment of the underlying cause, moist interactive healing, and quality of life (pain control). If the ulcer shows no signs of healing in 6 to 12 weeks, the wound should be biopsied, the diagnosis confirmed, and a plan of care instituted. In certain instances, biologicals may be used. A graphical representation of an approach to ulcer

care, in addition to common differential diagnoses of leg ulcers, is presented."

Tandara AA, Mustoe TA, "Oxygen in Wound Healing—More than a Nutrient.", *World J. Surg.* 2004;28(3):294-300.

"**This article provides an overview of the role of oxygen in wound healing.** The understanding of this role has undergone a major evolution from its long-recognized importance as an essential factor for oxidative metabolism, to its recognition as an important cell signal interacting with growth factors and other signals to regulate signal transduction pathways. Our laboratory has been engaged in the study of animal models of skin ischemia to explore in vivo the impact of hypoxia as well as the use of oxygen as a therapeutic agent either alone or in combination with other agents such as growth factors.

We have demonstrated a synergistic effect of systemic hyperbaric oxygen and growth factors that has been substantiated by Hunt's group. Within the past 10 years research in the field of wound healing has given new insight into the mechanism of action of hypoxia and hyperoxia as modifiers of the normal time-course of wound healing. **The article concludes with a discussion of why hypoxia and hyperoxia intercurrently play an important role in wound healing. Hypoxia-inducible factor 1 is crucial in that interplay.**"

Wright TE, Payne WG, Ko F, Ladizinsky D, Bowlby N, Neeley R, Mannari B, Robson MC, "The effects of an oxygen-generating dressing on tissue infection and wound healing.", *J. Appl. Res.* 2003; 3(4):363-370.

"**Oxygen is a necessary component of normal wound healing and is required for multiple cell functions, including the killing of bacteria by leukocytes. A new oxygen-generating dressing has been developed that provides intermittent periods of hyperoxia interspersed with periods in which the wound oxygen tension is allowed to autoregulate. The oxygen-generating dressing used in these experiments decreased the number of tissue bacteria in these infected wounds to less than 105 colony forming units (CFU) per gram of tissue. This, plus the stimulatory effect of oxygen on numerous healing processes, facilitated more rapid healing of the infected granulating wounds.**"

BIBLIOGRAPHY

Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT, "The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial.", *Eur. J. Vasc. Endovasc. Surg.*, 2003; 25(6):513-8.

Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H et al., "Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms.", *Arch. Surg.*, 1997; 132(9):991-996.

Boykin JV, "The nitric oxide connection: hyperbaric oxygen therapy, becaplermin, and diabetic ulcer management.", *Adv. Skin Wound Care*, 2000;13(4 Pt 1):169-174.

Cho M, Hunt TK, Hussain MZ, "Hydrogen peroxide stimulates macrophage vascular endothelial growth factor release.", *Am. J. Physiol. Heart Circ. Physiol.*, 2001, 280: H2357-H2363.

Falanga V (ed.), "Caveats to consider with growth factor therapy.", *Cutaneous Wound Healing*, 2001, publ Martin Dunitz. Ch 25, p381.

Gordillo GM, Sen CK., "Revisiting the essential role of oxygen in wound healing.", *Am. J. Surg.*, 2003; 186(3):259-263.

Gottrup F, "Oxygen in Wound Healing and Infection.", *World J. Surg.*, 2004, 28(3): 312-315.

Greif R, Akça O, Horn EP, Kurz A, Sessler DI, "Supplemental Perioperative Oxygen to Reduce the Incidence of Surgical-Wound Infection.", *N. Engl. J. Med.*, 2000; 342:1613-1614.

Hammarlund C, Sundberg T, "Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study.", *Plas. Reconst. Surg.*, 1994; 93:829-833.

Harding KG, Morris HL, Patel GK, "Science, medicine and the future: healing chronic wounds.", *B.M.J.*, 2002; 19;324(7330):160-3.

Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH, III, Jensen JA et al.,

"Wound tissue oxygen tension predicts the risk of wound infection in surgical patients.", *Arch. Surg.*, 1997; 132(9):997-1004.

Hopf HW, Humphrey LM, Puzifferri N, West JM, Attinger CE, Hunt TK, "Adjuncts to preparing wounds for closure: hyperbaric oxygen, growth factors, skin substitutes, negative pressure wound therapy (vacuum-assisted closure).",

Foot Ankle Clin., 2001; 6(4):661-682.

Hunt TK, Hopf H, Hussain Z, "Physiology of wound healing.", *Adv. Skin Wound Care*, 2000; 13(2):6-11.

Hunt TK, Ellison EC and Sen CK

World Progress in Surgery : Oxygen: At the Foundation of Wound Healing—Introduction
World Journal of Surgery 2004; 28(3):291-293

Jonsson K, Jensen JA, Goodson WH, III, Scheuenstuhl H, West J, Hopf HW et al., "Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients.", *Ann. Surg.*, 1991; 214(5):605-613.

Kalliainen LK, Gordillo GM, Schlanger R, Sen CK, "Topical oxygen as an adjunct to wound healing: a clinical case series.",

Pathophysiology, 2003; 9(2):81-87.

Knighton DR, Halliday B, Hunt TK, "Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance.", *Arch. Surg.*, 1986; 121(2):191-195.

Mustoe TA, Ahn ST, Tarpley JE et al., "Role of hypoxia in growth factor responses: differential effects of basic fibroblast growth factor in an ischemic wound model.", *Wound Rep. Regen.* 1994; 2:277-283.

Muth CM and Mutschler W, "Einfluss von hyperbarem Sauerstoff (HBO) auf die Wundheilung (Value of hyperbaric oxygen in wound healing).", *Trauma und Berufskrankheit (Trauma & Occupational Disease)*, 2004; 6(1): 16-20

Robson MC, Mustoe TA, Hunt TK, "The future of recombinant growth factors in wound healing.", *J. Surg.*, 1998; 176(Suppl 2A): 805-825.

Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, et al., "Wound bed preparation: a systematic approach to wound management."

Wound Rep. Regen., March 2003; 11: 1-28.

Sheikh AY, Gibson JJ, Rollins MD, Hopf HW, Hussain Z, Hunt TK, "Effect of hyperoxia on vascular endothelial growth factor levels in a wound model.", *Arch. Surg.* 2000; 135(11):1293-1297.

Sibbald RG, "An approach to leg and foot ulcers: a brief overview.", *Ostomy Wound Manage.*, 1998; 44(9):28-32, 34-5.

Tandara AA, Mustoe TA, "Oxygen in Wound Healing—More than a Nutrient.", *World J. Surg.*, 2004;28(3):294-300.

Wright TE, Payne WG, Ko F, Ladizinsky D, Bowlby N, Neeley R, Mannari B, Robson MC, "The effects of an oxygen-generating dressing on tissue infection and wound healing.", *J. Appl. Res.* 2003; 3(4):363-370.

**"OXYGEN IN WOUND
HEALING - MORE
THAN A NUTRIENT."**

Tandara 2004



A division of Insense Ltd.
Colworth Park, Sharnbrook,
Bedford, MK44 1LQ, UK

AM/OZ/03 V1.0 ©Insense Ltd. May 2007

www.archimed.co.uk



OXYZYME™
