# Non-Healing Wounds and Hyperbaric Oxygen: a Growing Awareness

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In this issue of *IMAJ* (*Israel Medical Association Journal*) Kulikovsky et al. [1] summarize the rationale, clinical indications and benefits of hyperbaric oxygen therapy for wounds that fail to heal (non-healing). Their comprehensive review emphasizes the high prevalence of this serious clinical condition in the industrial world. In Israel, the prevalence of non-healing wounds among the elderly is 3% to 5% and is steadily increasing as the population ages, with serious economic consequences for the country [2]. Diabetes mellitus is the most frequent underlying disease with non-healing wounds, accounting for most of the 1500 limb amputations a year in Israel. HBOT combined with standard wound care has the potential to reduce the amputation rate and morbidity in this group of patients [3].

As clearly summarized by Kulikovsky et al. [1], severe tissue hypoxia is the key feature in many patients with non-healing wounds. It impairs most processes required for wound healing, including angiogenesis, proliferation of fibroblasts, synthesis of collagen, as well as epithelial growth [4]. Many non-healing wounds are complicated by infection, and hypoxia impairs leukocyte function and microbial killing [5].

HBOT = hyperbaric oxygen therapy

Given the critical role of tissue hypoxia in the generation and propagation of non-healing wounds, it is appropriate to use hyperoxia to improve tissue oxygenation to reverse the cascade of pathologies and improve healing. To significantly increase oxygen availability to tissues requires an increase in ambient pressure that is easily provided by a hyperbaric chamber. The usual treatment protocol uses 100% oxygen at 0.2 MPa (2 atmosphere absolute). This yields a more than 20% increase in arterial blood oxygen content and thus significantly increases oxygen delivery. Yet, deliberations on the effect of hyperoxia on availability of molecular oxygen to tissues that are based on changes in arterial blood oxygen content undervalue the main effect of hyperoxia, which is related to changes in its partial pressure in the blood. Being a gas, the passage of oxygen into tissues occurs by diffusion. The driving force for diffusion of oxygen is determined by its partial pressure gradient between capillary blood and tissue cells and much less so by increased oxygen content [6]. Inhalation of 100% oxygen above atmospheric pressure can yield a tenfold increase in arterial blood oxygen tension (partial pressure) [7] and thus reaches $PO_2$ values above 1000 mmHg during hyperbaric exposure to oxygen at 0.2 MPa (2 ATA). The marked increase in oxygen tension gradient from the blood to metabolizing cells is the major mechanism by which hyperoxygenation of arterial blood can improve effective

ATA = atmosphere absolute

cellular oxygenation, even at low rates of tissue perfusion. In a typical ischemic diabetic foot the transcutaneous $PO_2$ is 20–30 mmHg (normal value 40–60 mmHg) and following HBOT can rise to therapeutic values above 200–400 mmHg and even more, depending on the local perfusion [8].

A pro-angiogenic response is another key element in wound repair. It is well known that tissue hypoxia is a strong stimulus for enhanced angiogenesis mostly by upregulating the production of pro-angiogenic factors [4]. In this regard, it should also be emphasized that HBOT has been repeatedly shown to greatly enhance the angiogenic response at the wound edge. This could result from enhanced production of pro-angiogenic factors in the hypoxic inflamed center of the wound and increased availability of oxygen at the periphery. Although strongly supported by clinical data from reports on HBOT for chronic wounds, the exact mechanisms of the demonstrated pro-angiogenic effects of hyperoxia have not been fully elucidated.

Non-healing wounds are frequently infected. HBOT exerts direct bacteriostatic and bactericidic effects mostly on anaerobic microorganisms [5]. Beyond a direct activity against microorganisms HBOT has been shown to reestablish defense mechanisms such as phagocytosis and microbial killing by polymorphonuclear leukocytes that are critically impaired by the hypoxic microenvironment in infected tissues [9]. Furthermore, the delivery and activity of a number of antibiotics are impaired in hypoxic environments and can be restored and even augmented by HBOT [9].

Hyperoxia exerts physiological effects that are not limited to pure reversal of ischemia but rather involve the immune response. This effect, which is often overlooked, involves the ability to harness and control an exaggerated inflammatory response, as frequently observed in non-healing wounds. A strong anti-inflammatory effect of hyperoxia has been demonstrated in diverse models of tissue ischemia and reperfusion [10] and various other models of inflammation [11-14]. Important aspects of the anti-inflammatory effects of hyperoxia include diminished intravascular rolling, adhesion and activation of leukocytes, and reduced macromolecular leakage into tissues. These effects may be due to increased intravascular oxygen, which may also explain the astonishing results in preventing restenosis after percutaneous coronary intervention [15]. Yet a direct, clinically significant, beneficial anti-inflammatory effect of hyperoxia in chronic non-healing wounds has not yet been conclusively demonstrated.

As summarized by Kulikovsky and team [1], appropriate clinical evidence (controlled studies and meta-analyses) support the role of HBOT in the treatment of hypoxic non-healing wounds. HBOT is therefore covered by leading medical insurance agencies around the world and is also included in the "medical service basket" in Israel. Yet, in some cases, patients face bureaucratic barriers that delay and sometimes even prevent HBOT from being used when it is clearly indicated. In some countries the reluctance to use HBOT is based on a perception that the treatment, which usually requires 30 sessions, is disproportionally expensive. This misconception is based on comparisons of the direct cost of HBOT to other interventions including amputation. However, when taking into account the total cost of the management of non-healing wounds, in particular those cases that result in amputation and include the cost of rehabilitation, limb salvage with HBOT is an extremely cost-effective mode of treatment [16,17, and Katz E and Bar-On T, unpublished data].

Based on the understanding of the role of hypoxia in non-healing wounds and the documented clinical effects of HBOT, it is standard practice to determine the transcutaneous oxygen tension near the non-healing wound before initiation of HBOT [18]. HBOT is indicated when low tissue oxygen tension near a non-healing wound (< 30–40 mmHg) increases above a threshold of 200 mmHg within 10 minutes of breathing 100% oxygen at 0.2–0.24 MPa (2–2.4 ATA) [18]. This preliminary procedure excludes patients with occluded peripheral blood vessels who are unlikely to benefit significantly from HBOT and, in addition, provides the orthopedic or vascular surgeon with essential information. When this preliminary procedure is used for selection of patients it is correlated with a markedly improved rate of healing when HBOT is combined with standard multidisciplinary wound care. Since it is well known that earlier correction of ischemia leads to a better clinical outcome, early diagnosis of tissue hypoxia is highly beneficial.

Kulikovsky et al. [1] discuss the possible side effects of HBOT. Toxic effects are encountered when oxygen is used at very high pressures in diving and during treatment of diving accidents. In clinical practice, side effects are rare because lower oxygen pressures are used and the treatment sessions are time limited. In addition, proper patient care and careful adherence to operating instructions decrease the incidence and the severity of pressure-related barotraumas to a negligible minimum.

All in all, HBOT is a powerful and safe modality in the management of hypoxic wounds and an important part of the coordinated medical-surgical approach to such patients, as emphasized by Kulikovsky and co-workers [1]. When combined with careful attention to underlying diseases and meticulous wound care including debridement, grafting, and control of infection, HBOT improves the outcome and diminishes the amputation rate.

The biochemist Nick Lane wrote in the introduction to his scholarly book, *Oxygen the Molecule that Made the World* [19], "…Oxygen is hailed as the Elixir of life; it seems to attract nonsense and misinformation like magnet." Misinformation and lack of knowledge, as well as lack of awareness, are the main reasons why hyperoxygenation is not as commonly used in medical practice as it should. To overcome these obstacles, medical students should be exposed to HBOT as part of their standard training. The review paper by Kolikovsky et al. [1] contributes to our knowledge on the importance of hyperbaric oxygen therapy to assist wound healing.

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