EDITORIAL

Topical oxygen is not hyperbaric oxygen (HBO_2).

C. A. PIANTADOSI

For some 40 years clinical investigators have consistently shown a correlation between oxygen partial pressure (PO_2) in tissue, avoidance of infection, and wound healing (1, 2). This dependence of wound healing on tissue PO_2 has led to controlled trials and gradual acceptance of HBO_2 therapy (HBO_2T) as an adjunct to healing of selected problem wounds (3). Similarly, there has also been some interest in the use of topical of O_2 therapy (TOT) in wound healing. The advantages of TOT include low cost, lack of systemic O_2 toxicity, and the possibility of home treatment (4).

Interest in TOT is being rekindled by current scientific knowledge that cell signaling by reactive oxygen species (ROS), such as hydrogen peroxide, is involved in pathways that regulate cell growth, differentiation, and proliferation (5). Normal mammalian cells not only consume O_2 for metabolic purposes, but they generate ROS. Low level ROS production serves essential intra- and intercellular communication functions. Thus, basal ROS production offers certain advantages, such as facilitating adaptation to changes in milieu, and even promotes cell survival during times of stress.

The effects of cellular ROS production vary significantly as a function of tissue PO_2. For example, O_2 (and ROS) normally destabilize hypoxia-inducible factor (HIF-1), a protein complex that promotes transcription of hypoxia-sensitive genes such as erythropoietin (6). When PO_2 and ROS production decrease in hypoxia, HIF-1 is activated because the O_2-sensitive α subunit is no longer rapidly degraded, allowing the active $\alpha\beta$ complex to form. In contrast, when tissue PO_2 is elevated ROS production increases. If ROS production exceeds anti-oxidant capacity, troublesome biological oxidations are produced including lipid peroxidation, protein thiol depletion, and nucleic acid oxidation. This principle has long been the cornerstone of the free radical theory of O_2 toxicity (7).

It is widely appreciated that ROS production in hypoxic wounds may be too low and that raising PO_2 may improve not only oxidative metabolism, but white blood cell function. It has also become increasingly apparent that O_2 enhances the ROS-dependent signaling mechanisms involved in cell survival and proliferation. Although the processes of cell metabolism and cell communication are closely linked, it is clear there is not a one-to-one correspondence between

them. In other words, modest changes in PO_2 in hypoxic tissues may have important benefits that are independent of aerobic metabolism.

At the tissue level, wound healing is a temporally and spatially organized process that requires coordination of coagulation, inflammation, angiogenesis, collagen deposition, and prevention of undesirable exogenous effects such as infection. All wounds are inevitably colonized by microbes, predominately endogenous bacteria, which in the wound environment are potential pathogens. Risks of wound infection and poor healing increase when local conditions favor bacterial growth instead of host defense (2). Consequently, a primary goal of wound management is to restore the host-microbial symbiosis for which adequate tissue perfusion and wound oxygenation are vital.

The point of this discussion is that changes in wound PO_2 have important physiological implications that are independent of aerobic metabolism. Therapies involving minor or locally limited changes in PO_2 may have beneficial effects on wound healing. Therefore, topical application of O_2 to problem wounds, although likely to produce only minimal changes in tissue O_2 content relative to HBO_2, has a theoretical rationale. However, unlike HBO_2, a benefit of TOT on problem wound healing has never been demonstrated scientifically. TOT is not HBO_2T.

HBO_2T is defined by having a patient breathe100% O_2 inside a treatment chamber at a pressure greater than sea level (1 bar, 1 ATA, 760mmHg) (3), a definition that dates to the 1950s (see 8). Today's conventional wisdom about HBO_2T suggests that chamber treatment pressures should be in the range of 1.4 to 3.2 bar (ATA). At 2 ATA, if pulmonary gas exchange and O_2 delivery mechanisms are normal, HBO_2 transports sufficient dissolved O_2 to meet most if not all of the metabolic O_2 requirements of resting tissues. Indeed, HBO_2 is also a potent constrictor of both arterial and venous vessels, insufficient to stop enhanced O_2 delivery but sufficient for independent benefit, such as the prevention or reduction of edema (9). In controlled animal experiments using HBO_2 (2.1 ATA for 90 minutes), wound PO_2 rises from nearly 0 to as high as 600 mm Hg (10). The peak value occurs toward the end of the treatment, and elevated tissue PO_2 of a lesser degree persists for approximately an hour. HBO_2 treatments once or twice a day benefit healing in many hypoxic wounds.

TOT on the other hand is defined by external application of O_2 to a wound in order to increase the PO_2 in the wound space (11). This is usually accomplished by shrouding the wound site, usually a limb, with a bag or other covering into which O_2 is pumped. The bag may be filled with gas at O_2 partial pressures slightly above 760mmHg, the value of 100% O_2 at sea level. If the pressure in the bag exceeds arterial systolic pressure, limb ischemia will occur. It is also ill-advised to allow the pressure to exceed arterial diastolic pressure (e.g. 70 mmHg) because this creates vascular congestion (12). Given these limitations, it is nonetheless possible for PO_2 in the wound space to exceed 800 mmHg during TOT. However, several important physiological questions have not been adequately addressed for TOT.

First, does TOT appreciably increase PO_2 in wounds as does HBO_2? There are reasons to think based on estimates of the diffusion constant for O_2 in tissue that TOT will increase tissue PO_2 to a depth of only 50 to100 microns (9). Furthermore, TOT produces a wound PO_2 gradient, which may be important in angiogenesis, that is opposite that of HBO_2. Second, if TOT does increase tissue PO_2 and the effect (no matter how small) can be maintained for a prolonged period of time, does it translate to a positive effect on wound healing? Third, are the effects of TOT independent of increases in wound temperature? Finally, if TOT does not increase tissue PO_2 but does improve wound healing, what types of mechanisms, e.g. host-microbial symbiosis

at the wound surface, should be sought to explain the effect? Answers to these questions will require a great deal of basic and clinical research.

To date, there are scant animal and human data and no published randomized controlled clinical trials of the effects of TOT on wound healing. Indeed, preliminary observations of the effects of TOT suggest that if it has a salutary effect, it is primarily on small wounds which already have a high closure rate with routine therapy. In addition, TOT, unlike HBO_2T, precludes the use of vacuum-assisted closure, which is playing an increasingly important role in healing of large wounds. Thus, scientific and practical considerations caution against lumping TOT with HBO_2T as equivalent approaches. Although some effects may eventually be shown to overlap, the two modalities clearly invoke distinct physiological responses in the wound. TOT today faces the same rigorous challenge of proof of efficacy that HBO_2T did a generation ago.

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