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## Hyperbaric oxygen – its mechanisms and efficacy

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### Abstract

**Background**—This paper outlines therapeutic mechanisms of hyperbaric oxygen therapy (HBO<sub>2</sub>) and reviews data on its efficacy for clinical problems seen by plastic and reconstructive surgeons.

**Methods**—The information in this review was obtained from the peer-reviewed medical literature.

**Results**—Principal mechanisms of HBO<sub>2</sub> are based on intracellular generation of reactive species of oxygen and nitrogen. Reactive species are recognized to play a central role in cell signal transduction cascades and the discussion will focus on these pathways. Systematic reviews and randomized clinical trials support clinical use of HBO<sub>2</sub> for refractory diabetic wound healing and radiation injuries; treatment of compromised flaps and grafts and ischemia-reperfusion disorders is supported by animal studies and a small number of clinical trials, but further studies are warranted.

**Conclusions**—Clinical and mechanistic data support use of hyperbaric oxygen for a variety of disorders. Further work is needed to clarify clinical utility for some disorders and to hone patient selection criteria to improve cost-efficacy.

### Introduction

Hyperbaric oxygen (HBO<sub>2</sub>) therapy is a treatment modality in which a person breathes 100% O<sub>2</sub> while exposed to increased atmospheric pressure. HBO<sub>2</sub> treatment is carried out in either a mono- (single person) or multi-place (typically 2 to 14 patients) chamber. Pressures applied while in the chamber are usually 2 to 3 atmospheres absolute (ATA), the sum of the atmospheric pressure (1 ATA) plus additional hydrostatic pressure equivalent to one or two atmospheres (1 atmosphere = a pressure of 14.7 pounds per square inch or 101 kPa). Treatments are usually about 1.5 to 2 hours long, depending on the indication and may be performed one to three times daily. Monoplace chambers are usually compressed with pure O<sub>2</sub>. Multiplace chambers are pressurized with air and patients breathe pure O<sub>2</sub> through a tight-fitting face mask, a hood, or an endotracheal tube. During treatment, the arterial O<sub>2</sub> tension often exceeds 2000 mmHg and levels of 200 to 400 mmHg occur in tissues. (2)

The initial effect of pressurizing the human body is intuitively obvious - elevating hydrostatic pressure increases partial pressure of gases and causes a reduction in the volume

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of gas-filled spaces according to Boyle's law. Gas volume reduction has direct relevance to treating pathological conditions in which gas bubbles are present in the body, such as arterial gas embolism and decompression sickness. The majority of patients who undergo HBO<sub>2</sub> therapy are not treated for bubble-induced injuries hence therapeutic mechanisms are related to an elevated O<sub>2</sub> partial pressure. A summary of these mechanisms is shown in Figure 1.

It is well accepted that breathing greater than 1 ATA O<sub>2</sub> will increase production of reactive oxygen species (ROS). (2) This is critically important as it is the molecular basis for a number of therapeutic mechanisms. ROS and also reactive nitrogen species (RNS) serve as signaling molecules in transduction cascades, or pathways, for a variety of growth factors, cytokines and hormones. (3–5) ROS is a collective term for O<sub>2</sub>-derived free radicals as well as O<sub>2</sub>-derived non-radical species such as hydrogen peroxide and hypochlorous acid. ROS are generated as part of normal metabolism by mitochondria, endoplasmic reticulum, peroxisomes, various oxidase enzymes and phospholipid metabolism. ROS act in conjunction with several redox systems involving glutathione, thioredoxin and pyridine nucleotides, and play central roles in coordinating cell signaling and also anti-oxidant, protective pathways. (3,4,6) (5) This point is central to the ensuing discussion – oxidative stress is not synonymous with oxygen toxicity.

RNS include nitric oxide ( $\cdot$ NO) and agents generated by reactions between  $\cdot$ NO, or its oxidation products, and ROS. Peroxide-dependent enzymes such as myeloperoxidase can catalyze reactions between nitrite, a major oxidation product of  $\cdot$ NO, and hydrogen peroxide or hypochlorous acid to generate oxidants such as nitryl chloride and nitrogen dioxide that are capable of nitration and S-nitrosylation reactions. (11–13) There are three nitric oxide synthase. The effect of hyperoxia on catalytic activity is reflected by values for the apparent Michaelis-Menten constant for O<sub>2</sub> and it differs among the three NOS isoforms. In part this is because enzyme activity is constrained by ferric-ferrous conversion at the active site. As a general statement, however, hyperoxia augments RNS production. (14–18)

Discussion in this review will focus on those HBO<sub>2</sub> indications most pertinent to Plastic and Reconstructive Surgery. General discussions of HBO<sub>2</sub> indications can be found in recent texts and for the general plastic surgeon, it is important to mention that consultation and advice on HBO<sub>2</sub> may be sought through the Undersea and Hyperbaric Medical Society and more locally with board-certified physicians. (19–21) That is, Undersea and Hyperbaric Medicine sub-specialty certification is obtainable through the American Board of Medical Specialists.

## Wound healing

HBO<sub>2</sub> is used to treat refractory diabetic lower extremity wounds and delayed radiation injuries. Clearly, the pathophysiology of these disorders differs but they share several elements include depletion of epithelial and stromal cells, chronic inflammation, fibrosis, an imbalance or abnormalities in extracellular matrix components and remodeling processes, and impaired keratinocyte functions. (22–27) Diabetic wound healing is also impaired by decreased growth factor production, while in post-radiation tissues there appears to be an imbalance between factors mediating fibrosis versus normal tissue healing. (22,23,27) The reader is referred to several recent reviews for general discussions on pathophysiology. (28–30)

## Clinical efficacy of HBO<sub>2</sub>

Wound healing HBO<sub>2</sub> protocols involve daily treatments of 1.5 to 2 hours for 20 to 40 days. The effectiveness of HBO<sub>2</sub> as an adjuvant therapy for diabetic lower extremity ulcerations can be examined from the perspective of hastened healing and also reduced risk of major

amputations. Clearly related, these two vantage points are not synonymous as current diabetic wound care often includes a ray or partial foot amputation as an acceptable approach to obtain wound closure and prompt rehabilitation.

This is the era of meta-analysis and despite drawbacks with these evaluations they are used regularly as a final judgment on efficacy of an intervention. According to the most recent evaluation, employing HBO<sub>2</sub> as a component to refractory diabetic wound management decreases risk of a major amputation with an odds ratio of 0.236 [95% confidence interval (CI) 0.133 – 0.418]. Adjunctive use of HBO<sub>2</sub> as a component to diabetic wound care improves healing with an odds ratio of 11.64 [95% CI 3.457 – 39.196] (31) This analysis was based on clinical trials conducted through 2007.(32–40) The results continue to demonstrate that HBO<sub>2</sub> markedly improves outcome. Another meta-analysis concluded that only four patients needed to be treated with HBO<sub>2</sub> to prevent one amputation.(41) Since this publication, two additional groups have reported benefits to use of HBO<sub>2</sub>; one was a double-blinded randomized trial. (42,43) The results continue to demonstrate that HBO<sub>2</sub> improves outcome. The double blinded trial was a single-center study that enrolled individuals with diabetes foot ulcers. Individuals were randomized to receive either HBO<sub>2</sub> (100% oxygen, 2.5 ATA for 85 minutes five days per week for 8-weeks) or control (room air, 2.5 ATA for 85 minutes five days per week for 8-weeks) and good wound care. The outcome was a healed wound by 12 months after the commencement of therapy. A total of 99 individuals were evaluated, 38 received HBO and 37 received control therapy. By one year of follow up 52% of those receiving HBO<sub>2</sub> healed and 29% of those receiving control (p=0.03).

The benefit of HBO<sub>2</sub> for radiation injury also has been shown in randomized trials and its utilization supported by independent evidence-based reviews.(44–46) It is important to state that for both diabetic wounds and radiation injuries, HBO<sub>2</sub> is used in conjunction with standard wound care management techniques. That was the format followed in clinical trials and it is fully understandable based on mechanisms of action. If used only in a post-operative period, or in the absence of appropriate surgical care, one should expect HBO<sub>2</sub> to be ineffective treatment. (47,48)

### Mechanisms of action

Animal trials have documented wound healing benefits of HBO<sub>2</sub>.(49–52) The basis for its efficacy continues to be investigated and appears to be a combination of systemic events as well as local alterations within the wound margin (see Fig. 1). Neovascularization occurs by two processes. Regional angiogenic stimuli influence the efficiency of new blood vessel growth by local endothelial cells (termed angiogenesis) and they stimulate the recruitment and differentiation of circulating stem/progenitor cells (SPCs) to form vessels *de novo* in a process termed vasculogenesis. (53–55) HBO<sub>2</sub> has effects on both these processes.

Bone marrow eNOS activity is required for SPCs mobilization and this is compromised by diabetes (56–60) Radiation, chemotherapy and several other factors also diminish SPCs mobilization, although mechanisms for these effects are unclear. (61–64) By stimulating ·NO synthesis in bone marrow, HBO<sub>2</sub> mobilizes SPCs in normal humans, patients previously exposed to radiation and in diabetics.(65–67) Importantly, in contrast to SPCs mobilization stimulated by infusion of growth factors; HBO<sub>2</sub> does not concomitantly elevate the circulating leukocyte count which may be thrombogenic. (68) In animal models, SPCs mobilized by HBO<sub>2</sub> home to wounds and accelerate healing. (50,52,69)

Separate from its effect on SPCs mobilization, HBO<sub>2</sub>-mediated oxidative stress at sites of neovascularization will stimulate SPCs growth factor production. (70,71) This is due at least in part to augmented synthesis and stabilization of hypoxia inducible factors (HIF). (72–74) These transcription factors are heterodimers of HIF- $\alpha$  and a constitutively expressed HIF- $\beta$ .

It is well recognized that expression and activation of HIF- $\alpha$  subunits are tightly regulated and their degradation by the ubiquitin-proteasome pathway typically occurs when cells are replete with O<sub>2</sub>. (75,76) However, whether hypoxic or normoxic conditions prevail, free radicals are required for HIF expression. (76–78) HBO<sub>2</sub> elevates HIF-1 and -2 levels in vasculogenic SPCs because of increases in ROS. One consequence of ROS-mediated stress is augmented production of the antioxidant thioredoxin and one of its regulatory enzymes, thioredoxin reductase. (74) Thioredoxin can act as a transcription factor and in SPCs appears to be the proximal species responsible for promoting the expression and activity of HIFs. (79–81) HIF-1 and -2 then stimulate transcription of many genes involved with neovascularization. A physiological oxidative stress that triggers the same pathway is lactate metabolism. (71)

Pluripotent mesenchymal stem cells were shown *in vitro* to be stimulated by HBO<sub>2</sub> to synthesize placental growth factor. This too is an ROS-dependent phenomenon and will significantly increase cell migratory and tube formation functions. (82) Microvascular endothelial cells exposed to HBO<sub>2</sub> in *ex vivo* studies up-regulate a variety of protein damage-control pathways that lead to enhanced oxidative stress resistance, cell proliferation and tube formation. (83) HBO<sub>2</sub> does not alter circulating levels of insulin, insulin-like growth factors, or pro-inflammatory cytokines [*e.g.* tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6 and IL-8] in normal healthy humans. (84,85) Vascular endothelial growth factor (VEGF) and angiopoietin, as well as stromal derived factor (SDF-1) influence SPCs homing to wounds and SPCs differentiation to endothelial cells. (86) (87) Synthesis of VEGF has been shown to be increased in wounds by HBO<sub>2</sub>, and it is the most specific growth factor for neovascularization. (72) HBO<sub>2</sub> also stimulates synthesis of basic fibroblast growth factor (bFGF) and transforming growth factor  $\beta$ 1 by human dermal fibroblasts, (88) angiopoietin-2 by human umbilical vein endothelial cells, (89) bFGF and hepatocyte growth factor in ischemic limbs, (90) and it up-regulates platelet derived growth factor (PDGF) receptor in wounds. (91) Extracellular matrix formation is closely linked to neovascularization and it is another O<sub>2</sub>-dependent process. (92) Enhanced collagen synthesis and cross-linking by HBO<sub>2</sub> have been described, but whether changes are linked to the O<sub>2</sub>-dependence of fibroblast hydroxylases, alteration in balance of wound growth factors, metalloproteinases and/or inhibitors of metalloproteinases, is as yet unclear. (92,93)

Before leaving the subject of wound healing, mention should be made of conflicting data and where further work is needed. The influence HBO<sub>2</sub> has on HIF isoform expression appears to vary with different tissues and possibly with chronology [*e.g.* looking early or late after wounding or an ischemic insult]. One recent model showing accelerated wound healing by HBO<sub>2</sub> reported lower HIF-1 levels at wound margins, along with reduced inflammation and fewer apoptotic cells. (51) In contrast, higher levels of HIF-1 have been linked to elevated VEGF in wounds in response to hyperoxia. (72,94) With regard to diabetes, there is a complex interplay present between ROS and RNS. (22,59,60) Impairments in eNOS function are related to hyperglycemia, insulin resistance, impaired enzyme synthesis, disordered caveolin associations and enhanced protein kinase C activity. (59,60,95) Production of O<sub>2</sub> $\cdot$  is augmented in diabetes and this will reduce bioavailability of  $\cdot$ NO because the two radicals react rapidly to generate alternative RNS. (96,97) Disordered balance between O<sub>2</sub> $\cdot$  and  $\cdot$ NO is reflected by elevated levels of nitrotyrosine in plasma of type II diabetics. (98) The reason for outlining these issues with regard to HBO<sub>2</sub> is because there is a need for more investigations. Data from diabetic animals and humans indicate that HBO<sub>2</sub> can overcome some aspects of eNOS inhibition but it is doubtful that all issues have been resolved. (66,67,99,100)

To summarize, HBO<sub>2</sub> can stimulate healing in refractory wounds and irradiated tissues. Therapy for refractory diabetic wounds is likely to reduce the risk of lower extremity

amputation by 2 to 3 times, with an absolute rate of major amputation reductions of about 20% (e.g., 11% versus 32%) and a number needed to treat of about 4. With respect to cost-effectiveness, a study from Canada indicated that over a 12-year period, the use of HBO<sub>2</sub> should save about \$9,000 in overall costs to the care of a patient with diabetes.(101,102) It is likely that these estimates can be honed further with improved patient selection criteria and the benefits in radiation injury are not well elucidated. The common mechanistic theme for both indications is oxidative stress responses improve neovascularization events. Cells within the wound exhibit increased collagen synthesis, growth factors production, improved cell migration and tube-formation functions. A separate free radical-based mechanism for augmentation of neovascularization by HBO<sub>2</sub> is through SPCs. Hyperoxia stimulates bone marrow SPCs mobilization and also improves their functions once they home to peripheral sites.

## Compromised Flaps and Grafts

HBO<sub>2</sub> is used on occasion to treat compromised flaps and grafts, a practice supported by Guidelines from the Undersea and Hyperbaric Medical Society. (21) This discussion was placed between wound healing and reperfusion injuries because, depending on the situation, graft/flap treatment may be more or less related to supporting tissues through either of these two main mechanistic categories. For example, in clinical practice a wound may not be ready for coverage by a graft and neovascularization/granulation tissue formation can be hastened according to mechanisms outlined above. This was the focus for a recent clinical series. (103) Alternatively, a major flap may suffer an ischemic insult in the process of its creation and thus mechanisms described in the next section are pertinent.

A comprehensive review of HBO<sub>2</sub> use for flaps and grafts was recently published. (104) There is no need to recapitulate the information except to say that there is one prospective, blinded clinical trial. Administration of HBO<sub>2</sub> prior to and for three days following skin grafting led to a significant 29% improvement in graft survival. (105) A problem with this trial, however, is that the success in the control arm of the study was markedly less than one would expect in current practice. As was emphasized in the review, support for use of HBO<sub>2</sub> in flap/graft compromise comes from a very large number of animal studies. (104,106) Comparative clinical trials support its use but more work is needed. (107,108)

## Reperfusion injuries and HBO<sub>2</sub>

Clinical studies have documented significant survival enhancement with HBO<sub>2</sub> for extremity re-implantation and free tissue transfer, and following crush injury. (109,110) As is the case with flaps and grafts, however, the amount of controlled clinical data is small and insufficient to perform an evidence-based assessment of HBO<sub>2</sub> efficacy. None-the-less, the breadth of clinical experience across a variety of disorders should spur closer assessment of its use. Clinical trials have shown that HBO<sub>2</sub> can reduce coronary artery re-stenosis after balloon angioplasty/stenting, (111,112) decrease muscle loss after thrombolytic treatment for myocardial infarction, (113–115) improve hepatic survival after transplantation and lead to more rapid return of donor liver function (116,117) and reduced the incidence of encephalopathy seen after cardiopulmonary bypass and following carbon monoxide poisoning. (118,119) In contrast to protocols for wound healing, HBO<sub>2</sub> treatments for reperfusion injuries are done for just a few days rather than weeks; they are performed at higher O<sub>2</sub> partial pressures (~2.5 to 3.0 ATA) and may occur multiple times in the same day.

An early event associated with post-ischemic tissue reperfusion is adherence of circulating neutrophils to vascular endothelium by  $\beta_2$  integrins. When animals or humans are exposed to HBO<sub>2</sub> at 2.8 to 3.0 ATA for at least 45 minutes, the ability of circulating neutrophils to adhere to target tissues is temporarily inhibited. (120–123) In animal models, HBO<sub>2</sub>-

mediated inhibition of neutrophil  $\beta_2$  integrin adhesion has been shown to ameliorate reperfusion injuries of brain, heart, lung, liver, skeletal muscle and intestine, as well as smoke-induced lung injury and encephalopathy due to carbon monoxide poisoning. (123–131) It also appears that benefits of HBO<sub>2</sub> in decompression sickness are related to the temporary inhibition of neutrophil  $\beta_2$  integrins, in addition to the Boyle's Law-mediated reduction in bubble volume as discussed in the introduction. (132)

Exposure to HBO<sub>2</sub> inhibits neutrophil  $\beta_2$  integrin function because hyperoxia increases synthesis of reactive species derived from iNOS and myeloperoxidase, leading to excessive S-nitrosylation of cytoskeletal  $\beta$  actin. (133). This modification increases the concentration of short, non-cross-linked filamentous (F)-actin which alters F-actin distribution within the cell. HBO<sub>2</sub> does not reduce neutrophil viability and functions such as degranulation, phagocytosis and oxidative burst in response to chemoattractants remain intact. (134,135) Inhibiting  $\beta_2$  integrins with monoclonal antibodies will also ameliorate ischemia-reperfusion injuries but in contrast to HBO<sub>2</sub>, antibody therapy causes profound immunocompromise. (136,137) HBO<sub>2</sub> does not inhibit neutrophil antibacterial functions because the G-protein coupled 'inside-out' pathway for activation (such as that triggered by endotoxin) remains intact, and actin S-nitrosylation is reversed as a component of this activation process. (133) (138) Probably the most compelling evidence that HBO<sub>2</sub> does not cause immunocompromise comes from studies in sepsis models, where HBO<sub>2</sub> has a beneficial effect. (139–141)

A separate anti-inflammatory pathway for HBO<sub>2</sub> involves impaired pro-inflammatory cytokine production by monocyte-macrophages. This action has been shown in animal models and human beings. (142–144) The effect on monocyte/macrophages may be the basis for reduced levels of circulating pro-inflammatory cytokines under stress conditions. (84) The molecular mechanism is unknown, but could be related to HBO<sub>2</sub>-mediated enhancement of heme oxygenase-1 and heat shock proteins (HSP) [e.g. HSP 70]. (7,10) Hence, once again, an oxidative stress response seems to occur.

Finally, HBO<sub>2</sub> has been shown in numerous models to augment ischemic tolerance of brain, spinal cord, liver, heart and skeletal muscle by mechanisms involving induction of antioxidant enzymes and anti-inflammatory proteins. (15,145–149) A common theme among some studies is alterations in HIF-1 production but, as was the case in wound healing models, timing of HBO<sub>2</sub> application appears to influence cellular responses. In several models, exposure to HBO<sub>2</sub> ameliorates post-ischemic injuries by decreasing HIF-1 expression. (150,151) When HBO<sub>2</sub> is used in a prophylactic manner to induce ischemic tolerance, however, its mechanism appears related to up-regulation of HIF-1 and at least one of its target genes, erythropoietin. (152)

In review, oxidative stress responses triggered by HBO<sub>2</sub> improve outcome from a wide variety of post-ischemic/inflammatory insults. HBO<sub>2</sub> also improves ischemic tolerance when used in a prophylactic manner. Augmented synthesis of reactive species temporarily inhibits adherence/sequestration of neutrophils by inhibiting  $\beta_2$  integrin function and in many tissues HBO<sub>2</sub> will induce antioxidant enzymes and anti-inflammatory proteins. More trials to assess clinical efficacy are needed.

## Treatment risks

This review has emphasized the positive aspects of HBO<sub>2</sub>-induced reactive species, but there is clearly a potential for negative effects. The risks for O<sub>2</sub> toxicity depend on the concentration and intracellular localization of reactive species. Because exposure to hyperoxia in clinical HBO<sub>2</sub> protocols is rather brief, studies show that antioxidant defenses are adequate so that biochemical stresses related to increases in reactive species are

reversible (8,10,153,154). Treatments often include so-called air breaks, where a patient breathes just air for 5 minutes once or twice through the course of a treatment. This intervention has been demonstrated to enhance pulmonary O<sub>2</sub> tolerance (1). CNS O<sub>2</sub> toxicity is manifested as a grand mal seizure. This occurs at an incidence of approximately 1 to 4 in 10,000 patient treatments. (155–157) Pathological changes in association with isolated O<sub>2</sub>-mediated seizures have not been found in studies with guinea pigs, rabbits and humans. (158) Progressive myopia has been reported in patients who undergo prolonged daily therapy, but this typically reverses within 6 weeks after termination of treatments. (159) Development of nuclear cataracts has been reported with excessive treatments that exceed a total of 150 to 200 hours, and the change does not spontaneously reverse. (160)

## Summary

This brief review has highlighted some of the beneficial actions of HBO<sub>2</sub> and the data that indicate oxidative stress brought about by hyperoxia can have therapeutic effects. Figure 1 provides a summary of mechanisms, all of which appear to stem from elevations in reactive species. While there has been substantial advancement of the field in recent years, more work is required to establish the place of HBO<sub>2</sub> in 21st century medicine. Investigations of fundamental mechanisms are still needed, and better patient selection criteria would improve cost-efficacy. An extended discussion on other indications for HBO<sub>2</sub> can be found in recent texts. (19–21)

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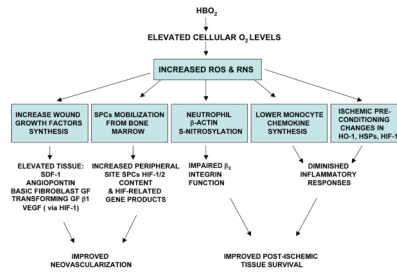
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**Figure 1.** Overview on therapeutic mechanisms of HBO<sub>2</sub> related to elevations of tissue oxygen tensions. The figure outlines initial effects (denoted by boxes) that occur due to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their consequences. Other abbreviations: GF=growth factor, VEGF=vascular endothelial growth factor, HIF= hypoxia inducible factor, SPCs=stem/progenitor cells, HO-1 =heme oxygenase-1, HSPs=heat shock proteins.