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HIGHLIGHTED TOPIC | *The Physiology and Pathophysiology of the Hyperbaric and Diving Environments*

Oxidative stress is fundamental to hyperbaric oxygen therapy

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Thom SR. Oxidative stress is fundamental to hyperbaric oxygen therapy. *J Appl Physiol* 106: 988–995, 2009. First published October 9, 2008; doi:10.1152/japplphysiol.91004.2008.—The goal of this review is to outline advances addressing the role that reactive species of oxygen and nitrogen play in therapeutic mechanisms of hyperbaric oxygen. The review will be organized around major categories of problems or processes where controlled clinical trials have demonstrated clinical efficacy for hyperbaric oxygen therapy. Reactive species are now recognized to play a major role in cell signal transduction cascades, and the discussion will focus on how hyperbaric oxygen acts through these pathways to mediate wound healing and ameliorate postischemic and inflammatory injuries.

wound healing; hypoxia-inducible factor; CD34; integrins; heat shock proteins

THERAPEUTIC MECHANISMS OF action for hyperbaric oxygen (HBO_2) are based on elevation of both the partial pressure of oxygen and hydrostatic pressure. Elevating the hydrostatic pressure increases partial pressure of gases and causes a reduction in the volume of gas-filled spaces according to Boyle's law. These actions have 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_2 therapy are not treated for bubble-induced injuries; hence therapeutic mechanisms are related to an elevated O_2 partial pressure. A summary of these mechanisms is shown in Fig. 1.

It is well accepted that reactive oxygen species (ROS) mediate O_2 toxicity, which for HBO_2 encompasses pulmonary injuries, central nervous system effects manifested by grand mal seizures, and ocular effects such as reversible myopia (29). ROS and reactive nitrogen species (RNS) also serve as signaling molecules in transduction cascades, or pathways, for a variety of growth factors, cytokines, and hormones (4, 25, 82, 123). As such, reactive species can generate either "positive" or "negative" effects depending on their concentration and intracellular localization. Although more is still to be learned about the role ROS and RNS play in therapeutic responses of HBO_2, this review will take stock of how far the field has progressed. The review will be organized around major categories of problems or processes where controlled clinical trials have demonstrated clinical efficacy for HBO_2.

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ROS are generated as natural by-products of metabolism and they include superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), and hydroxyl ($HO^{\bullet}$). ROS are increased in many organs by hyperoxia (60). Scavenging antioxidants combat the overproduction of reactive species. Enzymatic antioxidants include superoxide dismutase, catalase, and thioredoxin- and glutathione-dependent peroxidase(s) and reductase(s). Acting in conjunction with these enzymes are the nonenzymatic antioxidants vitamin C, vitamin E, thioredoxin, glutathione, uric acid, β-carotene, and carotene (124). Because exposure to hyperoxia in clinical HBO_2 protocols is rather brief (typically ~2 h/day), studies show that antioxidant defenses are adequate so that biochemical stresses related to increases in ROS are reversible (33, 34, 89, 97).

RNS include nitric oxide (NO) and agents generated by reactions between NO, or its oxidation products, and ROS. There are three NO synthase enzymes responsible for synthesizing $^{\cdot}$NO while converting L-arginine to L-citrulline: NOS-1 (neuronal NO synthase, nNOS), NOS-2 (inducible/inflammatory NO synthase, iNOS) and NOS-3 (endothelial NO synthase, eNOS). Peroxynitrite ($ONOO^-$) is the product of a reaction between $O_2^{\bullet -}$ and NO (10). Additionally, peroxide enzymes, and especially myeloperoxidase, can catalyze reactions between nitrite (NO_2), a major oxidation product of NO, and hydrogen peroxide, or HClO to generate oxidants such as nitryl chloride and nitrogen dioxide that are capable of nitration and *S*-nitrosylation reactions (18, 72, 99).

WOUND HEALING

HBO_2 is used in current practice to treat refractory diabetic wounds and delayed radiation injuries. A typical treatment protocol is daily exposures to 2.0–2.4 atmospheres absolute (ATA) for 90–120 min for 20–40 days. Treatments often

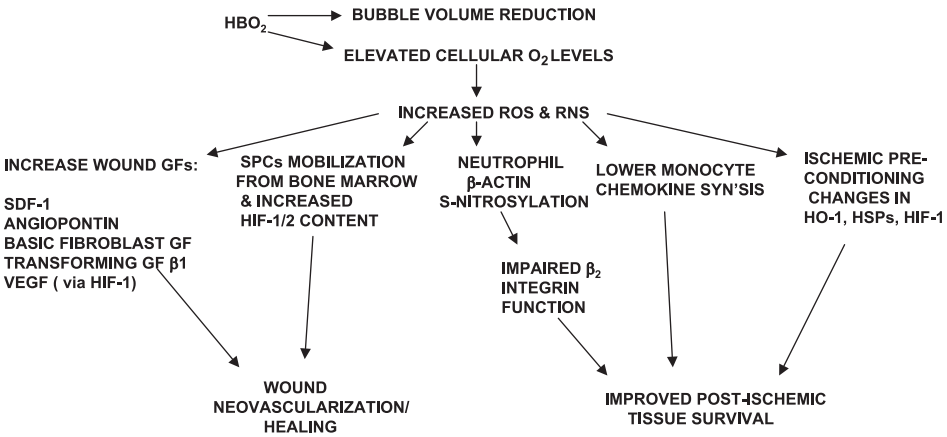

Fig. 1. Overview on therapeutic mechanisms of hyperbaric oxygen (HBO_2). The two primary effects of HBO_2 are to reduce the volume of bubbles in the body and elevate tissue oxygen tensions. The figure outlines effects that occur due to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) because of hyperoxia. GFs, growth factors; VEGF, vascular endothelia growth factor; HIF-1, hypoxia inducible factor-1; SPCs, stem/progenitor cells; HO-1, heme oxygenase-1, HSPs, heat shock proteins; Syn'sis, synthesis.

include so-called air breaks, where a patient breathes just air for 5 min once or twice through the course of a treatment. This intervention has been demonstrated to enhance pulmonary O_2 tolerance (52).

Discussion of the pathophysiology of diabetic wounds and delayed radiation injuries is beyond the scope of this review, and the reader is referred to several recent publications (32, 42). Common elements shared by both disorders 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 (17, 32, 42, 79, 109, 121). Diabetic wound healing is also impaired by deceased growth factor production, whereas in postradiation tissues there appears to be an imbalance between factors mediating fibrosis vs. normal tissue healing (17, 32, 121).

The effectiveness of HBO_2 as an adjuvant therapy for the treatment of diabetic lower extremity ulcerations is supported by six randomized trials and evaluations from a number of independent evidence-based reviews (6, 7, 49, 53, 69). The pathophysiology of radiation injury is obviously different from diabetic wounds, but the varied tissue abnormalities have been likened to a chronic wound (32). The benefit of HBO_2 for radiation injury also has been shown in randomized trials, and its utilization supported by independent evidence-based reviews (11, 30, 81). It is important to state that for both diabetic wounds and radiation injuries, HBO_2 is used in conjunction with standard surgical management techniques. That was the format followed in clinical trials demonstrating its efficacy. By itself, or if used only in a postoperative period, HBO_2 is frequently inadequate treatment (5, 76). Animal trials have also documented benefits of HBO_2 (45, 46, 80, 138). The basis for its efficacy is only partially understood, but 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 (27, 51, 112). Clinical HBO_2 has effects on both these processes.

HBO_2 reduces circulating levels of proinflammatory cytokines under stress conditions [e.g., endotoxin challenge (43)], and in wounded tissues or isolated cells, HBO_2 increases synthesis of many growth factors. HBO_2 does not alter circulating levels of insulin, insulin-like growth factors, or proinflammatory cytokines [e.g., tumor necrosis factor-α, interleukin (IL) -6, and IL-8] in normal healthy humans (28, 43). Vascular endothelial growth factor (VEGF) and angiopoietin, as well as stromal-derived factor-1 (SDF-1) influence SPCs homing to wounds and SPCs differentiation to endothelial cells (55, 92). Synthesis of VEGF has been shown to be increased in wounds by HBO_2, and it is the most specific growth factor for neovascularization (107). HBO_2 also stimulates synthesis of basic fibroblast growth factor and transforming growth factor-β_1 by human dermal fibroblasts (64), angiopoietin-2 by human umbilical vein endothelial cells (74), and it upregulates platelet-derived growth factor receptor in wounds (14). Extracellular matrix formation is closely linked to neovascularization, and it is another O_2-dependent process (57). Enhanced collagen synthesis and cross-linking by HBO_2 have been described, but whether changes are linked to the O_2 dependence of fibroblast hydroxylases, which have a K_m for O_2 of ~25 mmHg, well below that achieved in the presence of HBO_2 vs. some alteration in balance of wound growth factors, metalloproteinases and inhibitors of metalloproteases, is as yet unclear (36, 57, 135).

Oxidative stress at sites of neovascularization will stimulate growth factor synthesis by augmenting synthesis and stabilizing hypoxia-inducible factor (HIF)-1 (58, 87). Hypoxia inducible transcription factors are heterodimers of HIF-α and a constitutively expressed HIF-β (also called the aryl hydrocarbon receptor nuclear translocator subunit). Enhanced growth factor synthesis by HBO_2 is due at least in part to augmented synthesis and stabilization of HIFs (107, 115, 116). Although this clearly sounds paradoxical, even under normoxic conditions HIF activity is regulated by a variety of cellular microenvironmental modifications. It is well recognized that expression and activation of HIF-α subunits are tightly regulated, and their degradation by the ubiquitin-proteasome pathway typically occurs when cells are replete with O_2 (98, 103). However, whether hypoxic or normoxic conditions prevail, free radicals are required for HIF expression (16, 39, 100, 102, 103). In addition to ROS, synthesis of NO is required for VEGF-mediated angiogenesis (44), and many downstream effects of VEGF are stimulated via NO (8, 91).

There are three distinct HIF-α proteins: HIF-1α, -2α, and -3α. HIF-1 and -2 coordinate many cell responses involved with neovascularization by regulating gene transcription, and, although there is substantial overlap in their activity, there are also a number of genes preferentially regulated by either HIF-1 or -2 (126). The biological function of HIF-3 is unclear, and at least one splice variant negatively modulates HIF-1α and -2α, although its expression is restricted to specific tissues and subject to hypoxic conditions (77, 83).

The influence HBO_2 has on HIF isoform expression appears to be conflicting, and further work is needed to elucidate what are likely to be variations based on tissue-specific responses. Additionally, higher or lower levels of HIF isoforms may vary based on chronology (e.g., looking early or late after wounding or an ischemic insult). One recent model showing accelerated wound healing by HBO_2 reported lower HIF-1 levels at wound margins, along with reduced inflammation and fewer apoptotic cells (138). In contrast, higher levels of HIF-1 have been linked to elevated VEGF in wounds in response to hyperoxia (58, 107). Recently, exposure to HBO_2 was shown to elevate HIF-1 and -2 levels in vasculogenic SPCs. The basis for this effect is augmented production of the antioxidant, thioredoxin and one of its regulatory enzymes, thioredoxin reductase, in response to oxidative stress (115). Among other actions, thioredoxin has been shown to promote the expression and activity of HIFs (40, 62, 130). HIF-1 and -2 then secondarily can stimulate transcription of many genes involved with neovascularization, including SDF-1 and its counterpart ligand, CXCR4, as well as VEGF. A physiological oxidative stress that triggers the same pathway is lactate metabolism (87).

Bone marrow NOS-3 activity is required for SPCs mobilization (4). SPCs mobilization is compromised by diabetes, apparently because NOS activity can be impaired due to responses related to hyperglycemia and a reduced presence of insulin (13, 22, 37, 38). In addition, radiation and chemotherapy, along with other factors such as age, female sex, and coronary artery disease, are known to diminish SPCs mobilization (59, 94, 101, 125). By stimulating NO synthesis in bone marrow, HBO_2 mobilizes SPCs in normal humans and patients previously exposed to radiation (118), and preliminary observations suggest the same is true for diabetic patients (116, 133). In animal models, SPCs mobilized by HBO_2 home to wounds and accelerate healing (45, 46, 115). HBO_2 also improves clonal cell growth of SPCs from humans and animals (118). Functional enhancements of SPCs by HBO_2 appear to be related to augmentation of HIF-1 and -2 levels (115).

Therefore, to summarize, HBO_2 can stimulate healing in refractory wounds and irradiated tissues. One oxidative stress response that triggers improved function, at least for SPCs, involves elevations of thioredoxin and thioredoxin reductase, which secondarily increase HIF-1 and HIF-2. The influence of HBO_2 on HIFs in other cell types or tissues is variable. Increased synthesis of growth factors and collagen has been demonstrated. A separate free radical-based mechanism for augmentation of neovascularization by HBO_2 is bone marrow SPCs mobilization, which increases the number of circulating SPCs that may home to injured tissues.

REPERFUSION/INFLAMMATORY INJURIES AND HBO_2

For this review, we will group a variety of disorders together to facilitate the discussion on mechanisms of HBO_2, although we admit this approach grossly simplifies complex pathophysiological processes. Clinical HBO_2 protocols for these conditions are much shorter than for wound healing. Treatments occur for just a few days rather than weeks; they are performed at higher O_2 partial pressures (~2.5–3.0 ATA) and may occur multiple times in the same day.

Skin graft and flap failures may be due to ischemia-reperfusion injuries. A prospective, blinded clinical trial found that administration of HBO_2 before and for 3 days following the procedure led to a significant 29% improvement in graft survival (93). This is the only randomized clinical trial on skin grafts, but numerous animal studies support its conclusions (see citations in Ref. 67). Clinical studies have also documented significant survival enhancement with HBO_2 for extremity reimplantation and free tissue transfer, and following crush injury (15, 127). Other clinical trials have shown reductions in coronary artery restenosis after balloon angioplasty/stenting (105, 106), decreased muscle loss after thrombolytic treatment for myocardial infarction (31, 104, 108), improved hepatic survival after transplantation and more rapid return of donor liver function (84, 110), and reduced incidence of encephalopathy seen after cardiopulmonary bypass and following carbon monoxide poisoning (3, 128).

As is the case with wound healing, there appear to be complex and perhaps overlapping mechanisms for therapeutic effects of HBO_2 (see Fig. 1). An early event associated with tissue reperfusion is adherence of circulating neutrophils to vascular endothelium by β_2-integrins. When animals or humans are exposed to HBO_2 at 2.8–3.0 ATA (but not to just 2.0 ATA O_2), the ability of circulating neutrophils to adhere to target tissues is temporarily inhibited (63, 70, 117, 120, 137). In animal models, HBO_2-mediated inhibition of neutrophil β_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 (9, 65, 111, 114, 117, 122, 132, 134, 137). It also appears that benefits of HBO_2 in decompression sickness are related to the temporary inhibition of neutrophil β_2-integrins, in addition to the Boyle's law-mediated reduction in bubble volume as discussed in the introduction (78).

Exposure to HBO_2 inhibits neutrophil β_2-integrin function because hyperoxia increases synthesis of reactive species derived from NOS-2 and myeloperoxidase, leading to excessive S-nitrosylation of β-actin (113). This is a highly localized process occurring within neutrophils and not observed in other leukocytes, probably because of a paucity of myeloperoxidase. This modification increases the concentration of short, non-cross-linked filamentous (F)-actin, alters F-actin distribution within the cell, and it inhibits β_2 integrin clustering on the membrane surface. HBO_2 does not reduce neutrophil viability and functions such as degranulation, phagocytosis, and oxidative burst in response to chemoattractants remain intact (61, 117, 120). Inhibiting β_2-integrins with monoclonal antibodies will also ameliorate ischemia-reperfusion injuries, but in contrast to HBO_2, antibody therapy causes profound immunocompromise (85, 86). Probably the most compelling evidence that

HBO_2 does not cause immunocompromise comes from studies in sepsis models, where HBO_2 has a beneficial effect (23, 96, 119). HBO_2 does not inhibit neutrophil antibacterial functions because the G protein-coupled "inside-out" pathway for activation remains intact, and actin nitrosylation is reversed as a component of this activation process (113). The "denitrosylation" mechanism in neutrophils is an area of current investigation.

Monocyte-macrophages exhibit lower stimulus-induced proinflammatory cytokine production after exposure to HBO_2. This is seen with cells removed from humans and animals exposed to HBO_2 and also when cells are exposed to HBO_2 ex vivo (12, 71, 129). The HBO_2 effect on monocyte/macrophages may be the basis for reduced circulating cytokine levels after endotoxin stress, as was mentioned above (43). The mechanism is unknown, but could be related to HBO_2-mediated enhancement of heme oxygenase-1 and heat shock proteins (HSP; e.g., HSP70) (35, 97). Hence, once again, an oxidative stress response seems to occur. There are additional mechanisms involved with beneficial HBO_2 effects in reperfusion models. HBO_2 augments ischemic tolerance of brain, spinal cord, liver, heart, and skeletal muscle by mechanisms involving induction of antioxidant enzymes and anti-inflammatory proteins (24, 47, 56, 66, 90, 136).

HIF-1 is responsible for induction of genes that facilitate adaptation and survival from hypoxic stresses (103), and so it has been a focus of interest when examining HBO_2 therapeutic mechanisms in ischemia-reperfusion models. HIF-1 is involved with pro- as well an antiapoptotic pathways and in brain, promotes astrocyte mediated-chemokine synthesis (1, 88). In several models, exposure to HBO_2 appears to ameliorate postischemic brain injury by decreasing HIF-1 expression (26, 73). When HBO_2 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 (48). Thus, as was the case in wound healing models, timing of HBO_2 application appears to influence cellular responses.

There has been a long tradition of considering HBO_2 therapy for a variety of highly virulent infectious diseases, such as necrotizing fasciitis and clostridial myonecrosis, with a view that the microorganisms involved were particularly sensitive to elevated partial pressures of O_2. Several retrospective cohort trials indicate there is a benefit to including HBO_2 with antibiotics and surgery for necrotizing fasciitis (41, 95, 131). There is only one multicenter retrospective study where a trend toward increased survival was seen in the HBO_2 group [30% mortality (9 of 30 patients) with HBO_2 and 42% (10 of 24 patients) without HBO_2], but this was not statistically significant. Despite this observation, the authors stated support for use of HBO_2 because of apparent selection bias between groups (19). Retrospective comparisons examining efficacy of HBO_2 in clostridial myonecrosis support its use, but again there is ongoing debate (50).

With regard to mechanisms, most clinically significant anaerobic organisms are actually rather aerotolerant and thus tissue O_2 tensions, even those achievable with HBO_2, are expected to be only bacteriostatic for these organisms (68). More likely therapeutic mechanisms include impairment of exotoxin production, which is O_2 sensitive and can be inhibited at tissue partial pressures achievable with HBO_2 (50), and leukocyte killing, which is improve at progressively higher O_2 tensions (75). We suggest that a broader focus may be required to elucidate the as yet unclear pathophysiology of these serious infections and the role of HBO_2. A recent study of streptococcal myonecrosis showed that host responses to even minor traumatic injuries increase expression of vimentin in muscle tissue, which mediates adhesion/sequestration of microorganisms (21). There is also a role for intravascular platelet-neutrophil aggregation with vascular occlusion in these infectious processes (20, 54). These issues are much closer to the pathophysiological events seen with disorders such as ischemia-reperfusion injuries than traditional ideas in infectious diseases. There is ample room for further investigation.

In review, oxidative stress responses triggered by HBO_2 improve outcome from a wide variety of postischemic/inflammatory insults. HBO_2 also improves ischemic tolerance when used in a prophylactic manner. The basis for these effects is only partially understood. Augmented synthesis of reactive species temporarily inhibits endothelial sequestration of neutrophils by inhibiting β_2-integrin function and in many tissues HBO_2 will induce antioxidant enzymes and anti-inflammatory proteins.

SUMMARY

This review has highlighted some of the beneficial actions of HBO_2 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. Although there has been substantial advancement of the field in recent years, more work is required to establish the breadth of HBO_2 utilization in 21st century medicine. Investigations of fundamental mechanisms are still needed, and on the clinical front, patient selection criteria must be clarified to truly make HBO_2 a cost-effective treatment modality.

GRANTS

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