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Mechanistic perspective for experimental and accepted indications of hyperbaric oxygen therapy

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Abstract

There are many conditions for which hyperbaric oxygen therapy (HBOT) is currently being used in an investigational manner. This paper is a focused review of some conditions where we believe a mechanistic perspective supports further study on its efficacy.

Undersea and hyperbaric medicine is a field in need of greater effort to understand both basic mechanisms as well as clinical efficacy. It is of course a conundrum that to justify the effort and expense of basic studies one must have a clinical foundation suggesting that treatment has benefit. Clearly, the body of evidence supports additional studies on many disorders. It is also true that expansion of the field of indications requires performing a clinical investigation, but this is where HBOT is vulnerable. That is, there is strong temptation to apply a treatment like HBOT that poses so little risk of adverse effects.

As physicians, we are always striving to ease human suffering. Unfortunately, it is very easy to fall into the trap of applying HBOT to any speculative condition where no effective treatment exists. This is the point at which those who practice undersea and hyperbaric medicine and those who are consultants should make the effort to apply a high degree of discernment based upon the published literature. In this way, the field can scientifically and ethically expand to provide a beneficial therapeutic option to a larger number of people who may have no other options in managing their disease.

Key words:
Clinical indications;
Hyperbaric medicine;
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Therapeutic potential

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Introduction

General interest for hyperbaric oxygen therapy (HBOT) has gained considerable momentum in the last ten years; with the result that hyperbaric oxygen (HBO_2) is thought to be a new form of treatment by many in the medical field and a "cutting edge" therapy by many in the mainstream public. It is, however, neither new nor cutting edge. HBO_2 was first used as a clinical intervention in 1937 to treat decompression sickness [1], following over a hundred years of work gleaned in pressure physiology and the medical applications of oxygen. In the ensuing decades, additional pathological states were discovered to have a beneficial response to HBO_2 and medical reviews in different areas of the world have added to the list of conditions where HBO_2 may be considered as a component of treatment. For example, there are now 14 accepted indications by the Undersea and Hyperbaric Medical Society for the application of HBO_2 [2]. The European Committee for Hyperbaric Medicine Consensus Conference in 2004 considered 27 indications as accepted and an additional 13 as not accepted based on a three-level scale (http://www.echm.org). Variations on these lists of indications can also be found in publications by numerous organizations, such as the Japanese Society for Hyperbaric Medicine and the Chinese Society of Hyperbaric Oxygen Medicine.

What may be considered new and perhaps "cutting edge" is the better understanding of HBO_2 mechanisms of action. Therein lays the limiting factor for HBOT. As much as the basic science work has advanced our understanding, the information has been described for only a limited number of conditions. For instance, the work conducted in the 1980's on osteoradionecrosis expounded on the induction of angiogenesis by a steep oxygen gradient created by HBO_2 in the hypoxic, hypovascular post-irradiation tissue [3]. Thirty years later, vasculogenic stem cells were ascertained to be induced and mobilized and appear – at least in the diabetic model – to home to the wound/healing site [4, 5]. By virtue of establishing an oxidative stress HBO_2 also stimulates stem/progenitor cells to produce and release growth factors at the site of neovascularization [6, 7]. The inhibition of β_2 integrin adhesion molecules by HBO_2 was determined to ameliorate damage in ischemia-reperfusion injuries and to block the inflammatory cascade leading to neurological

sequelae in carbon monoxide poisoning [8-15]. For arterial gas embolism and decompression sickness, HBO_2 decreases the volume of the offending bubbles [16, 17]. One or more of these mechanisms have been applied to other disease entities, but direct data on the effects of HBO_2 for most accepted indications remains suggestive or unclear.

In the era of evidence-based medicine, HBOT is under considerable scrutiny and expectation to be supported by AHA Level 1 evidence, arguably much more so than most other specialized treatment. This is not surprising considering the historical and contemporaneous utilization of HBO_2 for unfounded and mechanistically illogical conditions. So while rigorously designed animal models provide solid information for both the mechanisms of action and the beneficial effects of HBO_2; and while human case reports, case series and retrospective comparison data provide well-substantiated evidence, human randomized clinical trials for the efficacy of HBO_2 are not only expected but, in some cases, necessary to convince the most skeptical in the medical community who would otherwise curtail this treatment as a viable option to patients. Unfortunately, not all human randomized clinical trials may be permitted to proceed, either for ethical reasons or due to lack of funding. For example, personal communications suggest that attempts by several groups to conduct randomized controlled trials for the addition of adjunctive HBOT to the conventional treatment of clostridial myositis (gas gangrene) were thwarted because institutional review boards deemed it unethical to proceed with such a randomized study.

If the practice of medicine is rigorously restricted to just the evidence provided by a randomized double-blinded, placebo-controlled trial, medical progress would stall and patients may be denied substantiated treatments shown to be beneficial. If this were the case, the majority of surgeries conducted in all surgical specialties would cease for lack of a randomized control trial to prove their efficacy. Since modern medicine advances by research, it is reasonable for hyperbaric medicine to expand through ethical investigational studies, as long as there is Institutional Review Board approval of the study, there is no required remuneration for treatment and the protocol is open to all eligible patients. This progress can be pursued in two ways: (1) by examining new mechanisms of already accepted indications for HBO_2; and (2) by looking at new conditions when our understanding of basic HBO_2 mechanisms make it feasible that there may be therapeutic benefit. The latter poses the bigger challenge to the specialty, as the indiscriminate application of HBO_2 makes the field vulnerable to criticism of "a treatment in search of a disease" or, worse, that it is quackery with outrageous claims. It is our opinion, therefore, that the approach to investigating new conditions should start from a basic science foundation where fundamental biochemical and physiological mechanisms already identified drive the next step in an investigation.

Possible additional mechanisms of accepted indications for HBO_2

Necrotizing fasciitis

Necrotizing fasciitis is an acute, fulminant and potentially fatal polymicrobial infection of the superficial and deep fascia leading to ischemic dermal necrosis by spread through the dermal vasculature. Numerous strong case series reports, cohort studies and retrospective reviews have shown the beneficial effect of HBO_2 in reducing the mortality, morbidity and extent of severe amputation and surgical resection employed to counter the unrelenting progression of infection [18-21]. The edematous, necrotic fascia and the infected dermal blood supply result in decreased perfusion pressure and ischemia. The acidic milieu of strict and facultative anaerobes is hypoxic, impairing phagocytosis by polymorphonuclear neutrophils [22]. HBO_2 corrects the hypoxia and thereby improves neutrophil function. HBOT further enhances certain antibiotics, such as aminoglycosides, that require oxygen for transfer across cell walls. Recent work using animal and human models suggest that additional pathological processes are occurring at a cellular level. It has been shown that cryptic Group A Streptococcus (GAS) binds to vimentin, a type III mesenchymal intermediate filament protein, on skeletal muscles following blunt injury and that vimentin up-regulation in injured muscles is associated with homing of circulating GAS to the injured site [23]. The vimentin-GAS tethering indicates that it is an induced stimulus to which strategies targeting this interaction could attenuate the myonecrosis. In animal and human studies, cells exhibit lower stimulus-induced pro-inflammatory cytokine production after HBO_2 (*e.g.* LPS-induced IL-1, IL-6, TNF-α) [24-27]. This suppression of inflammatory cytokines may be an aspect to HBO_2-mediated protection of hemorrhagic-, septic- and zymosan-induced shock in animal models. It is compelling information offering an additional mechanism of HBO_2 in arresting the damage of

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necrotizing fasciitis that is more complicated than our current understanding.

Threatened flaps and grafts

When a recently placed flap or graft becomes compromised, the cause is usually due to ischemia from an inadequate blood supply either in the recipient bed or in the flap. HBO_2 can salvage the hypoxic tissue until neovascularization or flap inosculation occurs. Clinical evidence to support use of HBOT is meager, however. There is but one prospective, blinded clinical trial supporting the efficacy of HBOT for compromised flaps and grafts. Administration of HBO_2 prior to and for three days following skin grafting led to a significant 29% improvement in graft survival [28]. Support for use of HBOT in flap/graft compromise comes from a very large number of animal studies [29, 30]. Comparative clinical trials support its use but more work is needed [31, 32]. A comprehensive review of HBO_2 use for flaps and grafts was recently published [29].

Investigational conditions treated with HBO_2

As previously discussed, medical science advances through basic science research and investigational studies. Investigating new applications for HBO_2 through a reasonable mechanistic approach allows for the field to stay focused and to avoid the random indiscriminate use for which HBOT has been much criticized. The number of investigations into the efficacy of HBO_2 has expanded for both chronic and acute conditions. The following is a brief review of conditions where mechanistic principles have been applied.

Traumatic brain injury

Treatment strategies for traumatic brain injury (TBI) have so far been focused on prevention and minimization of the secondary insult that occurs after physical impact to cerebral matter [33]. At any point, irreversible damage may occur, with the injury itself ongoing and expanding through edema, hypoxia and ischemia. The ischemia is secondary to raised tissue or intracranial pressure, release of toxic levels of excitatory neurotransmitters and impaired calcium homeostasis [34, 35]. The hypoxic neurons undergo anaerobic metabolism, which results in acidosis and an unsustainable loss in cellular metabolic reserve [36]. As hypoxia persists, neurons can no longer maintain homeostasis. Reactive oxygen and nitrogen species are generated and cell integrity degrades, resulting ultimately in neuronal cell death [37, 38]. Adjunctive HBOT has been shown to reduce tissue edema by an oxygen-induced vasoconstriction effect [39]. Yet, the mechanism by which this occurs is more complex than a simple increase in availability of oxygen for neuronal aerobic consumption. The case for treating TBI with HBO_2 is as much focused on functional outcomes as it is with survivability.

Several animal models showed improvements in cerebral PO_2, intracranial pressure and a decrease in mortality, with one demonstrating improvement in the mitochondrial redox potential, suggesting more rapid recovery of aerobic metabolism [40-42]. An inflammatory modulation process was shown in a murine model that reduces neutrophil infiltration into the injured brain. The attenuation of neutrophil reactivity by HBO_2 described by these investigators is notable although a direct link to β_2 integrins as shown in another neuro-inflammatory disorder, carbon monoxide poisoning, was not shown. Neuroinflammation in this study was linked to reduced expression of matrix metalloproteinase-9 in the peri-lesion brain tissue [43]. The outcomes demonstrated in this study were a reduction in secondary injury, in cell death and in reactive neuroinflammation by the administration of HBO_2 after traumatic brain injury. Further work by these same researchers identified a neuroprotective effect of HBO_2 by increasing Bcl-2 expression and intracellular oxygen availability that both contribute to preserve mitochondrial integrity and reduce the activation of the mitochondrial apoptotic pathway [44]. The implication from these animal models is that the effectiveness of HBO_2 is not just in the immediate stage of hypoxia where mortality is highest, but in the reactive inflammatory phase where cellular damage is progressive, resulting in neurological sequelae.

Clinical studies in humans are more complicated and controversial. Unlike animal studies where there is homogeneity in the brain trauma induced, in clinical trials there is variation in the area or magnitude of brain injury, length of time of injury, time to treatment initiation, as well as co-morbidities and other confounding factors. Taking into account also that various hyperbaric medicine centers have different treatment protocols, it is not surprising that results have varied. Two large, multi-center, randomized human clinical trials are underway, but the current available published evidence from human clinical trials is compelling. Since the 1970s, there have been case series and randomized trials examining the acute and late use of HBO_2 to treat TBI that have shown improved survival and improved aerobic metabolism [45-47].

A notable randomized controlled trial of 55 patients with acute brain trauma showed statistically significant improvement in mortality and morbidity in the group treated with HBO_2 through three measures: the Glasgow Coma Scale, the brain electric activity measure and the Glasgow Outcome Scale [48]. A recent prospective randomized controlled trial utilized quantitative measurements and biomarkers as indicators of the cellular and physiological effects of HBO_2 on patients who sustained TBI. In this latest investigation, the authors agree that hypoxia and ischemia are the critical factors leading to secondary injury in TBI, but they focused on the problem of ischemia that persists beyond the first to second week after injury. They put forth two reasons for this: (1) O_2 deliver to brain tissue is not only impaired by decreased cerebral blood flow (CBF) but also by reduced O_2 diffusion to cells which cannot be discerned by CBF measurements; and (2) oxidative metabolism is considerably reduced in large sections of the brain after TBI and mitochondrial dysfunction is correlated with this hypo-metabolic state [49]. In referencing prior studies, the authors noted that cerebrospinal fluid (CSF) lactate production and elevated levels of microdialysate lactate are markers for anaerobic metabolism caused by either a lack of O_2 or damage to the mitochondria. Consistent with previous studies, this study demonstrated a reduction of CSF lactate levels. They noted, however, that the microdialysate CSF to plasma ratio (L/P) appeared to be a superior marker for cerebral anaerobic metabolism and a measure of the cytoplasmic redox state that is highly specific for secondary ischemia. Patients receiving HBOT showed a significant decrease in microdialysate L/P ratio post-treatment, indicating a shift toward a better cellular redox state. Previous work has shown that cerebral metabolic rate of oxygen ($CMRO_2$) rises after mitochondrial function and cerebral aerobic metabolism improve with hyperoxia [50]. The HBOT treated patients in this study demonstrated significant elevation in $CMRO_2$ and CBF, indicating mitochondrial recovery by the increased utilization of O_2. In keeping with results from prior investigations, intracranial pressure (ICP) was significantly decreased in patients receiving HBOT [51-54]. Some of these studies have suggested that HBO_2 may promote blood-brain barrier integrity, thus reducing cerebral edema and hyperemia.

Ischemic tolerance/preconditioning

Ischemic preconditioning is a type of hormesis [55], which is a process in which a favorable biological response follows exposure to a low dose stressor that triggers compensatory/repair mechanisms that not only neutralize the stressor's effect, but repair other defects not caused by the primary stressor. First identified in the heart and then the brain, ischemic tolerance has been suggested as a viable clinical strategy to prepare vital organs to situations where ischemia is anticipated, such as during cardiac or brain surgery or where a stroke could occur [56]. Hyperbaric oxygen is just one method that has been tested to produce ischemic tolerance and is a likely safer preconditioning stimulus than a number of other stimuli such as primary hypoxia. Many studies using animal models have demonstrated HBO_2 induced ischemic tolerance in various organ systems, including the liver, brain, heart and spinal cord. Some have been able to describe the mechanism for this preconditioning. As with other investigational indications, a few human mechanistic studies have been reported.

Central nervous system

Using a rat model, HBOT induced neuroprotection from transient occlusion of the middle cerebral artery, resulting in decreased cerebral infarct volumes and better neurological outcomes [57]. Using the gerbil hippocampus as a model, a group of researchers attempted to determine the mechanism for induction of ischemic tolerance by HBO_2. Their results suggest that increased manganese superoxide dismutase and/or Bcl-2 expression mitigate against mitochondrial alterations triggered by ischemia [58]. A dosing effect shown in this study is also notable. Pretreatment with HBO_2 at 2 ATA (atmospheres absolute) once every other day for five sessions significantly induced expression of Bcl-2 and superoxide dismutase, but not with pretreatment at 3 ATA once daily for ten sessions. Using the same protocol of 2 ATA once every other day for five sessions, a later murine study demonstrated that HBO_2 preconditioning dramatically improved the neurobehavioral outcome at all study time points and reduced infarction volumes after cerebral ischemia. In this trial researchers found that HBO_2 induced a marked increase in hypoxia-inducible factor-1α (HIF-1) and one of its downstream target genes, erythropoietin (EPO) in the cortex and hippocampus [56]. HIF-1 is an important transcription factor functioning as a regulator for the induction of genes that facilitate cellular adaptation and survival under hypoxic conditions [56, 59] and is an essential mediator in hypoxia induced ischemic tolerance [60]. Several recent

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studies have shown that HBO_2 increases reactive oxygen species (ROS) generation [61, 62] and that increased ROS levels in turn upregulated HIF-1 expression [63-65]. Therefore, at least some beneficial effects of HBOT may be mediated by upregulation of HIF-1 and its target genes. For example, EPO expressed in the central nervous system exerts potent neuroprotective and anti-inflammatory effects [66-68].

Interestingly, the ischemic tolerance conferred by HBO_2 seems to be time sensitive. As demonstrated in another recent murine model, HBO_2 significantly reduced loss of hippocampal CA1 neurons secondary to transient forebrain ischemia when the last HBO_2 session was given 6 hours, 12 hours or 24 hours before ischemia, but not at 72 hours before the ischemia [69]. The investigators examined the changes of gene/protein expressions as a temporal factor in the HBO_2 ischemic preconditioning and found seven genes whose time course corresponded to HBO_2 induced neuroprotection, with three being significantly increased. This study implies that any human clinical trials into CNS HBO_2 ischemic tolerance should take into account the temporal advent of the ischemic insult after the HBOT preconditioning.

A human prospective randomized double-blind control trial published in 2005 evaluated the effect of HBOT preconditioning on the CNS by using neuropsychometric analysis and measuring systemic inflammatory response biomarkers after cardiopulmonary bypass surgery. The investigators emphasized the fact that any human study of this nature precluded direct neuronal evaluation, since enzyme induction or inhibition, free radical release, antioxidant status, and protein synthesis are aspects of the mechanism of action that can be evaluated by invasive testing. This human clinical trial utilized HBO_2 pretreatments at 2.4 ATA at 24, 12 and 4 hours before cardiopulmonary bypass surgery. Neuropsychometric evaluations conducted prior to surgery and at 4 months after surgery demonstrated significant neuropsychometric dysfunction in the untreated group compared to the preconditioned group. Further, the findings showed that inflammatory biomarkers such as soluble E-selectin, HSP-70 and leukocyte CD18 were significantly lower in the preconditioned group compared to the untreated group, although both groups showed elevation in the biomarkers from baseline. The investigators concluded that HBOT decreased the amplitude of the inflammatory reactivity but did not completely negate it [70].

Heart

Ischemia-reperfusion injury is a known complication any time there is a transient disruption in blood flow, which creates further tissue damage beyond that produced by the original ischemic event. Rats exposed to HBO_2 at 3 ATA exhibited cardiac preconditioning that appeared to be caused by an increase in catalase [71]. In other studies using HBO_2 at 2 or 2.5 ATA, preconditioned rats exhibited a significant reduction in the infarct size and improved recovery of function [72, 73]. One study suggested that cardioprotection was conferred by a mechanism involving increased nitric oxide (•NO) production due to increased expression of nitric oxide synthase 3 (NOS3) and its association with an agonist, HSP90 [72]. In 2010, a prospective randomized clinical trial was conducted on 81 patients undergoing coronary artery bypass graft surgery. Exposure to 2.4 ATA O_2 for two 30-minute intervals separated by 5 minutes administered 4 hours prior to surgery resulted in improved stroke volume and left ventricular stroke work, a smaller rise in troponin T, a reduction in intensive care unit length of stay as well as intra-operative and postoperative blood loss, and fewer complications such as low cardiac output syndrome, atrial fibrillation, pulmonary complications and wound infections [74].

Crohn's disease

Crohn's Disease is a chronic inflammatory gastrointestinal disease of unclear etiology where individuals exhibit elevated levels of proinflammatory cytokines, particularly tumor necrosis factor α (TNF). The chronically inflamed gastrointestinal tract becomes ulcerative and fibrotic, and fistula formation may occur [75, 76]. HBOT for refractory cases has been examined in a case series [77]. In a study of seven patients with perianal Crohn's Disease treated with HBOT, elevated pretreatment IL-1, IL-6 and TNF cytokines secreted from stimulated monocytes were all decreased in 7 days of treatment (compared to a control group of ten age and sex matched individuals). However, after the completion of 20 HBOT sessions, all three cytokines returned to their high pre-treatment levels [24].

In a later human in vitro model, HBO_2 was investigated for its effect on stimulus-induced pro-inflammatory cytokine production [25]. Human blood-derived monocyte/macrophages were stimulated first with lipopolysaccharide (LPS), lipid A, phytohaemagglutinin A (PHA) or TNF and then exposed to 2.4 ATA O_2 for 90 minutes. Treatment suppressed IL-1 synthesis in response to

all agents as well as TNF production in response to LPS, lipid A and PHA. Interestingly, when cells were exposed to hyperoxia for a longer time, *i.e.* 3 hours, the immunosuppressive effect no longer occurred, and if exposed for 12 hours, cells produced 123% more IL-1[25]. While one must be cognizant that ex vivo exposures to these partial pressures of O_2 grossly exceed what cells experience in vivo (even during HBOT), the marked differences in phenotype with exposure duration point to the problems of dosing when designing investigational trials. There also may be different cell responses. For example, splenic macrophage taken from mice exposed to 2.5 ATA O_2 for 1 hour daily for 5 days exhibited lower spontaneous IL-1 production, but not IL-6 [27]. In another study, a single 90 minute exposure to 2.8 ATA O_2 increased spontaneous TNF production by rat monocyte/macrophages derived from blood, spleen and lungs; yet after LPS stimulation additional production of TNF was seen by pulmonary and splenic macrophages, but not those derived from the blood [26].

Bisphosphonate osteonecrosis

Bisphosphonates are a class of drugs used to treat osteoporosis and to manage metastatic disease to the bone. In normal physiological function, there is a tight balance between osteoclast and osteoblast activity in order to maintain normal bone remodeling. Bisphosphonates block osteoclast function to hinder bone resorption and thus tip the balance in favor of bone formation. Unfortunately, some patients on chronic therapy develop necrotic lesions in the jaw. Concurrent use of steroids with bisphosphonates may increase this risk [78].

Osteoradionecrosis (ORN) is a type of delayed radiation injury of bones for which HBOT is indicated. Thanks to the work conducted by Dr. Robert Marx in the 1980s, we have a reasonable understanding of the pathophysiology and the therapeutic mechanism of action of adjunctive HBOT in previously irradiated mandibular bone. This work led to speculation that HBOT may be efficacious for osteonecrosis resulting from bisphosphonate use, although the primary pathophysiology of bisphosphonate osteonecrosis differs markedly from that due to radiation.

As with ORN, bisphosphonate-induced osteonecrotic lesions are refractory to debridement and antibiotic therapy [79] and lack effective therapeutic options [80]. Clinical experience using HBOT has been reviewed and currently includes a number of case reports and small series [80]. In a case series of 16 patients, persistent benefit of HBOT was much higher in those who discontinued bisphosphonate medications [80].

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