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Oxy-inflammation in hyperbaric oxygen therapy applications

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Abstract

Hyperbaric Oxygen Therapy (HBOT) is a non-invasive method of O_2 delivery that induces systemic hyperoxia. Hyperbaric chamber consists of a pressure vessel and a compressed breathing gas supply, which can regulate internal pressure. The chamber delivers 100% O_2 to patients according to predetermined protocols and is monitored by trained personnel. HBOT relies on increasing the inspired O_2 fraction (fiO_2) and elevating the partial pressure of O_2 (pO_2). O_2 is typically administered at pressures between 1.5 and 3.0 ATA for 60 to 120 minutes, depending on the clinical presentation. Currently, there are 15 indications for HBOT approved by the Undersea and Hyperbaric Medicine Society, categorized into three groups: emergency medicine, wound healing acceleration, and antimicrobial effects. The present narrative review aims to elucidate the mechanismsaction underlying HBOT, particularlyoxy-inflammation, in various pathologies within these categories.

Key Words: oxygen, oxidative stress, inflammation, decompression-illness, reperfusion-injury, reoxygenation, infection, biomarkers.

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Oxygen (O_2) comprises a third of human body mass, it represents an essential component of macromolecules such as proteins, carbohydrates, lipids and nucleotides and the major constituent of inorganic compounds of animal shells, teeth and bones. Among hospitalized patients, O_2 is the most prescribed drug[1] used to treat acute/emergent diseases or chronic pathological conditions such as Chronic Obstructive Pulmonary Diseases (COPD) cystic fibrosis, emphysema and Obstructive Sleep Apnea Syndrome (OSAS). Furthermore, high O_2 fraction (fiO_2) gas mixtures are administrated to anesthetized patients in order to avoid hypoxemia that can impair capability of the lungs to oxygenate blood because of the negative effects of anesthetics on the pulmonary function. At normobaric pressure, O_2 is delivered through nasal cannula, face mask, or endotracheal intubation while, at hyperbaric pressure, using a hyperbaric chamber. A hyperbaric chamber consistsofa pressure vessel and a compressed breathing gas supply which may be used to regulate the internal pressure. The chamber delivers 100% O_2 to the patients following predetermined tablesand monitored by trained personnel.

Hyperbaric Oxygen Therapy (HBOT)is a non-invasive O_2 delivery method that induces systemic hyperoxia. HBO_2 therapy is based on the increase of inspired fiO_2 combined with elevation of partial O_2 pressure (pO_2).[2] Typically, O_2 is administrated between 1.5 and 3.0 ATA for periods ranged from 60 to 120 min depending on the clinical presentation.[3] The US Food and Drug Administration (FDA) has approved HBOT as a safe adjunctive treatment to stimulate wound healing in patients with diabetes and it is known to accelerate the healing process in ischemic wounds and severe sepsis. Actually, there are 15 indications for HBOTapproved by the Undersea and Hyperbaric Medicine Society, that can be divided in three groups:[4] i) emergency medicine: air or gas embolism, Carbon Monoxide (CO) poisoning, Decompression Illness (DCI); ii) wound healing acceleration: acute thermal burn injury, compromised grafts and flaps, crush injury, compartment syndrome and other acute traumatic ischemia, delayed radiation injury (soft tissue and bone necrosis) enhancement of healing in selected problem wounds, idiopathic sudden sensorineural hearing loss, severe anemia; iii) exerting antimicrobial effects: clostridial myositis and myonecrosis, intracranial abscess, necrotizing soft tissue infections, refractory osteomyelitis.

The present narrative review aims to detail mechanisms of actions underlying HBOT, particularly oxy-inflammation, in some pathologies of these three groups.

Hyperbaric oxygen therapy related mechanisms

Breathing O_2 at hyperbaric pressure increases not only its partial pressure in tissues but also causes the Release Ofreactive Oxygen (ROS) and Nitrogen (RNS) species, signaling molecules involved in several physiological mechanisms phagocytosis of pathogens, modulatingactivities and a regulatory ability in signal transductionprocesses during transduction of intercellularinformation (Figure 1).[5] However, an excessive ROS/RNS production may cause irreversible damage to cells resulting in cell death by the necrotic and apoptotic pathways. Increased expression of inducible Nitric Oxide (NO) Synthase (iNOS) has been noted after HBO_2 exposure on rats, potentially leading to further RNS generation and macroscopically to deterioration of respiratory mechanics; hyperbaric exposure instead increased NOS expression without affecting respiratory properties.[6] To avoid ROS/RNS damage, human body activates endogenous antioxidant defenses: as observed by Bosco *et al.*, HBOTat 1.5-2.5 ATA plays a protective role against oxidative stress.[7] Furthermore, thiols such as glutathione raise as consequence of HBO_2 exposure, probably for their role in antioxidant response to protect cell components and preserve cellular homeostasis.[7] ROS can regulate transcription factors including nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), and hypoxia-inducible factor (HIF-1α). These transcription factors influence the expression of several genes that express signaling molecules such as interleukins (IL-1β, IL-6), tumor necrosis factor-α (TNF-α), and chemokines including IL-8.[8] During inflammation, cytokines bound their related receptors inducing ROS generation, kinases and transcription factor activation. Cytokine and chemokine release activates recruitment of immune system cells such as neutrophils, monocytes, lymphocytes (natural killer cells [NK cells], T cells, and B cells), and mast cells. HBOT may inhibit pro-inflammatory interleukins includingIL-1β, IL-6 and IL-8[9] while seems to stimulate the release of anti-inflammatory IL-1α.[10] Furthermore, another HBOT effect is represented by decreasing levels of high-sensitivity C-reactive protein (hs-CRP)[11] and of the pro-inflammatory cytokines interferon-γ (IFN-γ), NF-κB and TNF-α.[11] Experimental studies on small animals assessed that HBO_2treatment lowers HIF-1α levels. HBOT also suppresses Blood-Brain Barrier (BBB) permeability (as attested by the upregulation of BBB integrity markers zonula occludens-1 and claudin-5),[12] endothelial extravasation and cerebral edema subsequent to the trauma.[13] It decreases gene expression of inflammatory response cascade such as IL-8, caspase 3 and TNFα while higher levels of the anti-inflammatory IL-10 levels confirm the direct neuroprotective effect of HBOT.[12] HBOT exhibits bactericidal properties against anaerobic microorganisms that are sensible to high concentration of ROS at high pO_2.[2] These properties may be due to an increase of respiratory burst activity of neutrophil-like cells and the bacterial phagocytosis.[14] On one hand antimicrobial activity slows down wound healing promoting a pro-inflammatory environment, on the other hand enhanced apoptosis resolves inflammation favoring wound healing.[14]

HBOT promotes neovascularization through the combination of two different process: the stimulation of new blood vessel growth from local endothelial cells (angiogenesis) combined with the differentiation in the bed of the wound of circulating stem/progenitor cells to generate new vessels (vasculogenesis).[2] In bone marrow, HBOT stimulates NO Synthase (NOS) activity to produce NO, playing a crucial role in the mobilization of stem cells and promoting neovascularization. Another important neovascularization mechanism involves the role of HBOT related oxidative stress that induces Vascular Endothelial Growth Factor

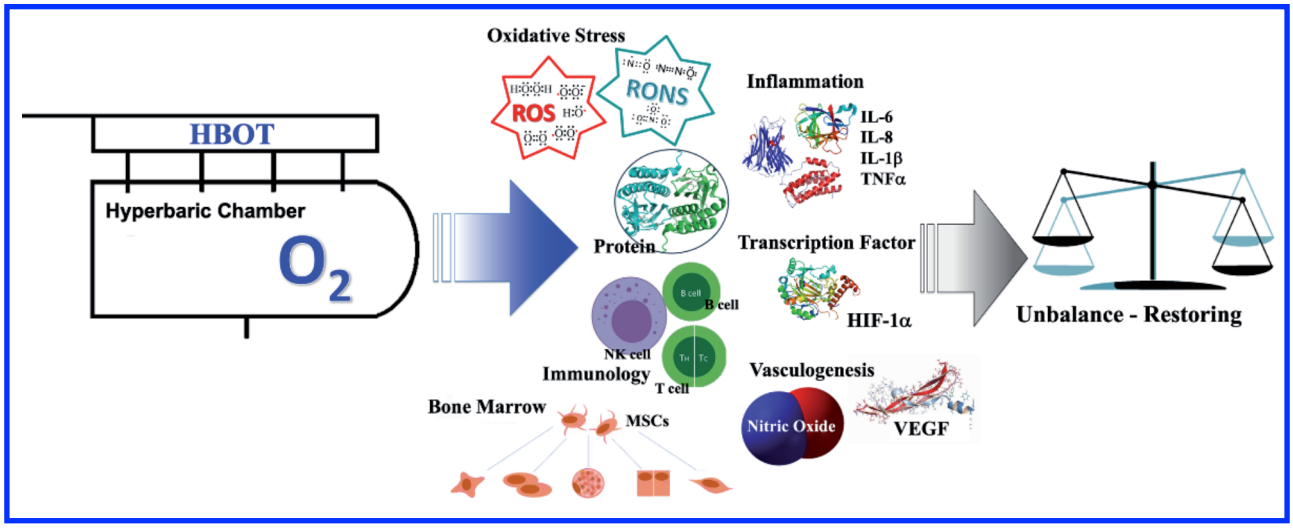

Figure 1. *Sketch of hyperbaric chamber and the effect of hyperbaric treatment. The O_2 effect results in an increased supply of reactive oxygen species (ROS) and reactive nitrite species (RNS), with a consequent change in expression of transcription factors, proteins, inflammation status and promotion of vascularization and enhanced immunomodulatory properties.*

(VEGF) activation favorited by HIF-1α.[15] Exposure of Bone Marrow Mesenchymal Stem Cells (BM-MSCs) to HBO_2 favorites the proliferation of osteogenically differentiated cells regulated by Wnt3a/β-catenin signaling pathway.[16] On the other hand, Human Adipose-Derived Stem Cells (hADSC) proliferation has been observed after HBO_2 exposure in presence of the pro-inflammatory cytokineTNF-α. The effect of TNF-α on hMSCs proliferation seems to be related to its concentration, suggesting a key role of this cytokine during bone tissue repair. Furthermore, HBOTmay promote osteogenic differentiation increasing the osteoblasts, calcium deposition, alkaline phosphatase activity and bone nodule.[17]

As reported by Thom *et al.*, HBO_2 stimulates stem progenitor cells (SPCs) through a NO related mechanism[18] where NO synthase activates metalloproteinase-9 to cleave the Stem Cell Factor (SCF) from its membranelinkage, leading to a SCF-mediated SPCs mobilization.Precursor cells from Colony Forming Cell (CFC) express VEGF receptor-2 (VEGFR-2), located in endothelial progenitors suggestinga role of some cells, mobilized by HBO_2, in the endothelial regeneration.

Hyperbaric oxygen therapy applications

Decompression illness (DCI) treatment

Decompression Illness (DCI) is caused by intravascular or extravascular bubbles that are formed as consequence of a reduction in environmental pressure (decompression). The term DCI is used to describe two different mechanisms which result in overlapping sets of symptoms: Arterial Gas Embolism (AGE) and Decompression Sickness (DCS). AGE occurs when expanding gas stretches and breaks alveolar capillaries, allowing alveolar gas to enter the arterial circulation. It can be caused by gas trapped as a result of airways obstruction or by presence of pulmonary blebs and bullae.[19] AGE manifestations include loss of consciousness, confusion, focal neurological deficits, cardiac arrhythmias or ischemia. DCS starts with the formation and the increase in size of extravascular and intravascular bubbles when the sum of the partial gas tensions (O_2, N_2, CO_2, He and water vapor) is greater than the local absolute pressure. In diving, this state is made possible by the increase in tissue inert gas partial pressure that occurs when the gas (usually N_2, occasionally He) is breathed at hyperbaric pressure. DCS diagnosis is based on a wide range of clinical manifestations,[20] that involve different parts of the human body, including musculoskeletal pain, skin rush, paresthesia, hypesthesia and, less common, motor weakness, ataxia, vertigo, hearing loss, dyspnea, pulmonary edema, shock and death. HBOT is the definitive treatment for DCI due to the effect of hyperbaric pressure to reduce bubble size, improved tissue oxygenation and hyperoxia that induces inhibition of leucocyte adhesion to damaged endothelium. Furthermore, 100% O_2 is amelioration of tissue hypoxia caused by bubble-induced ischemia, mechanical injuries and biochemical damages.[21] In the case of DCS, the treatment entity is chosen depending on the manifestation severity, patient response to HBOT and residual symptoms after the initial recompression until the complete resolution.[22] The most common recompression schedule is US Navy Treatment Table 6 (NTT6; here in Table1) in which patients are compressed to 2.82 bar (equivalent to 18 m sea water depth) while breathing 100% O_2, a pressure with an acceptable low risk of cerebral O_2-associated toxic effects[22] showing a high degree of success in resolving symptoms.[23] For subjects with AGE, administration of repetitive treatments is recommended until there is no further stepwise improvement, typically after 1-2 sessions, but occasionally up to 5-10.[23] As concerning DCS, in most cases a single treatment is enough to resolve the episode while for patients with residual symptoms after initial recompression, additional sessions are required to obtain a clinical stability.[24] Recently, an inflammatory mechanism has been proposed in DCI, in addition to the mechanical ones. In this contest, HBOT may play a key role in DCI symptoms resolution for its ant inflammatory properties to inhibit pro-inflammatory cytokines including IL-1β, IL-6 and IL-8.[25]

Carbon monoxide poisoning

Carbon monoxide (CO) poisoning occurs when enough CO is inhaled to develop symptoms that include headache, nausea, vomiting, lethargy, dizziness, slowed thinking, shortness of breath, and chest pain.25 CO primarily binds with hemoglobin (Hb) to form carboxyhemoglobin (COHb) preventing the blood from carrying O_2 and expelling CO_2 as carbaminohemoglobin (CO_2Hb). CO poisoning leads to neural cell death suggesting an energy due to reduced Adenosine Triphosphate (ATP) production and oxidative stress.[26] CO acts as double face molecule for its role as signaling molecule that regulates several functions in cardiovascular system. On the other hand, an overproduction of free radicals and high CO level seem to alter the signaling pathways of ROS and CO in neurons that also may contribute to the development of neurological disorders.[27] Furthermore, CO poisoning increases platelet activation trough the reaction of NO with superoxide anion (O_2^{2-}) to lead to peroxynitrite ($ONOO^-$) formation. Activated platelets promote neutrophil adhesion to degranulate and release Myeloperoxidase (MPO). MPO exacerbates the inflammatory effects by triggering further neutrophil activation, adhesion, and degranulation.

HBOT increases COHb dissociation rate respect to normobaric O_2 ameliorating Central Nervous System (CNS) injuries trough improvement in mitochondrial functions, inhibition of lipid peroxidation, reduction of leukocyte adhesion to damaged vasculature and reduction in brain inflammation.[28]

Reperfusion-reoxygenation injury

Ischemia/Reperfusion (I/R) injury of ischemic-hypoxic organs may cause damage in different pathologies including pancreatitis, sepsis, intestinal ulcer, soft tissue crush injuries, myocardial ischemia, and stroke or after cardiopulmonary bypass surgery.[29] Lung injuries occur during the reperfusion phase suggesting the release of several mediators including neutrophils that, activated by TNFα, mediate lung injury trough capillary obstruction, adhesion to

endothelial cells, ROS release and protease. As reported by Yang *et al.* in a mice model of intestinal ischemia-related injury, HBOT administered during artery ligation led to significantly lower TNF-α and IL-1β release; neutrophil sequestration in mice lungs was as well significantly lower in the HBO_2 treated group.[30] TNFα reduction after HBOT is attributable to the improved tissue oxygenation while neutrophils activation is inhibited administrating HBO_2 during either ischemia or reperfusion period and deregulating intercellular adhesion molecule-1.[31] HBOT benefits include also high energy compound preservation, reduction of ischemic-hypoxic related lipid peroxidation, and decrease of sequestration in reperfused tissues. In an indomethacin-induced enteropathy model, a significant reduction in TNF-α and IL-1β levels was obtained in HBO_2 treated rats; the cause of improved inflammation however has still to be determined, since it is not clear if TNF-α and IL-1β inhibition plays a secondary role in reducing

Table 1. *HBOT therapeutic indications for the treatment of the above-described pathologies.*

Disease	**HBOT therapeutic indication**	**N° of HBO_2 sessions**	**HBOT guidelines**
Decompression Illness (Arterial Gas embolism and Decompression Sickness)	Table 5 (US Navy) at 1.9-2.8 ATA Table 6 (Us Navy) at 2.82 ATA Table 7 (U.S. Navy) at 1.12-2.8 ATA	1-2 (Occasionally 5-10)	U.S. Navy Manual and Hyperbaric Oxygen Therapy Indications, 14th Edition
Carbon Monoxide Poisoning	Mild intoxication: 2.5 ATA for 90 min without air break Severe intoxication: 2.5-2.8 ATA for 113 min without air break	1-3 (first session within 24 h) Additional treatments are related to cognition alterations	Hyperbaric Oxygen Therapy Indications, 14th Edition
Ischemia/Reperfusion (I/R) injury*:			Undersea and Hyperbaric Medical Society (UHMS)
• Grafts and flaps	2.0-2.5 ATA for 90-120 min	1-2 treatment per day	
• Acute traumatic ischemia		2-2.4 ATA for 90-120 min (first session within 24 h)	1-3 treatment per day
Skin and Soft tissue infections (SSTIs)*:			
• intracranial abscess (ICA)	2.0-2.8 ATA for 60-90 min	2-3 treatment per day.	Hyperbaric Oxygen Therapy Indications, 14th Edition
• Diabetic foot ulcer (Wagner grade ≥3)	2.0-2.5 ATA for 90-120 min	Up to 30-40 treatment.	
• Necrotizing soft tissue infection (NSTI), type I	3 ATA for 90 min t.i.d. day 1-2	1-3 treatment per day (day1-2)	
	3 ATA for 90 min b.i.d. day 2-3	1-2 treatment per day (day 3-4)	
	3 ATA for 90 min once daily until stable	1 treatment per day until stable (Up to 30 sessions)	
Osteonecrosis	2.2 ATA for 112 min	Up to 40 sessions	Hyperbaric Oxygen Therapy Indications, 15th Edition
Sensorineural Hearing Loss (SNHL)	2.0-2.5 ATA for 90 min	1 treatment per day (up to 10-20 sessions)	Hyperbaric Oxygen Therapy Indications, 14th Edition

**The optimal number of HBOT session is unknown, strongly related to patient reactivity.*

inflammation.[32] HBOT shows also immunosuppressive properties blocking erythrocyte-specific B and helper T cell release and inhibiting immunoglobulin production of NZB and MRL/lpr spleen cells.

As demonstrated in a rat model of tourniquet-induced I/R skeletal muscle injury, those receiving HBO_2 in the last hour of ischemia had lower levels of lactate and glycerol, without any effect on glucose levels.[33] Glycerol is the final product of phospholipid degradation and has been supposed to be a biomarker of ischemic damage. HBOT reduces I/R glycerol concentration but it remains controversial if the glycerol rise is related to the glycolytic pathway or cell membrane damage.[33] Lactate release during ischemia, associated with K increase, may contribute to organ damage. Repeated HBO_2 sessions can stimulate aerobic metabolism increasing ATP production and reducing circulating lactate level. Glutamate is a contributing factor to the development of brain I/R injury that enhances ROS generation such as hydroxyl radical (•OH).[34]

HBO_2has been studied also in models of brain I/R injury. For example, HBOT inhibits dopamine release avoiding its reaction with O_2 and •OH to block the formation of the dopaminergic neurotoxin 6-hydroxydopamine. In a rat model of I/R brain injury, after a 30 minutes long occlusion of the middle cerebral artery, glutamate and hydroxyl radicals in the striatum peaked remained elevated during the reperfusion period in non-treated animals, whilst this rise was significantly attenuated in HBO_2-treated rats; HBO_2 seems therefore to reduce glutamate release and •OH generation contributing to protect nervous tissue.[35] Low ATP production and Na^+K^+ATPase activity during ischemia can be ameliorated by HBOT to supply enough O_2 to brain tissue, improving energy metabolism therefore reducing glutamate accumulation. The capacity of HBO_2 to reduce •OH formation may be related to inhibition of dopamine accumulation, believed to play a key role in ROS generation.

Antioxidant enzymes, such as Catalase (CAT) and Superoxide Dismutase (SOD), activity is essential in I/R injury prevention as observed investigating their scavenging ability in I/R injured muscle. HBOT-related SOD and CAT activity in muscle I/Ris controversial, probably depending on fiO_2 and muscle type. While Gregorevic *et al.* observed a reduction of CAT activity and an increase of that of SOD,[36] Bosco *et al.* found an increase of CAT activity that seems to reflect the activation of antioxidant defenses against ROS/RNS.[33] Furthermore, HBO_2 is able to prevent lipid peroxidation following by decrease of CAT and SOD. After I/R, HBO_2 exposure reduces CAT expression as consequence of decreased membrane lipid peroxidation, evidenced by decreased malondialdehyde (MDA) concentration.[33]

Skin and soft tissue infections

Soft Tissue Infections (SSTIs) involve skin, subcutaneous fat, fascial layers, and musculotendinous structures[37] with manifestations that can range from mild to severe. Mild infections are localized at the level of the skin and the underlying tissues and include cellulitis, erysipelas, impetigo, ecthyma, folliculitis, furuncles, carbuncles and trauma-related infections. Severe SSTIs involve deep tissues and include deep abscesses, diabetes foot and decubitus ulcers, Necrotizing Fasciitis (NSTI), Fournier gangrene. SSTIs are typically caused by *Staphylococcus aureus* and *Streptococcus pyogenes* while *S. aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* are the predominant pathogens isolated from hospitalized patients with SSTIs.[38]

A severe type of deep abscesses is the Intracranial Abscess (ICA), derived by infections such as sinusitis, otitis, mastoiditis, or dental infection, hematogenous seeding and cranial trauma.[39] In addition to surgery and antibiotic treatment, HBOT may confer several benefits (Figure 2). High fiO_2 value can inhibit the growth of anaerobic pathogens and the neutrophil-mediated phagocytosis of infecting organisms.[39] Furthermore, HBOT seems to promote the metabolic environment of acidosis and low oxidation-reduction potential enhancing the activity against pathogen organism and favoring the O_2-dependent active transport of some antibiotic trough the bacterial wall.

Diabetic foot ulcer is a lesion of skin and deeper tissues of the foot that leads to sore formation, representing the major complication of diabetes mellitus that prevents a regular transport of glucose into cells to avoid hyperglycemia. Hyperglycemia leads to an excess of ROS generation, especially O_2^{2-}, that inhibits NO production, resulting in vasoconstriction and hypoxia. Furthermore, hyperglycemia induces thickening of capillary membranes, reducing O_2 diffusion to surrounding tissue, decreasing endothelial NO Synthase (eNOS) activity and HIF-1 release. Diabetic chronic wounds promote the infiltration/accumulation of immune and pro-inflammatory cells such as polymorphonuclear neutrophils and macrophages. Macrophage become hyperpolarized exhibiting an altered clearance associated to the he dysregulation of the cell membrane protein Selectin P Ligand (SELPLG), resulting in the release of pro-inflammatory molecules. The hyperglycemia induces an upregulation of α-defensin proteins promoting IL-8 expression and enhancing the recruitment of immune system cells followed by the release of other pro-inflammatory cytokines and chemokines.

HBOT delivers O_2 in injured tissues[40] promoting neovascularization and collagen deposition at the site of hypoxic tissues reversing hypoxia caused by diabetes mellitus and stimulating several growth factors including VEGF, basic Fibroblast Growth Factor (FGF), Transforming Growth Factor beta-1 (TGF-β), NO, and Platelet Derived Growth Factor (PDGF).[41] Furthermore, HBOT induces the mobilization of endothelial SPCs through eNOS increasing NO availability.[41] HBOT reduces expression of inflammatory cytokines including IL-1 and IL-2, increasing angiogenesis, reducing the metalloproteinase expression, and promoting both antibiotic and leucocyte function against pathogens.[5]

The worst type of SSTIs is represented by NSTI, also known as necrotizing fasciitis, a bacterial fast-progressing and life-threatening disease characterized by widespread necrosis in the soft-tissue compartment. NSTI is often accompanied by systemic toxicity due to severe inflammatory response syndrome which may progress to hemodynamic instability, septic shock, multiple organ failure, and death. NSTI may evolve in a clinical picture in which an intense inflammatory response leads to an excessive platelets acti-

vation resulting in endothelial damage, vascular occlusion, and widespread necrosis in the deep tissues.

During infections, activation of neutrophils and inflammatory molecules, induced by shock-related I/R leads to in increased production of free radicals, resulting in increased oxidative stress. HBOT is an auxiliary intervention to standard care in NSTI due to its antimicrobial properties, modulating oxidative stress trough the release of ROS and RNS[42] that seem to be effective against various pathogens. In NSTI patients, HBO_2 diminishes the presence of tissue edema and hypoxia at infection site, promoting ROS generation that can react with bacterial DNA and macromolecules resulting in lethal cell effects. Some authors found an increase of MPO and SOD after HBOT session in subjects with NSTI suggesting an immunomodulatory action of HBO_2 by oxidative stress induction and consequent antioxidant defense reaction.[43] Oxidative stress seems to play a crucial role for MPO release from immune cells and O_2^{2-} as MPO substrate to promote pathogen elimination by neutrophils. Furthermore, heme oxygenase-1 (HO-1) activity is fundamental against bacterial infection and HBO_2 treatment increases HO-1 expression stimulating endogenous anti-inflammatory cytokines and antioxidant defenses.[44]

Similarly, to oxidative stress markers,[43] high levels of inflammatory markers are associated with disease severity and mortality. In severe septic shock patients, IL□1β, IL□6 and Granulocyte Colony-Stimulating Factor (G-CSF) have been proposed as indicators to predict early mortality, while IL-6 and G-CSF are indicated as potential predictors of organ dysfunction deterioration, suggesting a pivotal role of IL-1β, IL-6, and IL-10 in sepsis onset. Some authors observed that IL-1β, IL-6, IL-10, and IL-18 seem to play a key role in NSTI pathophysiology,[45] suggesting an excessive pro inflammatory response during severe infection triggered by toxin production and cytokines cascade activation. In presence of septic shock, this intense cytokine release can damage the endothelium, leading to a Systemic Inflammatory Response Syndrome (SIRS) and resulting in a multiple organ failure and elevated mortality.[46] HBOT seems to have regulatory properties on the IL-1β expression during infectionand to stimulate immune-modulatory activities including IL-10 modulation in animal model, depending on timing and dosage.[47] In patients with Group A-StreptococcusNSTI, HBOT may induce immunomodulatory effects by reducing G-CSF and IL-6 levels. In the case of septic shock, it seems endothelial layer could play a crucial role

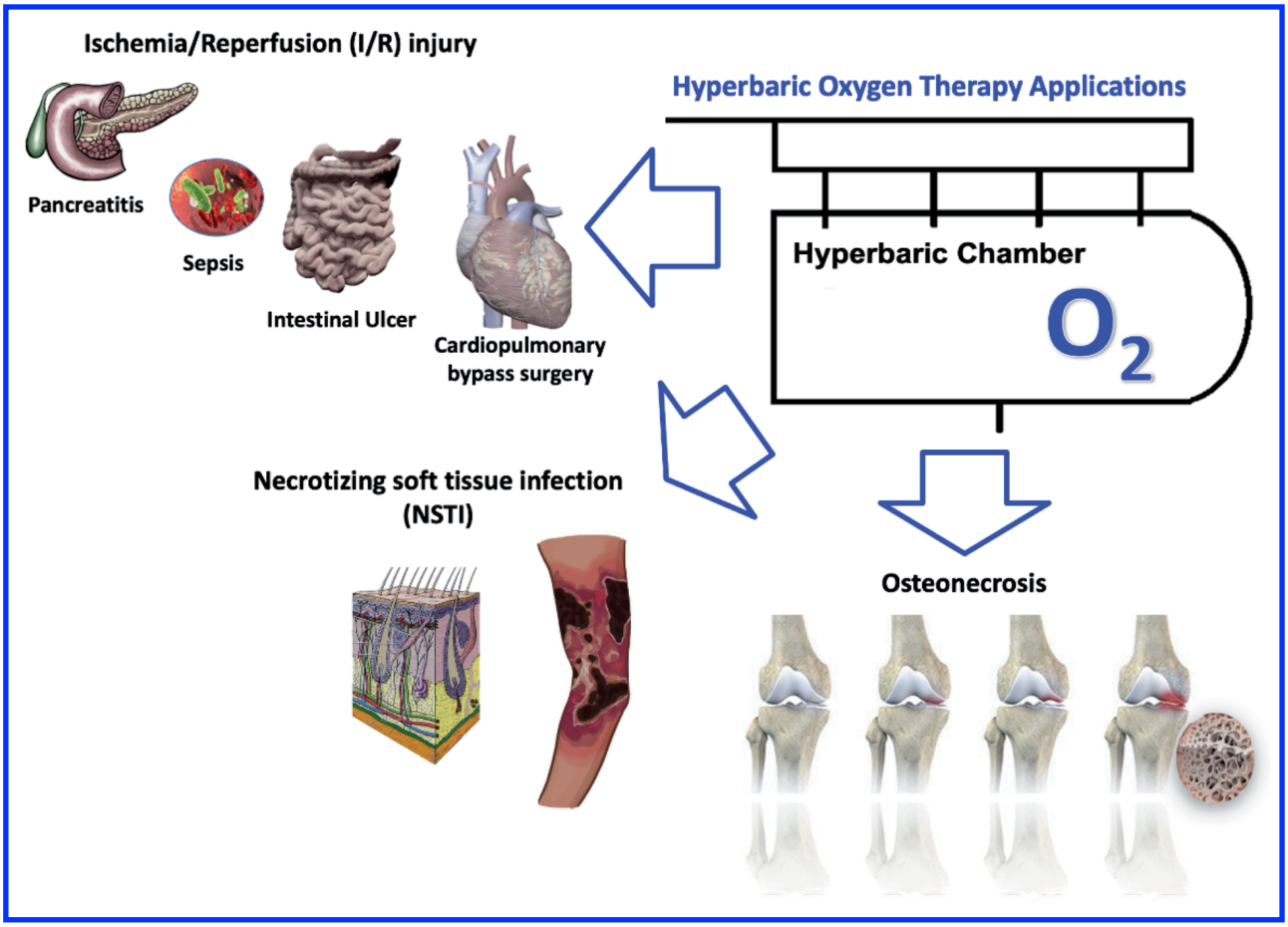

Figure 2. *Hyperbaric Oxygen therapy (HBOT) is an adjuvant treatment in various conditions: ischemic/reperfusion, necrotizing soft tissue infection, compartment syndrome and orthopedic.*

due to adhesion molecule expression on the endothelium and leukocyte that trigger a cascade reaction with the release of immune cells to the endothelium layer. Among these molecules, soluble intercellular adhesion molecule-1 (sICAM-1), a known marker of endothelial activation, may be correlated to sepsis severity, organ function alterations and patient mortality.[48] sICAM-1 may act trough a regulatory mechanism to reduce inflammation giving protection from damage caused by excessive inflammation response. Release of sICAM-1 by Neutrophil Elastase (NE) and A disintegrin and metalloproteinase domain 17 (ADAM17) seems to reduce leukocyte adhesion to endothelium surface. This mechanism is combined with the sICAM-1activity as potential competitive antagonist to residual endothelial ICAM-1 by binding to its ligands on the leukocyte surface. HBO_2 immunomodulatory effects increase sICAM-1 in NSTI patients with NSTI and septic shock respect to the non-septic shock patients,[49] leading to an improved survival rate of subject with severe illness. Furthermore, O_2 modulates ADAM17 when ROS increase activity of NE and ADAM17 and this might be a possible usefulness of HBO_2 treatment to improve survival in NSTI patients, exploiting its immunomodulatory effects. HBOT seems therefore to reduce the risk of amputation in patients with NSTI in patients with limb localization and reduces the mortality in subjects with Fournier gangrene.[50]

Osteonecrosis

Avascular necrosis (AV), known also as osteonecrosis, is a pathologic process that results from the death of bone tissue due to the interruption of blood supply.[51] The most common type is the Avascular necrosis of the Femoral Head (AVFH), associated to ischemic process and other mechanism including oxidative stress, blood coagulation and cell death. Other sites at AV risk are femoral condyles, head of the humerus, and the proximal regions of the talus and scaphoid bone. These areas located farthest from the bone's blood supply and are covered by cartilage, which limits their exposure to nearby blood vessels, making them susceptible to ischemic necrosis.[52] AVFH may be a consequence of an altered bone remodeling, in which Osteoprotegerin (OPG), the Receptor Activator of NF-kB Ligand (RANKL), and the Receptor Activator of NF-kB (RANK) system play a key role. RANK, a transmembrane protein present on osteoclasts and their hematopoietic precursor cells (circulating monocytes), binds to RANKL stimulating osteoclast differentiation, activation and enhancing their adherence to bone surfaces. Then, RANK initiates intracellular signaling pathways by recruiting TNF receptor-associated factor 6 (TRAF6), leading to NF-kB activation. OPG, released by osteoblasts, acts to reduce RANKL's interaction with RANK, thereby inhibiting osteoclast genesis and bone resorption.[53] Any perturbation of OPG/RANKL/RANK system may lead to a pathological condition such as degradation and collapse of the femoral head.

HBO_2 has been proposed as adjunctive therapy bone diseases (Figure 2), including AVFH reducing pain symptoms.[52-54] During AVFHat early stages, HBO_2 promotes oxygenation of hypoxic tissues, reducing edema and inducing vasoconstriction. Furthermore, HBO_2 improves ischemic bone cell oxygenation without the need for the energy required for O_2 dissociation from circulating hemoglobin.[52] As reported by Vezzani *et al.*, HBOT upregulates circulating OPG early after initiation of treatment, thus suggesting a reduction in osteoclast activation and formation.[54] Some authors observed mRNA expression of OPG, RANKL and RANK genes were comparable in healthy tissues while most necrotic tissue showed higher and/or very low OPG and RANKL protein levels compared to their respective mRNA, suggesting the existence of a post-translational control especially in the ill tissues.

HBO_2 may enhance healing of necrotic wounds by stimulating angiogenesis, fibroblast proliferation, osteoblast proliferation, and collagen formation[55] and these mechanisms are trigged by modulation of O_2 sensitive transcription factors as well as ROS-mediated signaling pathways themselves.[42] During the early treatments, HBO_2 may enhance endogenous antioxidant defense activity and detoxify capacity improving cell protection against free radical damage.[2] Bosco *et al.* found that HBOT results in an anti-inflammatory action in patients with AVFH decreasing circulating TNF-α, IL-6, and ROS levels.[55] TNF-a together with IL-1 and Il-6 cause a strong activation of osteoclasts and have multiple links with ROS generated through inflammation in AVFH. Such reduction in bone-resorbing cytokines can therefore positively influence the RANK/RANKL pathway modulating osteoclast activation and differentiation andmitigate overall inflammation, leading to beneficial resolution for the patient.[54]

Sensorineural hearing loss

Sensorineural Hearing Loss (SNHL) is an impairment of the structure and/or function of human auditory apparatus characterized by injuries of cochlear Hair Cells (HCs), Spiral Ganglion Neurons (SGNs), auditory transmission pathways and nervous tissue.[56] Other SNHL-associated symptoms include tinnitus, aural fullness, dizziness and vertigo. Oxidative stress is a common cause of several types of SNHL, including age-related, genetic, and ototoxic drug- and noise-induced hearing loss.[57] Indeed, cochlea is susceptible to an excessive ROS production, induced by external factors such as noise or ototoxic drugs, that overwhelm the antioxidant defenses of hair cells, resulting in a cochlear cell degeneration. The alteration of mitochondrial functions triggers the c-Jun N-Terminal Kinase/Mitogen-Activated Protein Kinase (JNK/MAPK) apoptotic pathway in hair cells against oxidative stress.

Furthermore, SNHL may also have a thrombotic origin that leads to the obstruction of cochlea vessels. Under thrombotic conditions, oxidative stress can alter RBC function resulting in a hypercoagulable state and enhancing binding to vascular endothelial cells, improving the susceptibility to SNLH.[58]

Inaddition to cell damage, ROS circulation promotes inflammation trough the production of pro inflammatory cytokines such as IL-1β, IL-6 and TNFα. An excessive noise stimulation increases Blood-Labyrinth Barrier (BLB) resulting in an elevated level of circulating white blood cells, neutrophils, and monocytes and exacerbating the infiltration of inflammatory factors into the cochlea. HBOT is used to

treat patients with SNHL associated with steroid therapy or as salvage therapy. HBOT increase O_2 supply to cochlea, reducing hypoxia, edema and improving body response to infection and ischemia, improving RBC, hematocrit and hemoglobin levels and antioxidant defenses trough the release of SOD.[59]

Conclusions

Hyperbaric Oxygen Therapy (HBOT) is a significant medical intervention that leverages the increased partial pressure of O_2 to treat various acute and chronic conditions. The therapy's mechanisms of action, which include the modulation of ROS and RNS, provide both therapeutic benefits and pose potential risks if not properly managed. HBOT's efficacy in treating conditions such as DCI, carbon monoxide poisoning, I/R injuries, and severe skin and soft tissue infections underscores its versatility and critical role in medical care. Its application ranges from enhancing wound healing and exerting antimicrobial effects to promoting neovascularization and modulating inflammatory responses.
For DCI, HBOT reduces bubble size and improves tissue oxygenation, proving essential for divers and others experiencing rapid decompression. In cases of carbon monoxide poisoning, HBOT accelerates the dissociation of carboxyhemoglobin, reducing neural damage and inflammation. For I/R injuries, the therapy mitigates tissue damage through improved oxygenation, reduced oxidative stress, and modulation of inflammatory cytokines. HBOT's role in treating severe skin and soft tissue infections, particularly in diabetic foot ulcers and necrotizing fasciitis, highlights its antimicrobial properties and ability to enhance tissue repair and immune response. Despite, its broad applications and benefits, HBOT must be administered carefully, considering the potential for oxidative stress and cell damage due to excessive reactive species generation. Proper protocols (Table 1) and trained personnel are essential to maximize benefits and minimize risks. Future research should continue to refine HBOT protocols and expand its therapeutic indications, potentially uncovering new mechanisms and applications that can further benefit patients across various medical fields.

Take messages

Versatile treatment: HBOT is a versatile treatment modality effective in a wide range of medical conditions, including decompression illness, carbon monoxide poisoning, ischemia/reperfusion injuries, and severe skin and soft tissue infections.
Mechanisms of action: The therapy works by increasing the partial pressure of oxygen in tissues, enhancing reactive oxygen and nitrogen species production, which are crucial in pathogen phagocytosis and cellular signaling.
Wound healing and antimicrobial effects: HBOT promotes wound healing and exerts antimicrobial effects by enhancing oxygen delivery to tissues, reducing inflammation, and improving immune response.
Inflammation modulation: The therapy modulates inflammatory responses by inhibiting pro-inflammatory cytokines and promoting anti-inflammatory cytokines, crucial for conditions like necrotizing fasciitis and diabetic foot ulcers.
Neovascularization: HBOT stimulates neovascularization, combining angiogenesis and vasculogenesis, which is vital for tissue repair and regeneration, particularly in hypoxic and ischemic conditions.
Risks and management: While beneficial, HBOT poses risks related to oxidative stress. Proper administration protocols and trained personnel are essential to ensure safety and efficacy, highlighting the need for ongoing research and protocol refinement.

List of abbreviations

ADAM17, A disintegrin and metalloproteinase domain 17
AGE, arterial gas embolism
AP-1, activator protein-1
ATP, adenosine triphosphate
AV, Avascular necrosis
AVFH, avascular necrosis of the femoral head
BBB, blood-brain barrier
BLB, blood-labyrinth barrier
BM-MSCs, bone marrow mesenchymal stem cells
CNS, central nervous system
DCI, decompression illness
DCS, decompression sickness
CAT, catalase
CO, carbon monoxide
COHb, carboxyhemoglobin
CO_2Hb, carbaminohemoglobin
COPD, chronic obstructive pulmonary diseases
eNOS, endothelial NO synthase
FDA, Food and Drug Administration
FGF, fibroblast growth factor
fiO_2, oxygen fraction
G-CSF, granulocyte colony-stimulating factor
HBOT, hyperbaric oxygen therapy
HO-1, heme oxygenase-1
hADSC, human adipose-derived stem cells
Hb, hemoglobin
HIF-1α, hypoxia-inducible factor
hs-CRP, high-sensitivity C-reactive protein
ICA, intracranial abscess
IFN-γ, interferon-γ
IL, interleukin
I/R, ischemia/reperfusion
iNOS, inducible nitric oxide synthase
JNK/MAPK, c-Jun N-terminal kinase/mitogen-activated protein kinase
MDA, malondialdehyde
MPO, myeloperoxidase
NE, neutrophil elastase
NF-κB, nuclear factor kappa B
NK cells, natural killer cells
NO, nitric oxide
NSTI, necrotizing fasciitis
NTT6, US Navy treatment Table 6 (NTT6)
O_2^{2-}, superoxide anion
•OH, hydroxyl radical
$ONOO^-$, peroxinitrite

OPG, osteoprotegerin
OSAS, obstructive sleep apnea syndrome
PDGF, platelet derived growth factor
pO_2, partial oxygen pressure
RANK, NF-kB receptor
RANKL, NF-kB Ligand
RNS, reactive nitrogen species
ROS, reactive oxygen species
SCFs, stem cell factor
SELPLG, cell membrane protein selectin P ligand
sICAM-1, soluble intercellular adhesion molecule-1
SIRS, systemic inflammatory response syndrome
SNHL, sensorineural hearing loss
SOD, superoxide dismutase
SPCs, stem progenitor cells
SSTIs, Soft tissue infections
TGF-β, transforming growth factor beta-1
TNF-α, tumor necrosis factor-α
TRAF6, TNF receptor-associated factor 6
VEGF, vascular endothelial growth factor

Contributions

Conceptualization, AV, SM-S and GB; methodology, AV, SM-S and GB; writing—original draft preparation, AV and AB; writing—review and editing, SM-S, MP, EC and GB; visualization, AB, SM-S, MP, EC and GB; supervision, SM-S and GB. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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