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Hyperbaric oxygen therapy: Antimicrobial mechanisms and clinical application for infections

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) is a treatment procedure that involves breathing 100% O_2 for a certain time and under a certain pressure. HBOT is commonly administrated as a primary or alternative therapy for different diseases such as infections. In this paper, we reviewed the general aspect of HBOT procedures, the mechanisms of antimicrobial effects and the application in the treatment of infections. Parts of the antimicrobial effects of HBOT are believed to result of reactive from the formation of reactive oxygen species (ROS). It is also said that HBOT enhances the antimicrobial effects of the immune system and has an additive or synergistic effect with certain antimicrobial agents. HBOT has been described as a useful procedure for different infections, particularly in deep and chronic infections such as necrotizing fasciitis, osteomyelitis, chronic soft tissue infections, and infective endocarditis. The anti-inflammation property of HBOT has demonstrated that it may play a significant role in decreasing tissue damage and infection expansion. Patients treated by HBOT need carful pre-examination and monitoring. If safety standards are strictly tracked, HBOT can be considered a suitable procedure with an apt rate of complication.

1. Introduction

Antibiotics have decreased the morbidity and mortality rate of microbial infections and are considered a main advancement of modern medicine [1]. Antibiotics have had a remarkable influence on increasing the life span of patients by altering the clinical outcome of bacterial infections. They also play a critical role in the achievement of some advanced therapeutic procedures such as surgery, implant placement, transplantation and chemotherapy. Unfortunately, antibiotic efficacy has decreased over time due to the devolvement of antibiotic resistant pathogens. The resistance phenomenon has been reported in all classes of antibiotics as a result of mutations in microorganisms. Selection pressure from antimicrobial agents offers a competitive circumstance that results in an increase of mutated resistant strains. Recently, the discovery of antibiotics is not easily predicted, and so far resistance has disseminated to all antimicrobial agents, regardless of the chemical features or molecular mechanisms of the antibiotics [2–4]. For better management of the global antimicrobial resistance challenge, a reduction in the amount of antibiotic usage for choice pressure diminution, proficient infection control policy in order to decrease the spread of resistant pathogens, and alternative treatments, is direly needed [4,5]. Hyperbaric oxygen therapy (HBOT) is a treatment procedure that includes the breathing in of 100% O_2 for a set period of time and under a certain pressure. HBOT has been described as either a primary or alternative technique for the treatment of infections. Regarding the increase in antibiotic resistance frequency, the use of HBOT may be effective in the treatment of acute infections caused by antibiotic resistant pathogens [6]. The aim of this study is to give an overview of HBOT antibacterial mechanisms and application complications for the treatment of infections.

2. HBOT procedure

HBOT is a technique in which a patient is exposed to 100% oxygen (O_2) for a determined period of time and a certain pressure, which is higher than atmospheric pressure, in a special monoplace or multiplace chamber. O_2 pressure for HBOT should be at least 1.4 atmosphere absolute (ATA) or higher. In a monoplace chamber, an individual patient

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breathes in directly pressurized 100% O_2. In the multiplace chambers more than one patient, breath pressurized 100% O_2 indirectly by a head hood, mask or endotracheal tube. HBOT should not be confused with tropical O_2 therapy. Tropical O_2 therapy is local delivery of O_2 under pressure to a particular part of the body [7]. Delivering O_2 to the lungs leads to an increased level of circulation and tissue O_2 during HBOT. HBOT is commonly administrated as a primary or alternative therapy of inflammation, carbon monoxide (CO) poisoning, chronic wounds, ischemia and infections [8].

3. Clinical application of HBOT in infections

Currently, there is sufficient evidence to suggest that HBOT offers valuable advantages, either alone or as an adjunct treatment, for patients with infectious diseases. It has been demonstrated that HBOT considerably stimulates the levels of O_2 concentration in blood, which is typically very low at normal atmospheric condition but is enough to provide the primary need for normal tissue. This finding shows the basic mechanism behind the administration of HBOT in patients suffering from CO toxicity and acute anemia [9,10]. During the HBOT procedure, the O_2 pressure in arterial blood can increase to 2000 mmHg, and the high blood-to-tissue oxygen pressure gradient increases the tissue O_2 pressure to 500 mmHg [11,12]. This effect is considered to be valuable for the healing of inflammatory and microcirculatory disorders in ischemic circumstances and the compartment syndrome. HBOT also offers anti-edema effects by vasoconstriction, decreases leucocyte chemotaxis and adhesion, attenuates ischemic-reperfusion damage and suppresses the formation of inflammatory mediators. Moreover, the effects of HBOT on the immune system dependent conditions have been extensively studied. For instance, HBOT has been revealed to inhibit the autoimmune syndrome and the immune reaction in antigens, and has also been described as decreasing circulating lymphocytes and leukocytes and adjust immunology in order to maintain the durability of an allograft [13]. HBOT is reported to improve chronic skin damage healing by inducing angiogenesis. The mechanisms of the beneficial effects of HBOT on vascular endothelium, as the responsible tissue for angiogenesis, has been the subject of several studies. HBOT has been described to induce partial high tensions of O_2 in circulating plasma. This stimulates O_2 dependent collagen matrix formation, which is an essential phase in wound healing [14]. HBOT mat be a useful approach in the treatment of some infections especially in deep and recalcitrant infections such as necrotizing fasciitis, osteomyelitis and chronic soft tissue infections and infective endocarditis [15,16]. The benefit of HBOT for sepsis, urinary tract infections and meningitis are not well known. The most frequent clinical application of HBOT is for several skin soft tissue infection and osteomyelitis infections which are associated with hypoxia, caused by anaerobic and infections due antibiotic resistant bacteria [17,18]. Table 1 is an overview of some clinical studies investigating the application of HBOT for different infections. The results of *in vitro* or animal models is not included in the table.

3.1. Diabetic foot infections

Foot ulcers are frequent complication in diabetic individuals with the incidence as high as 25%. Infections are a common (40%–80%) and costly problem of these ulcers that can increase the risk of morbidity and mortality [19,20]. Diabetic foot infections (DFIs) are commonly polymicrobial infections and both obligate and facultative anaerobic bacterial pathogens were isolated from these infections [19,21]. Several factors can have an effect on wound healing in diabetic patients, including deficiency of fibroblastic function, collagen formation, cellular immune mechanisms, and phagocyte function. Impaired cutaneous oxygenation has been reported by many studies as being the strongest risk factor resulting in amputation of DFIs. Low O_2 pressure and hypoxia have unfavorable effect on the innate function of leukocytes and fibroblasts during inflammatory response and healing [16,22]. HBOT is one of the current options for the treatment of DFIs. The application of HBOT was reported to have considerably increased the frequency of healing in foot ulcers, of diabetic individuals, and decreased the need of amputations and debridement that require surgical equipment. HBOT also decreased the necessity of other expensive and technically more involved surgical procedures, such as skin flaps and grafts. HBOT is a beneficial method for the treatment of non- healing diabetic foot ulcers, because the low cost of HBOT compared to that of surgical procedures, commonly only accessible in a clinical setting, limited complication and toxicity [23]. Chen et al reported that more than 10 sessions of HBOT increased the wound healing rate by 78.3% in diabetic patients [16].

3.2. Necrotizing soft tissue infections

Necrotizing soft tissue infections (NSTIs) are commonly polymicrobial infections caused by the synergistic occurrence of different aerobic or anaerobic, in the most cases gas producing, bacterial pathogens. NSTI development is often fulminant, and although it is uncommon, it can cause a high mortality rate [24,25]. Quick and appropriate diagnosis and treatment can possibly increase the chance of a favorable result [26]. HBOT has been recommended as an adjunctive method in the treatment of NSTIs. However, the use of HBOT in the treatment of NSTIs is controversial; because no prospective controlled study has been available for this life-threatening disorder. Such assessment would be difficult to perform because of the relatively low frequency of disease [27]. Nevertheless, HBOT could be associated with increased survival and organ salvage and should be considered in the case of NSTIs [28]. A retrospective study indicated that in spite of the higher cost and longer hospitalization duration, HBOT significantly reduced the mortality rate of patients with NSTI [27].

3.3. Surgical site infections

Surgical Site Infections (SSIs) are infections affecting either the incision or soft tissue at a surgical site. SSIs are further classified in terms of anatomic location. Despite progress in the infectious control procedure, for example sterilization technique and the use of antimicrobial agents for prophylaxis and advancement of surgical techniques, SSIs have continued to be a postoperative problem. SSIs can increase the costs of hospitalization and prolong the duration of the hospital stay. In addition, they can increase the risk of morbidity and decrease the life quality in patients after surgical procedure [29,30]. SSIs have mono- or polymicrobial etiology caused by both anaerobic and aerobic bacteria [31]. The effects of HBOT on the prevention of deep SSIs in neuromuscular scoliosis operation were studied in a retrospective survey. Pre-surgery HBOT may decrease the incidence of SSIs and promote wound healing in neuromuscular scoliosis operations. HBOT is a harmless and beneficial supplement for the prevention of deep SSIs in complicated spine abnormalities in high risk neuromuscular cases [32]. Partial pressures O_2 and wound tissue O_2 levels have been reported to be associated with oxidative killing of pathogens and have been indicated to prevent SSIs [33]. Decreased local blood and O_2 levels are the factors that stimulate the development of SSIs [32]. In addition to other infection control strategies, HBOT has been recommended for the reduction of SSI incidence, particularly during clean-contaminated operation such as colorectal surgery [33].

3.4. Thermal burns

Burns are injuries of skin and subcutaneous tissues of organs as a result of high temperature, electricity, chemicals or radiation [34]. Severe burns are associated with high rate morbidity and mortality in patients [35]. HBOT increases the levels of O_2 in burned tissues. There are controversial reports of HBOT efficiency in the treatment of burns in animal and clinical studies [35–38]. Brannen et al., in a randomized

Table 1
Overview of some clinical studies investigating the application of HBOT for different infections.

Infections	Study papulation	Treatment sessions	Pressure (ATA)	Exposure Time (min)	Main findings	Ref
Burns	53	based on outcome	2.5	90	All the patients survived	[35]
Burn	40	10	2.5	80	Faster healing, shorter hospitalization	[34]
Brain abscess	41	20 (range, 4–52)	2.5–2.8	25–	Less treatment failures, improved outcome	[111]
SSIs	42	30	2.4	90	Reduce the rate of post-surgical deep infections in complex spine deformity	[32]
SSIs	32	based on outcome	2-3	90	Valuable addition to the armamentarium available to physicians for treating postoperative organ/space sternal SSI	[112]
SSIs	6	based on outcome (28–106)	2.5–2.8	75	Adjuvant treatment to the standard therapy of early postoperative deep infections	[113]
NSTI	48	based on outcome	3	90	Not reduce the mortality rate, number of debridement, hospital duration, or duration of antibiotic use	[114]
NSTI	44	based on outcome	2.8	60	Improved survival and limb salvage	[28]
NSTI	32	based on outcome	2.8	45	Adjuvant treatment, consideration of HBOT should never delay operative therapy	[115]
NSTI	37	based on outcome	2.5	45	The results of this study cast doubt on the suggested advantage of HBO in reducing patient mortality and morbidity when used as adjuvant therapy for NF.	[116]
DFIs	100	based on outcome (20 to 30)	2–3	90	Useful adjunct in the treatment of nonhealing DFIs	[23]
DFIs	42	Group1: < 10 Group 2: > 10	2.5	120	The amputation rate was decreased	[16]
DFIs	94	40	2.5	85	Facilitates healing of chronic DFIs	[117]
DFIs	35	38 ± 8	2.2–2.5	90	Effective in decreasing amputations	[118]
DFIs	28	20	2.5	90	Effective in accelerating the healing rate of nonischemic chronic DFIs	[119]
DFIs	36	20	2.5	90	Healing response in chronic DFIs	[120]
DFIs	38	40–60	2.5	90	Accelerate the rate of healing, reduce the need for amputation	[121]
DFIs	18	30	2.4	90	Valuable adjunct when reconstructive surgery is not possible	[122]
Osteomyelitis	6	30	2.0–2.4	30	Effective following failure of primary therapy of osteomyelitis	[47]
Osteomyelitis	14	30	2.5	120	Effective and safe for chronic refractory osteomyelitis	[123]
Osteomyelitis	1	30	2	–	Early use of HBOT for a compromised host who develops recurrent osteomyelitis	[124]
Osteomyelitis	12	based on clinical outcome	2.5	90	Adjunctive therapy for patients who develop sternal infection and osteomyelitis after cardiothoracic surgery	[125]

ATA: atmospheres absolute, DFIs: Diabetic foot infections, HBOT: Hyperbaric oxygen therapy, NSTI: Necrotizing soft tissue infections, SSIs: Surgical site infections.

prospective study containing 125 burn patients, reported that HBOT has no significant effect on the rate of mortality, number of surgery, and length of hospitalization for the improvement of burn patients [39]. Mean healing times have been reported to be shorter in patients exposed to burn HBOT (mean: 19.7 days versus 43.8 days) [35]. The use of HBOT in conjunction with comprehensive burn management led to the significant control of sepsis in burn patients [40]. Shorter mean healing time and smaller fluid requirements have been reported in patients given HBOT [41]. Prospective studies with a larger number of patients are needed to confirm the role of HBOT in the treatment of extensive thermal burns.

3.5. Osteomyelitis

Osteomyelitis is defined as infections of the bone or marrow by bacterial pathogens. The treatment of osteomyelitis is difficult due to the relative paucity of blood vessels in bone and the fact that antibiotics often do not sufficiently penetrate bone [42]. The chronic osteomyelitis is a form characterized by the persistence of pathogens, mild inflammatory response, and the incidence of necrosis and fistulous tracts in bone tissue. Refractory osteomyelitis is a chronic bone infection that persists or reappears after applicable mediations have been completed. It is also referred to as refractory osteomyelitis when an acute form cannot be treated by confirmed management strategies, including antimicrobial and surgical intervention [43]. Remarkably, increased O_2 levels in the osteomyelitis lesion has been shown after inhalation of 100% O_2 during HBOT [44]. The refractory form of osteomyelitis has low frequency, thus it is more difficult to design randomized controlled trials in order to study the effects of HBOT on this infection [45]. A number of case series and cohort studies suggest that HBOT improves clinical outcomes of osteomyelitis [46–48]. HBOT might increase the effectiveness of refractory form of osteomyelitis treatment by several mechanisms, such as increased neutrophil activity, inhibition of bacterial pathogens, enhanced antibiotic effects, decreased inflammation and enhanced healing mechanism. Inhibition of infection has been shown in 60–85% of patients with chronic, refractory, osteomyelitis after use of HBOT as adjunctive treatment [49].

3.6. HBOT for fungal infections

Recent estimates suggest that more than 3 million people have chronic or invasive fungal infections, causing more than 600,000 deaths every year [50]. Several factors contribute to poor outcomes in the treatment with antifungal drugs, such as modifications in the essential immune status of the patients, underlying primary disorders, time used for infection identification, heterogeneity in virulence characteristics of pathogens, and the condition of the infection site environment [51]. Attractive features of HBOT for severs fungal infections include its common clinical application for different conditions, guaranteed safety, and its noninvasive procedure [50]. Few *in vitro* and *in vivo* studies have demonstrated that HBOT is effective as an antifungal approach against *Aspergillosis* and *Zygomycosis* [52,53]. The reducing effect on biofilm through HBOT has been reported in *Aspergillus fumigatus* colonies in vitro through fungistatic mechanisms. Here, a lack of fungal superoxide dismutase (SOD) genes increased the effect of HBOT on fungal growth inhibition. However, no synergy was detected between HBOT and voriconazole or amphotericin B *in vitro* or *in vivo* with the dosing regimen tested [50]. Hypoxia conditions in the course of fungal infections and the obvious requirement for fungal adaptation to low levels of O_2 for host adaptation and virulence, show that further research on these mechanisms may prove to be clinically valuable. The effects of O_2 on fungal-host interactions might be complex and handling of O_2 concentrations and/or O_2 induced signaling pathways *in vivo* may have both helpful and harmful effects on the outcome of fungal infections [54].Currently, it is unclear how increased levels of O_2 on the inhibition or promotion of fungal growth would affect the antifungal immune

response in an immunocompromised patient and need to further studies. Due to changes in target gene expression, it is speculated that *in vivo* hypoxic conditions unfavorably affect antifungal drug delivery to sites of infection and their usefulness.

4. Antimicrobial effects of HBOT

Due to the hyperoxic conditions induced by HBOT, several physiological and biochemical alterations happen, which stimulate the antimicrobial effects that can increase or improve typical treatment [55]. HBOT is well described as being effective when applied as either a primary or complementary therapy in the treatment of infections. HBOT has bactericidal/bacteriostatic effects against both aerobic, and principally anaerobic, bacteria [56]. HBOT promotes the healing of infections by three main mechanisms including direct bacteriostatic or bactericidal effects, enhancement of the immune systems antimicrobial effects, and additive or synergistic effects with certain antimicrobial agents.

4.1. Direct antimicrobial effect of HBOT

Direct antimicrobial effects of HBOT are believed to be the result of formation of reactive oxygen species (ROS). The term 'ROS' refers to reactive radicals, including superoxide anion (O_2^-), peroxide (O_2^{-2}), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH^{\cdot}$), and hydroxyl (OH^-) ions that are produced continually as alternative metabolites of several cell biological pathways (Fig. 1) [57,58]. The interactions between O_2 and cellular contents, particularly respiratory flavoenzymes, occur in association with ROS formation. Under a certain circumstance (known as oxidative stress), the levels of ROS increase in cells due to a disturbed balance of ROS formation and its degradation [59,60]. HBOT induces oxidative stress and eliminates the desired condition for bacteria that lack antioxidant defense pathways [61]. During oxidative stress, generated $O_2^{\cdot -}$ is catalyzed by superoxide dismutase to H_2O_2 and reduces Fe^{3+} via the Haber-Weiss reaction. H_2O_2 can then oxidize Fe^{2+} by the Fenton reaction to produce $OH^{\cdot}$ and Fe^{3+}, thus it may start a deleterious redox sequence of ROS generation and damage. Since Fe^{2+} is capable of binding to cellular structures, $OH^{\cdot}$ can produce in the vicinity of DNA, proteins, and lipids and as a result, induces its destructive effect. Fe^{2+} has a sequence-specific affinity for interacting with DNA and contributing to the Fenton reaction. The cellular targets for ROS toxic effects are DNA, RNA, proteins and lipids [62,63]. ROS induces antimicrobial activity via a dose-dependent mode of effect [5,6]. DNA is the main target in H_2O_2-depended cytotoxicity over an interaction that damages bases by breaking up the deoxyribose construction. ROS induces physical damage in incorporated or free nucleotides. Additionally, it breaks single or double-stranded DNA in the double helix, which can also be broken by by-products of induced lipid peroxidation by ROS (Fig. 2) [64,65]. The high concentrations of ROS prompts direct damage to lipids. The damaging $OH^{\cdot}$ can trigger peroxidation of lipids and could stimulate the oxidation of poly unsaturated phospholipids in cell membranes, and thus cause a failure in its function [66]. The peroxidation of lipids has been described after phagocytosis of bacteria by neutrophils and ROS induction, however, it is not documented whether it induces bacterial killing [67]. ROS can disrupt the lipid bilayer organization of the cell membrane that may

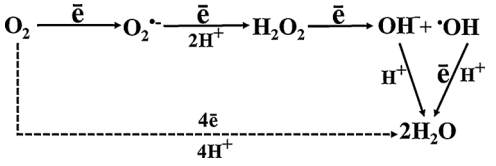

Fig. 1. ROS formation: the consecutive addition of an ē to O_2 is association with ROS formation.

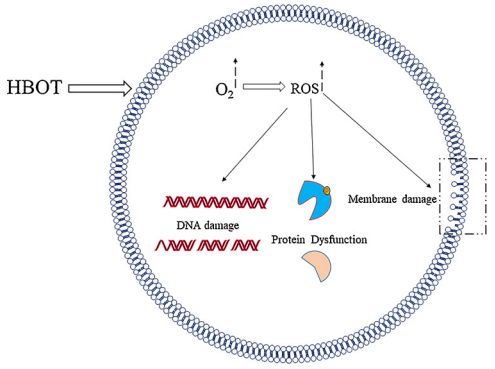

Fig. 2. The inhabitation of microbial growth by ROS formation and biological targets: ROS generation is the antimicrobial mechanism of hyperbaric oxygen therapy (HBOT). The cellular targets for ROS toxic effects are DNA, proteins, and lipids.

disable membrane-located receptors and proteins and can finally lead to cell fluidity, efflux of cytosolic contents and losing of enzyme function [68,69]. Proteins are also a molecular target of ROS. Which can cause damage such as, oxidation of sulfhydryl groups, reduction of disulfides, oxidative adduction of amino acid residues near metal-binding locations through metal-depended oxidation, interaction with aldehydes, modification of prosthetic or metal groups, protein-protein cross-linking and peptide destruction [63]. Proteins can subject different specific oxidative changes at cysteine, methionine, tyrosine, phenylalanine and tryptophan residues. H_2O_2 can induce an oxidative alteration in proteins such as elongation factor G, DnaK, alcohol dehydrogenase E, enolase, OppA, OmpA and the F0F1-ATPase of *E. coli* [67,70].

4.2. Enhancement of the antimicrobial effects of the immune system

There is a significant difference in the description of HBOT effects on mechanisms of the immune system. The anti-inflammation effects of HBOT has been reported to play an important role in reducing tissue damage and infection development. HBOT has considerable effects on the expression of cytokines and other regulators of the inflammatory process. Different alterations of gene expression and protein production have been described after HBOT in different experimental systems. HBOT induces the overexpression and down-expression growth factors and cytokines respectively and subsequently influences the immune responses (Fig. 3). The increased O_2 levels during HBOT is demonstrated to cause some cellular effects such as the suppression of interferon-γ [71], proinflammatory cytokines such as IL-1, IL-6, and TNF-α [72], a transient decrease in the CD^4:CD^8 T cell ratio [73], the reduction of serum soluble IL- 2 receptor (sIL-2R) levels, enhancement of plasma fibronectin (Fn) [74], significant elevation of IL-10 [13], inhibition of the TGFβ-pathway [75] and induction of lymphocyte apoptosis by a mitochondrial pathway [13,76]. Hypoxia is a common consequence of tissue lesions. Although, hypoxia is a stimulator of tissue repair, it increases the chance of infection progression and results in weak healing [49]. Decreased pro-inflammatory cytokine expression and elevated IL-10 expression are effects caused by HBOT that have been demonstrated in animal models of septic shock and ischemia damage [77]. Decreased zymosan-induced expression of toll-like receptor NF-jB signaling pathway and suppression of pro-inflammatory cytokine production during multiple organ failure of animal models were reported during HBOT [78]. Inhibition of TNFα, IFNγ, PGs, IL-1, IL-6 and endothelin release by HBOT may have an influence on the inflammatory response. The healing of infection is a dynamic, well-coordinated and highly regulated procedure which includes several phases such as inflammation, tissue formation, revascularization, and tissue remodeling [79]. Inflammation is an essential process for new tissue generation during

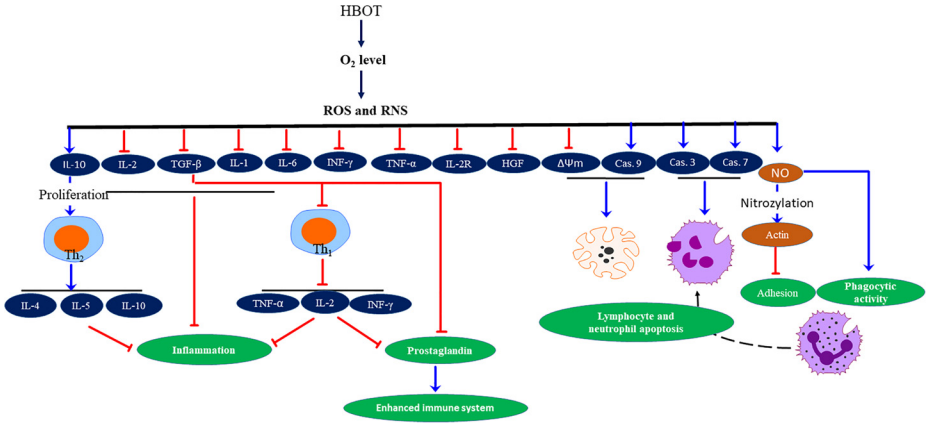

Fig. 3. Enhancement of immune system antimicrobial effects by HBOT: The increased O_2 levels during HBOT cause some cellular effects such as the suppression of proinflammatory mediators, transient decrease in the CD_4:CD_8 T cell ratio, and prompting of lymphocyte and neutrophil apoptosis. In general, these effects can enhance the immune system's antimicrobial mechanisms and infection healing.

infection healing. Some monocyte/macrophage derived mediators may play a useful or detrimental role in the healing of infections. Impaired healing procedure, has been described by excessive inflammation associated with increased levels of TNFα [80,81]. Some studies reported that healing improves by inhibition of excessive TNFα expression [82,83]. However, such inhibition during HBOT could negatively influence host resistance to bacterial infection [84,85]. The precise consequences of such antagonistic crosstalk during HBOT, inflammation, infection healing and the host resistance to bacterial infection remains to be determined experimentally. Generally, the final effects of HBOT on different inflammation mediators, as well as resistance of the host to bacterial infections is not fully described and needs further laboratory and clinical observation. The anti- inflammatory property of HBOT may be due to the downregulation of IFNγ, PGs, TNFα, IL-1, and IL-6 production [85]. The clearance of neutrophils from infected tissue is critical for the resolution of inflammation which happens via apoptosis [8]. The O_2 level of the environment is a critical factor for the antibacterial activity of neutrophils. The bactericidal mechanism promotes potential respiratory bursts achieved via the production of superoxide radicals which needs large amounts of O_2 [86]. There is a significant increase in O_2 needed and consumption quantity during respiratory burst in infectious tissues. The induction of ROS formation and thus the antibacterial effect is depended on the local O_2 partial pressure. This procedure, which is certainly the most essential defense mechanism against invading pathogens, is not effective under hypoxic circumstances. In addition, studies have reported that the pathogen burden in infectious tissues reduces consistently as O_2 pressure is elevated. A single 90 min pre-treatment with HBOT induces the respiratory burst activity of neutrophil-like cells and increases phagocytosis of *Staphylococcus aureus* [8]. HBOT has a pro-apoptotic effect on neutrophils due to the induction of caspase 3/7 activity and morphological changes related to apoptosis. Both hyperoxia and pressure have been reported to contribute to the HBOT-induced promotion of antimicrobial activity and apoptosis of neutrophils by a non- consistent pattern [8]. Increased O_2 after HBOT evidently increases bacterial killing capability of neutrophils. HBOT inhibits the adhesion of neutrophil. The adhesion of neutrophil is mediated by beta-integrin interaction with intercellular adhesion molecules (ICAM) on the endothelial surface. HBOT suppresses neutrophil beta-2 integrin (Mac-1 (CD11b/CD18)) activity by a nitric oxide (NO) mediated process and neutrophil counter ligand ICAM-1 on vascular endothelium [87,88]. This may be helpful in permitting neutrophil migration to the site of infections [49]. Inhibition of neutrophil beta-2 integrin is mediated via nitrosylation of actin, which is finally associated with HBOT induced increase in NO formation [8,89]. Phagocytosis of pathogens by neutrophils need a precise rearrangement of the actin cytoskeleton. The nitrosylation of actin was shown to stimulate the polymerization of actin. Therefore, it is believed that this could be the reason for the promotion of phagocytic activity of neutrophil subsequent HBOT pre-treatment [8]. HBOT prompts apoptosis in the human Jurkat T-cell line by a mitochondrial pathway. Induction accelerated lymphocyte cell death has been reported after HBOT exposure via mitochondrial pathways. The inhibition of caspase-9, but not caspase-8, has been proven to block apoptosis induction by HBOT. These results show the immunomodulatory effect of HBOT [76].

4.3. Synergistic effect with certain antimicrobial agents

In the clinical setting, HBOT is commonly administered in combination with antibiotic therapy in the treatment of an infection. Therefore, hyperoxia induction during HBOT may affect the activity of antibiotics [90]. It has been revealed that some bactericidal agents such as β-lactams, quinolones and aminoglycosides partly depend on bacterial aerobic metabolism in addition to their target-specific effects. Therefore, the efficiency of these drugs is influenced by the presence of O_2 and the metabolic character of the pathogens [15]. The potential *in vivo* O_2 concentration in the infectious tissues and its effect on antibiotic sensitivity of the pathogens are the key factors when setting susceptibility cutoff points for assessing the therapeutic property of an antimicrobial agent. It has been reported that low levels of O_2 increase the resistance of *Pseudomonas aeruginosa* strains to piperacillin/tazobactam and *Klebsiella pneumoniae* strains to azithromycin. By contrast, some bacteria become more susceptible to tetracycline agents in the presence of low levels of O_2 [91]. The aim of HBOT, as an alternative treatment, is to induce the aerobic metabolism of bacteria and to reoxygenate the O_2-depleted infectious tissues and therefore increase the microbial susceptibility to antibiotics [15]. Bacteria exposed to HBOT and simultaneously treated with antimicrobial agents exhibited significant changes in the cytoplasmic structure morphology; such as deformation and disorganization [92]. HBOT promotes aerobic metabolism leading to enhanced induction of ROS production in bacteria [15,93]. The administration of adjunctive HBOT twice a day with an 8 h' interval (280 kPa (2.8 bar) for 114 min) in combination with subcutaneous tobramycin (20 mg/kg/day) has shown a decrease in the bacterial load in *Staphylococcus aureus* infective endocarditis. Results have also shown decreased inflammatory reactions in rat models that indicate the potential effect of HBOT as an adjunctive therapy of *S. aureus* infective endocarditis [15]. HBOT (under the pressure of 3 ATA at 37 °C for 5 h) increased the effects of imipenem on *P. aeruginosa* infections of macrophages [92]. The combination of HBOT and cefazolin have shown to be more effective than cefazolin alone in the treatment of osteomyelitis caused by *S. aureus* in animal models [94]. HBOT, by re-oxygenation of biofilm, can considerably increase the bactericidal effect of ciprofloxacin on *P. aeruginosa* after 90 min of exposure. The combination of ciprofloxacin and HBOT therefore may potentially improve the eradication of *P. aeruginosa* biofilm in infectious tissue [95]. The enhanced bactericidal effect on *P. aeruginosa* biofilm of ciprofloxacin by HBOT is in part contributed by endogenous ROS formation as indicated by the higher susceptibility of a catalase-deficient mutant [96]. Significant

effect increases of vancomycin, teicoplanin, and linezolid in combination with HBOT have been reported against methicillin-resistant *Staphylococcus aureus* (MRSA) in an animal model mediastinitis [90]. Metronidazole is an antimicrobial agent that has been used for many years in the treatment of anaerobic and polymicrobial infection such as diabetic foot infections (DFIs) and surgical site infections (SSIs) [97,98]. The reduced form of metronidazole is effective against bacteria in an anaerobic circumstance [97]. The effect of HBOT in combination with metronidazole should be studied in the future through *in vitro* and *in vivo* studies.

5. The bactericidal effect of hyperbaric oxygen on antibiotic resistant isolates

Antimicrobial drugs tend to lose their effect over time due to the development and spreading of antibiotic resistant bacterial pathogens [3,99]. HBOT may be suitable for the treatment and prevention of multi-drug resistant pathogens and could be considered in cases of antibiotic therapy failure [100]. The bactericidal effect of HBOT against some clinically important drug resistant bacteria were reported. The exposure to HBOT (for 90 min at 2ATM) remarkably decreased the growth of MRSA [101]. HBOT also improved the antibacterial effect of several antimicrobial agents against MRSA infections in the rate model [90]. An obvious effective treatment of OXA-48 type carbapenemase-producing *K. pneumonia* osteomyelitis has been reported using HBOT without any concomitant antibiotics [100].

6. The complication of HBOT

The risks of O_2 toxicity depends on the level and intracellular localization of induced ROS. Due to the fact that exposure to hyperoxia in clinical HBOT procedures is rather brief, studies show that antioxidant responses are sufficient so that biological stresses induced by high levels of ROS are reversible. Induced damage of DNA by ROS appears to play a significant role in the stimulation of mutations and cancer. Under HBOT, the dissolved O_2 in the blood and also the generation of ROS are significant elevated. The exposure to high levels of O_2 may induce destructive effects in humans and it has been hypothesized that the toxic effects of excessive exposure to O_2 are related to an induced generation of ROS. The stimulation of oxidative DNA base injury by HBOT is well known DNA strand damage and oxidative base damage can be detected in peripheral blood, immediately, after a single session of HBOT, which demonstrates an increase in antioxidant defenses. DNA damage is not initiated when HBOT begins but is increases slowly after increased exposure time. To describe the antioxidant defenses after HBOT, exposed blood from subjects before and after HBOT with ROS generating mutagens has been studied and confirmed the premise of protective effects caused by HBOT that are not limited to a particular type of DNA damage [102,103]. This increased protection lasts for several days and in a cellular effect. The biochemical basis of this effect still has to be explained thoroughly but what is known is that antioxidants that scavenge ROS distant from nuclear DNA seem to be involved. The transcriptional response patterns to certain ROS are influenced on a cellular level, and 'classical' antioxidant responses that are promoted by high levels of ROS can be suppressed when cells adapt to low levels of ROS [104]. Assessment of oxidative effects of long-term repetitive HBOT on different brain regions of rats have been assessed by levels of lipid peroxidation and protein oxidation. Activities of superoxide dismutase and glutathione peroxidase have been suggested as an indicator of a strong protective mechanism against the hyperoxic condition, which is an adaptive reply for effective repair mechanisms [103]. This promotes an adaptive mechanism which defends lymphocytes against oxidative DNA damage prompted by a recurrent HBOT or by exposure to H_2O_2. The role of inducible enzyme heme oxygenase-1 (HO-1) has been demonstrated in this adaptive protection [105]. Increased levels of free iron due to HO-1 induction can promote increased levels of cellular ferritin [106]. HBOT- exposed lymphocytes indicate a small but reproducible increase in cellular ferritin, which might suggest that the underlying protective response is established based on the stimulation of ferritin, which may act as antioxidant by inhibiting the formation of the DNA-damaging hydroxyl radical via the Fenton pathway [105]. HBOT often include so-called air breaks, where a patient respires only air for 5 min intervals once or twice throughout the course of the treatment [107]. Perhaps due to the particular atmospheric circumstance to which the individual is exposed, there are concerns about the side effects of HBOT. HBOT is safe if it does not exceed 2 h and the pressure does not exceed 3 ATM [108,109]. Potential side effects during HBOT, experienced most often with therapy of 4 ATA, include; barotrumatic lesions, O_2 toxicity, confinement anxiety and visual effects [109,110]. The main side effects are characterized by the presence of equalization disorder in the middle ear, however, serious complications rarely occur [110]. Patients treated by HBOT require careful pre-examination and monitoring. Absolute contraindications to HBOT include untreated pneumothorax (risk of becoming a tension pneumothorax), restrictive airway disorders (air becomes trapped with decompression and can lead to alveolar rupture with gas expansion), and simultaneous chemotherapy (has associated morbidity) [109]. If safety guidelines are strictly followed, HBOT is an effective modality with an acceptable rate of side effects.

7. Conclusion

HBOT is a primary or alternative option for the treatment of infections. Regarding an increased frequency of antibiotic resistant pathogen, HBOT can be effective in the treatment of acute infections. HBOT promotes the healing of infections by direct bacteriostatic or bactericidal effects, enhancement of immune system antimicrobial effects, and additive or synergistic effects with certain antimicrobial agents. If safety guidelines are strictly followed, HBOT is an effective procedure with an acceptable rate of side effects.

Conflict of interest

There is no conflict of interest.

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