



The Role of Hyperbaric Oxygen Treatment for COVID-19: A Review

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Abstract

The recent coronavirus disease 2019 (COVID-19) pandemic produced high and excessive demands for hospitalizations and equipment with depletion of critical care resources. The results of these extreme therapeutic efforts have been sobering. Further, we are months away from a robust vaccination effort, and current therapies provide limited clinical relief. Therefore, several empirical oxygenation support initiatives have been initiated with intermittent hyperbaric oxygen (HBO) therapy to overcome the unrelenting and progressive hypoxemia during maximum ventilator

support in intubated patients, despite high FiO₂. Overall, few patients have been successfully treated in different locations across the globe. More recently, less severe patients at the edge of impending hypoxemia were exposed to HBO preventing intubation and obtaining the rapid resolution of symptoms. The few case descriptions indicate large variability in protocols and exposure frequency. This summary illustrates the biological mechanisms of action of increased O₂ pressure, hoping to clarify more appropriate protocols and more useful application of HBO in COVID-19 treatment.

Keywords

COVID-19 · Hyperbaric oxygen therapy · Hypoxemia · Inflammation

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1 Introduction

Coronavirus disease 2019 (COVID-19) is a health emergency that is saturating the care and receptive capacities of many national health systems. While most of the patients (up to 81% of the total) do not show any symptom or present with flu-like illness, others can develop severe respiratory compromise and must be hospitalized due to interstitial pneumonia with consequent hypoxia (Wu and McGoogan 2020). Besides, recent works suggest that most

severe cases are characterized by a complex pattern of systemic activation consequent to cytokine storm resulting in immune system impairment and pro-inflammatory imbalance (Mehta et al. 2020).

Given the significant mortality and morbidity associated with COVID-19, the beneficial potential of adjunctive therapies cannot be dismissed. Several treatments, such as antiviral, antimalarial, or immunosuppressant drugs, are tested, as well as hyperbaric oxygen (HBO). To date, evidence of the clinical utility of HBO in COVID-19 is still limited (De Maio and Hightower 2020; Moon and Weaver 2020), but the interest is growing, and at least three trials have been registered online (ChiCTR 2020; US National Library of Medicine 2020). The objective of this article is to review and discuss HBO mechanisms of action and data addressing possible benefits, adverse effects, and potential applications in treating COVID-19 patients.

2 Hyperbaric Oxygen (HBO): Mechanisms of Action

HBO therapy is based on the laws of gas physics related to pressure and involves the intermittent inhalation of 100% oxygen in pressurized chambers. Most studies have involved oxygen administration between 1.5 and 3.0 atmosphere absolute (ATA), a range in which risks of adverse effects are minimized while obtaining therapeutic effects.

HBO increases the partial pressure of oxygen in plasma and tissues (Camporesi and Bosco 2014) and is commonly used in the treatment of decompression sickness, carbon monoxide intoxication, arterial gas embolism, necrotizing soft tissue infections, chronic skin ulcers, severe multiple trauma with ischemia, and ischemic diabetic foot ulcers (Moon 2019; Thom et al. 2011b). The differences and advantages of HBO therapy from atmospheric oxygen absorption are the following: (a) the improvement in diffusion efficiency of oxygen through the alveolar barrier; (b) the higher physically dissolved oxygen content in the blood, more than the combined hemoglobin transport capacity; and (c) the increased diffusion distance

of oxygen. Altogether, these properties meet the demand of aerobic metabolism in hypoperfused regions of the body.

3 Hyperbaric Oxygen (HBO) and Inflammation

HBO has beneficial effects in reducing the inflammatory state by modulating oxidative stress, including lipid peroxidation, and increasing antioxidant enzymes (Thom 2011; Bosco et al. 2007). Accordingly, in animal models, HBO can modulate the inflammatory response and cytokine level (Halbach et al. 2019; Pedoto et al. 2003) or reduce TNF- α production and lung neutrophil sequestration (Yang et al. 2001). Studies in humans have confirmed this experimental evidence concerning the benefit emanating from HBO during different inflammatory states (Bosco et al. 2018; Marmo et al. 2017; Li et al. 2011). In the diabetic patient, whose peripheral arterial vascularization is compromised, HBO is indicated for its ability to increase tissue oxygenation and limit ischemic damage through several mechanisms (Thom et al. 2011a). In the same vein, HBO can improve the perfusion of peripheral systems by reducing the risk of multiple organ failure (MOF) (Bosco et al. 2014; Rinaldi et al. 2011; Yang et al. 2006).

Oxidative stress and reactive species of oxygen (ROS) and nitrogen have complex effects on cell signaling mediators such as HIF-1 α and NK-kB. There are competing pathways that influence levels of these agents in cells, and some evidence exists for a beneficial influence of HBO in certain situations (Bosco et al. 2018). The HIF-1 α and NF-kB cross talk regulates essential inflammatory functions in myeloid cells. HIF-1 α increases macrophage aggregation, invasion, and motility. Whereas HIF-1 α drives the expression of pro-inflammatory cytokines, enhanced microbial clearance can limit the overall production of inflammatory mediators. HIF-1 α enhances intracellular bacterial killing by macrophages and promotes granule protease production and release of nitric oxide (NO) and TNF- α , which in turn further contribute to antimicrobial control. HIF-1 α in myeloid cells

increases the transcription of key glycolytic enzymes, resulting in increased glucose uptake and glycolytic rate. HBO can increase HIF-1 α via an oxidative stress response mediated in part by thioredoxin to increase the recruitment of stem cells. HBO can also increase the activity of iNOS in leukocytes and eNOS in platelets (Thom et al. 2006, 2008, 2011a, 2012).

4 Coronavirus Disease 2019 (COVID-19) Pathogenesis: Between Inflammation and Cytokine Storm

To date, there is no vaccine and no specific antiviral medicine shown to be effective in preventing or treating COVID-19. Those suffering severe illness appear to have higher initial viral load and prolonged viral shedding suggestive of a failure to clear the infection due to an inadequate immune response (Liu et al. 2020b). Based on murine studies and viral shedding and IgG production patterns present in the past severe acute respiratory syndrome (SARS) outbreak due to SARS-CoV-1, lung injuries may arise due to an excessive or aberrant host inflammatory response.

Severe COVID-19 manifests clinically as acute lung injury associated with high initial virus titers, macrophage/neutrophil accumulation in the lungs, and elevated pro-inflammatory serum cytokines (Conti et al. 2020; Kowalewski et al. 2020). During infections, pathogens first encounter the innate immune system that directs anti-pathogen effects and induces adaptive immune responses. One innate inflammatory pathway involves the inflammasome, a multimeric protein complex that is responsible for the activation of caspase-1. Caspase-1, in turn, processes members of the IL-1 family of cytokines into their active forms leading to their secretion. These cytokines, including IL-1 α , IL-1 β , and IL-18, are pro-inflammatory and may induce either protective or damaging host response. IL-1 and IL-18 participate in the control of viral replication. IL-18, through its ability to increase interferon-gamma, seems to have a

strong host pro-survival effect in coronavirus infections (Liu et al. 2020a).

IL-1 α and IL-1 β induce recruitment of neutrophils, polarize T-cells, and promote dendritic cell activation for priming. However, IL-1 β overproduction is linked to a wide range of inflammatory pathologies, including those caused by respiratory viruses (Kim et al. 2015). IL-1 β plays a central role in many inflammatory responses because of its auto-catalytic production and because it can trigger the synthesis of alternative cytokines and other inflammatory agents. Several coronavirus accessory proteins and the envelope (E) protein trigger robust activation of the inflammasome NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3). The E protein is involved in virulence and specifically correlates with enhanced pulmonary damage, edema accumulation, and death. This protein establishes an ion channel in host cells to induce NLRP3 inflammasome activation resulting in overproduction of IL-1 β . The central issue concerning possible effects of HBO pertains to the pathological role of inflammasome activation and, specifically, the role of IL-1 β (Debut and Smadja 2020).

5 Hyperbaric Oxygen Therapy (HBO) and Coronavirus Disease 2019 (COVID-19)

From the clinical standpoint, prediction of arterial oxygenation at increased atmospheric pressure in patients with pulmonary gas exchange impairment can be extrapolated from published clinical data and the application of gas laws (Moon et al. 1987). A few published case series of HBO-treated COVID-19 patients appear to follow similar ratios, reporting improved survival (Guo et al. 2020; UHMS 2020) and success in preventing mechanical ventilation (Thibodeaux et al. 2020). Yet it is still unclear whether the clinical course of those patients, when improved, was due to HBO itself or only time. In the following sections, we will detail possible positive and negative interactions between HBO and COVID-19, as depicted in Fig. 1. According to the

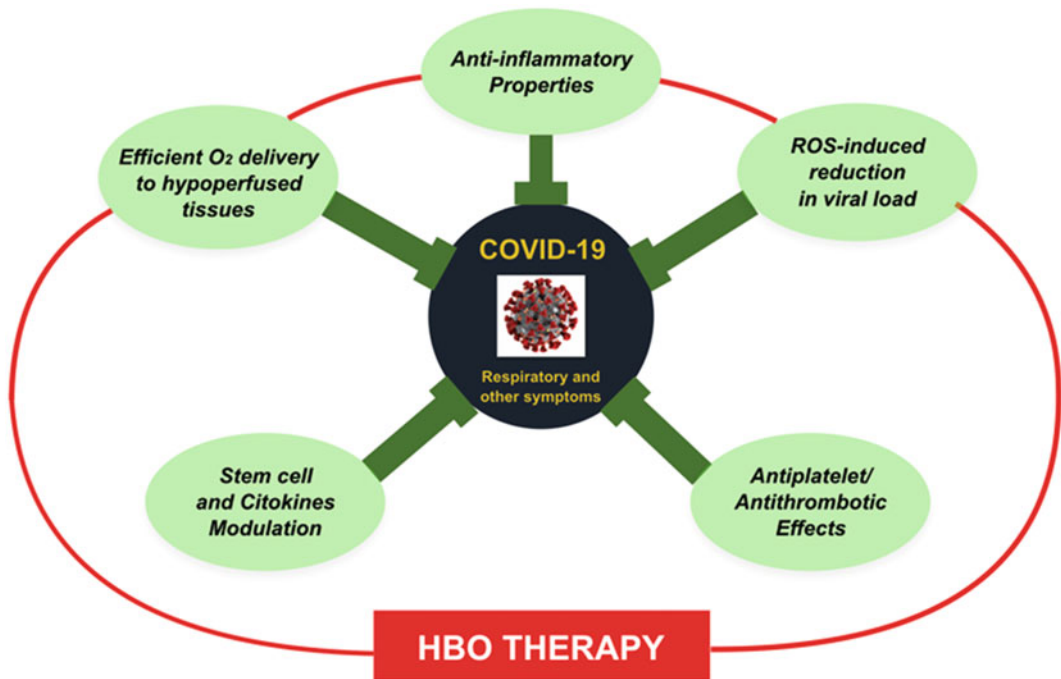


Fig. 1 Possible effects of hyperbaric oxygen (HBO) therapy in coronavirus disease 19 (COVID-19) patients

available literature, the increased amount of oxygen in the plasma could mobilize stem cells, block the inflammatory cascade, interfere with interstitial fibrosis development in the lungs, delay the onset of severe interstitial pneumonia, and reduce the risk of multiple organ failure (MOF) due to an overall abated COVID-19 viral load. However, all these possible effects have yet to be demonstrated and should be weighed on possible harms deriving from the administration of HBO.

6 Hyperbaric Oxygen Therapy (HBO) and Viral Diseases

With data showing the anti-inflammatory potential of HBO, questions have been raised of whether HBO may serve as an adjunct antiviral treatment in patients with viral pneumonia. However, interactions between HBO and viral infections are still poorly understood. Several studies have shown that oxidative stress can play a role in the progression of the HIV disease

(Baugh 2000). It has also been suggested that oxidative stress can contribute to increased viral replication, transcription, or reactivation of latent infection (Peterhans 1997; Pace and Leaf 1995). Nevertheless, previous studies regarding HBO and viral replication reported uncertain effects (Hosokawa et al. 2014; Peng et al. 2012; Savva-Bordalo et al. 2012; Wong et al. 2008; Gabrilovich et al. 1990).

There is consensus in the literature that a viral infection per se does not trigger oxidative stress, while it is the host defense armamentarium that induces ROS to counter viral effects. Viruses use phospholipids and proteins taken from the host membranes to make their capsid (envelop), and ROS avidly react with phospholipids, modifying their structure, thus function. The rationale in using HBO in viral infections could thus be linked to the increased production of ROS. Since a higher viral load is associated with a more severe manifestation of COVID-19, it could be reasonable to test HBO to hamper viral replication and possibly to reduce the viral load, firstly on cultured cells and then on patients

presenting with a moderate but potentially evolving disease.

7 Hyperbaric Oxygen Therapy (HBO), Cytokine Storm, and Stem Cells

Recently, intermittent hyperoxia or different oxygen partial pressures demonstrated to have an impact on stem cell proliferation, cytokine expression, and neuroprotection (MacLaughlin et al. 2019; Schulze et al. 2017; Milovanova et al. 2009). Also, Gardin et al. (2020) have suggested that the exposure of mesenchymal stem cells to HBO in in vitro simulated inflammatory conditions with pro-osteogenic factors increases the differentiation toward the osteogenic phenotype. In severe COVID-19, release of IL-1 beta and IL-6 seems to sustain a pro-inflammatory state, predisposing to pulmonary fibrosis (Conti et al. 2020; Kowalewski et al. 2020). Specifically, IL-6 and IL-8 have been associated with faster progression of pulmonary fibrosis, while IL-10, TGF-beta, IL-4, and IL-13 have not shown statistically significant associations (Papiris et al. 2018). In such an environment, HBO could attenuate the production of pro-inflammatory cytokines, as already described in response to post-surgery inflammation (Bosco et al. 2007) and in modulation of immune responses (Thom 2011). More specifically, a single preoperative HBO session the day before pancreatic surgery demonstrated to alter the inflammatory response, decreasing the pro-inflammatory IL-6 and increasing the anti-inflammatory IL-10 (Bosco et al. 2014). Also, a course of HBO treatments determined a significant reduction in TNF- α and IL-6 plasma levels in patients with avascular femoral necrosis (Bosco et al. 2018). Therefore, HBO could be used in COVID-19 to reduce cytokine levels and to enhance mobilization of stem cells from the bone marrow, especially mesenchymal stem cells, to the most damaged sites (Debut and Smadja 2020).

8 Hyperbaric Oxygen Therapy (HBO) and Other Possible Effects in Coronavirus Disease 19 (COVID-19)

Nitrogen oxide has multiple and fundamental capacities, including vasodilation, reduced platelet activation, and decreased leukocyte adhesion to the endothelium and consequent diapedesis (Bosco et al. 2010; Thom 2009). Breathing oxygen underwater (12-m depths) – a condition like HBO therapy – showed to improve the antioxidant activity of lymphocytes and to preserve calcium homeostasis, suggesting a protective role in the physiological functions of lymphocytic cells (Morabito et al. 2011). Overall, these effects of HBO could counteract several modifications recently demonstrated in COVID-19 patients, such as disturbances of aggregation (Ciceri et al. 2020; Xu et al. 2020a) and coagulation (Lodigiani et al. 2020), and immune system impairment (Giamarellos-Bourboulis et al. 2020). For example, daily treatments with HBO could reduce platelet activation and aggregation in the lungs, thus hampering the development of pulmonary microcirculation dysfunction and catastrophic inflammation already reported in autoptic and pathologic studies (Luo et al. 2020; Xu et al. 2020b).

9 Possible Adverse Effects of Hyperbaric Oxygen Therapy (HBO)

Conventional HBO therapy has several drawbacks. From the logistical standpoint, dedicated large-scale equipment and complex structure are needed to administer HBO. Given the high infectivity of SARS-CoV-2, disinfection measures should be further strengthened, and the attending personnel should follow medical protection guidelines of the European Committee for Hyperbaric Medicine (ECHM) and the European Underwater and Baromedical Society (EUBS) (ECHM- EUBS 2020; UHMS 2020).

The main side effects of HBO are limited to the pulmonary and neurological areas. Pulmonary toxicity usually manifests with tracheobronchial irritation. Oxygen toxicity has been previously reported (Heyboer et al. 2017; Clark et al. 1999; Thorsen et al. 1998; Clark and Lambertsen 1971), but current protocols below 3 ATA minimize this risk. Randomized studies in animal models report damages to the complex phospholipidic system of the lung surfactant, with a consequent increase in alveolar surface tension causing atelectasis and hyperoxic toxicity (Webb et al. 1966). Changes in protein and phospholipid complexes in the surfactant after prolonged periods of oxygen exposure have also been reported (Prokof'ev et al. 1995; Bergren and Beckman 1975). Treatment protocols aimed at limiting O₂ exposure at high ATA have shown that the effect on the surfactant of such exposures is of no clinical relevance (Fife and Piantadosi 1991). Further, it is now consolidated that HBO does not compromise lung function in patients without chronic lung disease (Hadanny et al. 2019), but specific effects on COVID-19 patients are unknown.

Clinical signs of neurological toxicity include visual impairment, tinnitus, nausea, facial spasms, dizziness, and disorientation. In the worst-case scenario, seizures and loss of consciousness may develop, which can be rapidly treated with removal of the oxygen mask and restoration of atmospheric pressure. More recent hyperbaric therapy protocols have allowed overcoming or minimizing these issues, mainly through air respiration pauses, reduction of each session duration (< 2 h), and the use of pressures below the threshold of neural toxicity (US Navy 2008). Other effects, such as those reported on the crystalline lens, are usually reversible over time (Anderson and Farmer 1978). Additionally, adverse effects of HBO seem of smaller concern in case of COVID-19 in the face of rather limited number of patients in whom such therapy could be considered and applied.

10 Conclusions

HBO therapy demonstrates multiple beneficial effects and rare, but preventable, adverse

consequences. Since the pathophysiology of COVID-19 has not yet been clarified, several questions about the potential clinical utility of HBO in treating this infection remain unanswered. We believe that the literature findings summarized in this article provide the practitioners with the necessary evidence to consider HBO as adjunctive treatment for COVID-19. Further, patients should be treated carefully, in hospital-based facilities that can manage the patient transport issues and can provide adequate infection control strategies to ensure safety of healthcare personnel. Through careful monitoring of the patient during the HBO treatment, major side effects could be early detected and avoided. Nevertheless, HBO therapy should be considered carefully, after weighing harms and potential benefits, and it should be tailored to the patient and beforehand verified through a rigorous scientific process.

Acknowledgments We would like to thank Prof. Nazareno Paolocci for his precious iconographic contribution.

Conflicts of Interest All authors declare no conflicts of interest in relation to this article.

Ethical Approval This review article does not contain any studies with human participants or animals directly performed by any of the authors.

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