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Can hyperbaric oxygen safely serve as an anti-inflammatory treatment for COVID-19?

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A B S T R A C T

Introduction: SARS-CoV-2 affects part of the innate immune response and activates an inflammatory cascade stimulating the release of cytokines and chemokines, particularly within the lung. Indeed, the inflammatory response during COVID-19 is likely the cause for the development of acute respiratory distress syndrome (ARDS). Patients with mild symptoms also show significant changes on pulmonary CT-scan suggestive of severe inflammatory involvement.
Hypothesis: The overall hypothesis is that HBO_2 is safe and reduces the inflammatory response in COVID-19 pneumonitis by attenuation of the innate immune system, increase hypoxia tolerance and thereby prevent organ failure and reduce mortality.
Evaluation of the hypothesis: HBO_2 is used in clinical practice to treat inflammatory conditions but has not been scientifically evaluated for COVID-19. Experimental and empirical data suggests that HBO_2 may reduce inflammatory response in COVID-19. However, there are concerns regarding pulmonary safety in patients with pre-existing viral pneumonitis.
Empirical data: Anecdotes from "compassionate use" and two published case reports show promising results.
Consequences of the hypothesis and discussion: Small prospective clinical trials are on the way and we are conducting a randomized clinical trial.

Introduction

SARS-CoV-2 affects part of the innate immune response and activates an inflammatory cascade stimulating the release of cytokines and chemokines, particularly within the lung [1,2]. The export of these factors attracts neutrophils and monocytes to the site of infection, infiltrating the organ. Unfortunately, neutrophils are particularly inefficient in clearing viral infections, and their presence may be more detrimental than beneficial due to the release of a battery of caustic agents directed at killing the pathogen, but they could also damage the surrounding tissue [3]. The destruction of host cells may release subcellular elements that could trigger secondary inflammatory reactions. Thus, SARS-CoV-2 infection activates a robust inflammatory response that if it is not controlled, could result in a "cytokine storm" with detrimental systemic consequences [4]. Indeed, the inflammatory response during COVID-19 is likely the cause for the development of acute respiratory distress syndrome (ARDS) in patients, which is a condition of very low arterial oxygen concentration or hypoxia and bilateral pulmonary opacities [5]. A post-mortem biopsy of pulmonary tissue from a 72-year-old man that died 3 weeks after the onset of symptoms was described as "diffuse alveolar damage, with reactive type II pneumocyte hyperplasia, intra-alveolar fibrinous exudates were present and loose interstitial fibrosis and chronic inflammatory infiltrates" [6]. Even patients that have mild symptoms and survived COVID-19 displayed significant changes on pulmonary CT-scan, with diffuse ground-glass opacities, crazy-paving patterns, and consolidation, suggesting a severe inflammatory involvement [7].

So far, specific treatments have been difficult to advance among more than 160 clinical trials registered since March 2020 [8]. Recently, a double-blind clinical trial using the drug Remdesivir, which was originally developed for the treatment of Ebola virus, showed an improvement in the resolution of severely ill COVID-19 patients, opening a ray of hope [9]. However, a cure for the disease is still yet to come. Several groups are also rapidly working on the development of a possible vaccine, but this endeavour may be months or years away from reality.

Hyperbaric Oxygen (HBO_2) consists of exposure to 100% oxygen under increased atmospheric pressure. This procedure allows the

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delivery of oxygen at high partial pressure reaching tissues rapidly at elevated concentrations. HBO_2 has been used for almost a century, initially for decompression sickness (DCS), but it was soon noted that it had several anti-inflammatory effects [10,11]. HBO_2 is shown to be effective in treatment of radiation injury [12–14] and wound healing [15]. In all cases, HBO_2 has been used with great safety, and with very few adverse effects.

The hypothesis

The overall hypothesis is that HBO_2 is safe and reduces the inflammatory response in COVID-19 pneumonitis by attenuation of the innate immune system, increase hypoxia tolerance and thereby prevent organ failure and reduce mortality.

We propose that HBO_2 could be an early intervention for COVID-19 patients, utilized at the first signs of decline in oxygen blood saturation levels as well as for critically ill patients, A few treatments with HBO_2 has the potential to reduce inflammation, restore normal defence mechanisms and thereby reduce the detrimental effects of oxygen requirement in COVID-19 pneumonitis.

Evaluation of the hypothesis

Recent evidence from animal studies suggest that HBO_2 ameliorate inflammation in Decompression Sickness (DCS) induced Acute lung injury (ALI) through polarization of macrophages from inflammatory macrophage subtype (M1) to resolving or anti-inflammatory sub type (M2) [16,17]. Hyperbaric oxygen has been shown to polarize macrophages from M1 to M2 associated with IL-10 and thereby reduce inflammation [18,19] and 30 min HBO_2 ex vivo inhibit monocyte IL-1β and TNF-α [20]. Interestingly, the switch from M1 to M2 was described in a human study of ALI/ARDS [21].

HBO_2 allows the delivery of oxygen at high partial pressure reaching tissues rapidly at elevated concentrations, which could reverse the hypoxic condition and preserve cellular metabolism [22]. Indeed, HBO_2 has been shown to preserve mitochondrial activity [23]. Moreover, HBO_2 improved kidney function after infection [24], protected organs from ischemia/reperfusion injury [25,26], reduced UV skin damage [27], and avoided kidney damage in diabetic patients [28]. Studies using an experimental animal model of sepsis that is characterized by an overwhelming inflammatory response showed a significant improvement in mortality after a single HBO_2 treatment (2.4 Atmospheres absolute (ATA), 60 min) very early after the initial insult. The improved outcome was correlated to a reduction in inflammation [29]. This observation echoes prior investigations using multiple HBO_2 treatments to improve the outcome of rodent sepsis [18]. Additionally, HBO_2 was reported to reduce bacterial infections [24,30,31] and LPS toxicity [32,33]. HBO_2 has been noticed to display several anti-inflammatory effects [10,11,29], perhaps due to modulation of oxidative stress [34], or a direct effect on the innate immune system [35]. HBO_2 significantly reduces inflammatory cytokines through several transcriptional factors, including Hypoxia Inducible Factor 1 (HIF-1) [36,37] and nuclear factor kappa-light-chain-enhancer of activated B cells

(NFkB) [18–20,38]. Other studies have shown that HBO_2 activates additional transcriptional factors, including Nuclear factor erythroid 2-related factor 2 (Nrf-2) and Heat shock factor 1 (HSF1), that are involved in the expression of several defense proteins [39]. HBO_2 has been evaluated in clinical trials as safe and may be effective for a number of acute inflammatory conditions such as pancreatitis [40], ulcerative colitis flares [41]. There is a wide range of pressures and times used for HBO_2 treatments, with preferences for the use of 1.6 to 2.5 ATA. Anti-inflammatory effects have been observed in conditions of 2 ATA for 60 min in the lung of healthy individuals. Thus, we hypothesize that the "dose" can be estimated as "area under the curve". If the "area under the curve" is representing the dose, 2 ATA for 60 min would be equivalent to 2.4 ATA for 50 min. The chosen protocol for the study aimed to enable inclusion of centres with practices (and hardware) for a range of pressures.

Oxygen is known to have several toxic effects when used for a prolonged time. Toxicity is dose dependent and measured in Units of pulmonary Toxic Dose (UPTD) also called Oxygen Tolerance Unit (OTU); tables for maximal dose is regulated for divers. One UPTD is equivalent of breathing 100% oxygen for 1 min at 1 Bar. Surprisingly UPTD is not recorded in medical practice despite oxygen for medical use is a regulated drug. It is well accepted that oxygen induce toxic changes in the lungs and airways but chronic oxygen toxicity in other organs including immunological effects are less explored [42]. Reversible and non-reversible oxygen toxicity in the eyes are well known side effects of HBO_2 that normally occur after 20–40 HBO_2 treatments [43]. It has been suggested that $Fi0_2$ below 0.5 (50% O_2) is safe but it is known that many factors including viral infections, mechanical ventilation and other drugs can synergistically add to oxygen toxicity[42]. Acute severe toxicity is normally only seen in hyperbaric settings $>$ 200 kPa and include CNS toxicity presenting as blurred vision and in worst case self-limiting seizures [44], occurring in $<$ 1/10.000 treatments. Paradoxically intermittent HBO_2 has also been shown to protect lungs against oxygen toxicity by upregulation of anti-oxidative factors [45,46]. Even though concerns of pulmonary toxicity are theoretical for the proposed treatment duration [47], the extent of COVID-19 pathology is unknown and potential toxic effect of oxygen should be monitored in a randomized clinical trial.

Empirical data

The potential for the use of HBO_2 in the case of COVID-19 was demonstrated by two case reports from Wuhan, China, which showed an improvement in the condition of severely ill patients by increasing blood oxygen saturation levels and reducing lung inflammation [48]. In a recently published case series Louisiana, USA, 5 patients with "impeding intubation" was treated with hyperbaric oxygen, patients symptoms was immediately relieved and they all recovered after 1–6 treatments without intubation and mechanical ventilation [49]. In addition, HBO_2 has been reported to be safe during the use of mechanical ventilation [50].

Consequences of the hypothesis and discussion

Currently, half a dozen new clinical trials are underway in several countries, including case-controlled trials that may generate a rapid information that could be of utility in dealing with the current pandemic. HBO_2 is used on "compassionate grounds" just as other anti-inflammatory drugs such as Chloroquine, cortisone and L-6 inhibitors but randomized trials are absent and/or have been discouraging. Well designed and sufficiently powered randomized trails are needed to confirm safety and efficacy of HBO_2 for both current and future viral respiratory diseases. Hence, we have designed and planned a clinical trial in accordance with ICH-GCP and "the Helsinki Declaration": "Safety and Efficacy of Hyperbaric Oxygen for Improvement of Acute Respiratory Distress Syndrome in Adult Patients With COVID-19; a Randomized, Controlled, Open Label, Multicentre Clinical Trial" (NCT04327505). We have ethical- and competent authority approval, initiated our first center and have included our first few subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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