REVIEW ARTICLE

Physiologic and biochemical rationale for treating COVID-19 patients with hyperbaric oxygen

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ABSTRACT

The SARS-Cov-2 (COVID-19) pandemic remains a major worldwide public health issue. Initially, improved supportive and anti-inflammatory intervention, often employing known drugs or technologies, provided measurable improvement in management. We have recently seen advances in specific therapeutic interventions and in vaccines. Nevertheless, it will be months before most of the world's population can be vaccinated to achieve herd immunity. In the interim, hyperbaric oxygen (HBO_2) treatment offers several potentially beneficial therapeutic effects. Three small published series, one with a propensity-score-matched control group, have demonstrated safety and initial efficacy. Additional anecdotal reports are consistent with these publications. HBO_2 delivers oxygen in extreme conditions of hypoxemia and tissue hypoxia, even in the presence of lung pathology. It provides anti-inflammatory and anti-proinflammatory effects likely to ameliorate the overexuberant immune response common to COVID-19. Unlike steroids, it exerts these effects without immune suppression. One study suggests HBO_2 may reduce the hypercoagulability seen in COVID patients. Also, hyperbaric oxygen offers a likely successful intervention to address the oxygen debt expected to arise from a prolonged period of hypoxemia and tissue hypoxia. To date, 11 studies designed to investigate the impact of HBO_2 on patients infected with SARS-Cov-2 have been posted on *clinicaltrials.gov*. This paper describes the promising physiologic and biochemical effects of hyperbaric oxygen in COVID-19 and potentially in other disorders with similar pathologic mechanisms. ∎

INTRODUCTION

As SARS-CoV-2 infection (COVID-19) rates accelerated in early 2020 many patients deteriorated rapidly, became ventilator-dependent, and died. Clinicians and medical researchers sought to develop strategies to treat and prevent this new worldwide public health threat. Initially they employed existing technologies and medications because no specific therapies were available, and care was mostly supportive. Some inquired about and even recommended hyperbaric oxygen (HBO_2) therapy because of its demonstrated success in providing oxygen and reducing end-organ damage in patients with severe hypoxemia due to carbon monoxide poisoning or severe anemia [1]. These inquiries came as both questions and suggestions addressed to the Undersea and Hyperbaric Medical Society's (UHMS) Medical Frequent Asked Questions (MEDFAQs) program and as telephone contacts to the UHMS Home Office from callers including

KEYWORDS: anti-inflammatory; COVID-19; hyperbaric oxygen; hypercoagulability; hypoxemia; mesenchymal stem cells; oxygen debt; tissue hypoxia

the current President of the American Board of Preventive Medicine (ABPM), who is also a past president of the Aerospace Medical Association and a senior representative of the Office of Naval Research [2].

A publication from China reported dramatic results in five critically ill patients treated with HBO_2 [3]. A second five-patient case series published by Thibodeaux, et al. showed that patients who received hyperbaric oxygen when intubation seemed imminent were able to avoid mechanical ventilation [4]. Gorenstein and colleagues reported a study of 20 patients treated with hyperbaric oxygen compared to propensity score-matched controls. They concluded that HBO_2 is safe and possibly effective [5]. Additional unpublished anecdotal reports aggregating a total 70 patients show impressive and rapid improvement in compromised patients even in the setting of progressive respiratory failure [6-9]. A typical course of hyperbaric oxygen in these series was five daily treatments at 2.0 ATA pressure. Early on, two prominent hyperbaric experts discussed issues related to treating COVID-19 with hyperbaric oxygen and noted that the UHMS position statement recommended treatment only within clinical trials [10].

One author of this document (DD) shared her personal experiences treating 19 COVID-19 patients with hyperbaric oxygen [6], which included transcutaneous oxygen for patient monitoring. These measurements were done during and after hyperbaric treatment and upon returning the patient to the ICU or hospital bed. She observed that transcutaneous oxygen proved useful as a monitoring tool [6], and outcomes were favorable. Two prior publications have reported experiences in applying transcutaneous oxygen measurements as a monitoring tool in critically ill patients [11,12].

The incidence of COVID-19 has continued to increase, with recent post-holiday spikes, which has led to a much-improved understanding of which treatments are effective and which are not. Much of this evolution in treatment has been through using known medications in new applications. The National Institutes of Health (NIH) has published and continuously updates its Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (accessed on 26 December 2020) [13]. This publication provides broad guidance on the management of patients with COVID-19. Specific guidance is given for pharmacologic interventions, and each is assigned a grade for level of evidentiary support. A discussion of hyperbaric oxygen, however, is not included in these guidelines.

The UHMS tasked its Research Committee to develop recommendations and advice for treating COVID-19 with hyperbaric oxygen. This work is an outgrowth of that effort and a product of a research committee enhanced by additional members with special experience, knowledge, or interest. Some of this discussion has been previously posted on the UHMS website. Paganini et al. have also previously discussed the biological mechanisms of action of hyperbaric oxygen and identified potential logistic difficulties and toxicities of treatment [14].

Background and key aspects of COVID pathology and pathophysiology

SARS-CoV-2, which produces COVID-19 infection, is a single-stranded RNA-enveloped virus that causes severe respiratory disease in humans [15,16]. The most common symptoms include fever, cough, muscle aches, fatigue, and dyspnea. Non-pulmonary involvement can include cardiac, neurologic, and renal damage. Non-pulmonary symptoms may also include anosmia, ageusia, abdominal pain, nausea, and diarrhea. Abnormalities characteristically seen on chest imaging of these patients include extensive lung opacities and bilateral infiltrates [17]. Numerous publications have now addressed the characteristic findings for COVID lung pathology, which often result in ARDS (acute respiratory distress syndrome) [18]. An early paper from China reported diffuse alveolar damage (DAD), prominent alveolar edema, proinflammatory concentrates, fibrin deposition within pneumocytes, and pulmonary microthrombi [19]. Li and Ma in June 2020 reported some key differences between COVID-associated ARDS and ARDS caused by other disorders. Notably, they reported the usual onset for COVID ARDS was eight to 12 days after diagnosis, while in other disorders, it characteristically occurs within seven days. They also reported that in COVID-induced ARDS, lung compliance is normal in some patients, which is uncharacteristic in ARDS from other etiologies [20]. An interesting publication by Hariri et al. challenges the concept that the ARDS seen with COVID-19 is pathologically novel and distinctly different from the ARDS that has been shown to occur with SARS (severe acute respiratory syndrome) or H1N1 virus (also known as swine flu) [21]. Their findings demonstrate that the pathologic findings of ARDS in COVID are not substantially different in frequency or severity from those resulting from other viruses, especially SARS, when DAD, acute fibrinous organizing pneumonia (AFOP), organizing fibrosis, superimposed pneumonia, and microthrombi are compared. A review by Bohn and

Table 1: Events leading to the overexuberant immune response in the viral host [15]

Sequences and effects of viral invasion and immune response	Consequences of these effects and immune response
viral invasion at ACE2 receptor	replication and release of virus
early phase immune response	monocytes, macrophages, dendritic cells and sensitized T-lymphocytes act to remove infected cells
vigorous invasion of active immune cells in the lung	systematic overproduction and loss of regulation of proinflammatory and inflammatory cytokines and chemokines including NLRP-3, IL-1β, IL-6, IL-2, IP-10, GM-CSF, IFN-γ, TNFα, M1P1a
extrapulmonary involvement	extrapulmonary organ involvement leads to activation of procoagulant response and multiorgan failure

colleagues of the pathophysiology of COVID infections provides a succinct overview of the pathophysiologic processes involved with disease consequences and progression [15].

The leading cause of death from COVID-19 is respiratory failure from ARDS. A much smaller number succumb to multiorgan failure (MOF) [15,23]. In vitro cell studies show a delayed release of cytokines in respiratory epithelial cells and macrophages in the early stages of infection [23-25]. Later, the cells secrete high levels of proinflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor (TNF), and chemokines CCL-2, CCL-3, and CCL-5 [26-33]. Table 1 shows the sequence of events involved in the major aspects of COVID-19 pathophysiology.

A normal concern for any clinician considering hyperbaric oxygen for COVID-19 patients is the possibility of inducing or increasing pulmonary oxygen toxicity in these patients, some with severe pre-existing lung pathology [34]. Most clinical measures of oxygen toxicity are non-specific (e.g., cough, chest pain, dyspnea, and chest tightness), and these symptoms are likely already present in many patients with COVID-19. Also, most hospitalized patients with COVID-19 are already receiving high levels of and prolonged exposure to normobaric oxygen, which can itself cause oxygen toxicity. Cases treated to date with HBO_2 have not shown evidence of worsened pulmonary status due to the sustained exposure to high oxygen levels either in the chamber or between treatments in the ICU or hospital bed. In fact, the consistently reported response to hyperbaric oxygen has been improved respiration. The presentations by Drs. Thibodeaux, Lee and Gorenstein at a webinar sponsored by the UHMS on July 20, 2020 (*https://www.uhms.org/covid-19-information.html*) were consistent in this observation. The authors (Gorenstein and Thibodeaux) noted that if oxygen toxicity was enhanced by HBO_2, the hyperbaric group would have demonstrated deterioration of their r espiratory status and worsened outcomes. Both Drs. Gorenstein and Thibodeaux confirmed their impression that the hyperbaric-treated patients did not exhibit signs or symptoms of pulmonary oxygen toxicity [35]. The likely reality is that this patient population needs high-dose supplemental oxygen, and HBO_2 therapy accomplishes this exceptionally well without a detectable increase in oxygen toxicity.

Extreme respiratory failure resulting in hypoxemia and tissue hypoxia

The hallmark of serious life-threatening COVID infection is profound hypoxemia and secondary tissue hypoxia due to pneumonia, often bilateral and often leading to ARDS. Some patients with severe hypoxemia cannot be adequately oxygenated in spite of the administration of high fractions of oxygen along with mechanical ventilation. A recent short report sheds additional light on our understanding of the pathophysiology of hypoxemia in COVID patients [36]. This study used intracranial Doppler to detect microbubbles produced by the venous injection of agitated saline in 18 mechanically

ventilated COVID-19 patients. The authors were able to detect bubbles in the cerebral circulation of 83% of these patients and proposed that the dilated pulmonary vasculature in COVID patients leads to shunting of blood through the pulmonary circulation and a failure to filter out these bubbles in the pulmonary capillaries. The same process causes ventilation perfusion (V/Q) mismatch and the failure to oxygenate blood returning to the heart, which leads to systemic hypoxia unresponsive to oxygen administration.

German researchers in a single institution made a retrospective review of 213 patients and reported that 27% of their COVID admissions were given ventilator suport [37]. Of this group, 57% most likely died from refractory respiratory failure. A Chinese group reported that in a similar group of COVID-19 patients, a mortality rate of 50% was seen where patients died of respiratory failure despite mechanical ventilation. They discuss the role of extracorporeal membrane oxygenation (ECMO) as intervention for patients in whom ventilator support is inadequate [38].

Exaggerated immune response with resultant inflammatory response

The upregulation of cytokine and chemokine responses in COVID-19 causes apoptosis of endothelial cells that damages the pulmonary microvascular and alveolar epithelial cell barriers. In turn, vascular leakage and alveolar edema result, eventually followed by hypoxemia and a cytokine storm [39-41]. Much of this early reaction is precipitated by the activity of monocytes, macrophages and sensitized T lymphocytes. Cytokine storm, defined as an excessive immune response to an external triggering event, follows and is thought to be one of the major contributors to the development of ARDS and MOF. COVID-19 activation of transcription factor NF-kappa beta (NF-κB) in macrophages of the lung, liver, kidney, central nervous system, gastrointestinal system, and cardiovascular system, plays a major role in this process. This activation of NF-κB in turn leads to the production of IL-1, IL-2, IL-6, IL-12, tumor necrosis factor alpha (TNF-α), lymphotoxin-alpha (LT-α), lymphotoxin-beta (LT-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), and other chemokines [29]. The rapid increase in cytokines and chemokines attracts large numbers of neutrophils and monocytes, which results in excessive inflammatory infiltration and resultant lung injury. In patients with COVID-19 there are high levels of expression of IL-1β, interferon (IFN), and TNF-α, as well as IL-2R (IL-2 receptors) and IL-6, which positively correlate with disease severity and mortality [31,32]. These cytokines are known to be mediators of the inflammatory response. See Table 1 for a simplified depiction of sequence and involvement of the prominently involved cytokines.

Hypercoagulability

Since the very first cases in the COVID-19 pandemic, hypercoagulability has been recognized as one of the hallmarks of its clinical presentation and consequences [43,44]. It has been a significant cause of death in patients with severe disease [45]. This hypercoagulable state can lead to deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction, and strokes [46]. It is also frequently associated with disseminated intravascular coagulation (DIC), though the characteristic multifocal bleeding that results after the consumption of coagulation factors and platelets typical of DIC has not yet been described in COVID patients [47]. The presence of widespread thrombosis and microangiopathy in pulmonary vessels and microthrombi in alveolar capillaries was a consistent finding in a post-mortem study of deceased COVID-19 patients [48]. This effect most definitely contributes significantly to the respiratory failure pathognomonic of COVID-19.

A retrospective analysis of 99 patients from China demonstrated several abnormalities in coagulation studies [49]. Thirty-six percent of patients had elevated D-dimer levels; 16% showed a reduced activated partial thromboplastin time (APTT); 6% had an increased APTT; 30% had a shortened prothrombin time (PT), while 30% had an extended PT. In contrast, Levi et al. report that the typical findings are a mildly prolonged PT, a rare decrease in platelet count and fibrinogen levels at the upper limits of normal [50]. In both reports, higher D-dimer levels were associated with an increased mortality rate [49,50].

A commentary by Connors and Levy discusses thromboinflammation, the interaction between inflammation and coagulation [51] The inflammatory reaction characterizing the hyperactive immune response of the host patient appears to be the primary source of the hypercoagulative state and is mediated by cytokines, notably IL-6. Mukund and associates have observed that the microvascular events, including activation of the coagulation cascade, are in part driven by complement activation [52]. They also state that plasmin is a crucial mediator that serves to "prime" interactions between

complement and the platelet-activating systems that involve the pulmonary epithelium. They suggest that recognition of this interaction may offer opportunities for therapeutic intervention.

Oxygen debt

The concept of oxygen debt originates from studies in exercise physiology and can be traced back to a classic work by Hill and Lupton in 1923 [53]. Oxygen debt can be thought of as the minimum requirement for tissues to maintain aerobic metabolism minus the oxygen supply available. This oxygen debt continues to accumulate as long as the inadequacy of supply exists. It is typically expressed in liters of oxygen undersupplied per meters squared of body surface area. When oxygen is inadequate to supply the baseline metabolic requirements of tissue, a progressive and cumulative oxygen debt is established.

Oxygen debt has been described in hemorrhagic shock, severe anemia, septic shock, and birth asphyxia [54-56]. One publication from Wuhan, China, discusses the importance of providing adequate oxygen to COVID patients to avoid the accumulation of oxygen debt [57]. There are not large numbers of publications defining and providing guidance for the management of oxygen debt. However, the essential elements for its occurrence exists – i.e., hypoxemia of significant severity and persistence to require that body tissues adopt anaerobic pathways of glycolysis with resultant production of lactic acid.

Body tissues and organs extract on average 5 to 6 mL of oxygen for every 100 mL of blood flow to support their metabolic needs [58]. Some tissues, including the heart, brain and retina, have even higher oxygen requirements. In anemic patients, especially those who become anemic suddenly by virtue of a bleed, reductions of hemoglobin to 6 gm/dL are a usual threshold for critical oxygen debt, and drops in hemoglobin below 3.6 gm/dL are certainly inadequate [58].

Van Meter states that survival is not possible if the oxygen debt exceeds 33 L/m^2. MOF occurs at a debt of $22L/m^2$, whereas those whose debt is no more than $9L/m^2$ typically survive without residual organ dysfunction or injury [58].

Byproducts of this process requiring anaerobic metabolism include lactic acid [59]. Van Hall et al. discuss an increased need for oxygen to clear the excess accumulated lactate. This imposes a need for additional oxygen following successful restoration of adequate levels of oxyhemoglobin. In a review article from 2005 Rixen and Siegel discussed the importance of oxygen debt in determining the severity of hemorrhage and post-traumatic shock. They state that oxygen debt may be a more important determinant of the severity of hemorrhagic shock than estimates of blood loss, volume replacement, blood pressure or heart rate [60].

A prominent feature of COVID-19 is hypoxia secondary to respiratory failure. There are reports in the literature demonstrating COVID-19 patients with severe arterial hypoxemia with no signs or symptoms of respiratory distress or dyspnea. Guan has reported dyspnea in only 18.7% of 1,099 hospitalized COVID-19 patients, despite low PaO_2/FiO_2 (ratio of arterial oxygen tension to fractional inspired oxygen). Eighty-six percent of these patients had abnormal CT scans, and 41% of these patients required supplemental oxygen [60]. This phenomenon has been termed silent or happy hypoxia in the literature [61]. The understanding of the physiology of silent hypoxia continues to evolve in the literature of critical care and respiratory medicine. New mechanisms for this disconnect between objectively measured hypoxemia and subjective perception of breathlessness continue to be discussed. One such mechanism is the presence of a right-to-left intrapulmonary shunt that induces hypoxia [62]. A shift in the oxygen dissociation curve is another factor that may contribute to silent hypoxia. Fever, prominent with COVID-19, causes the curve to shift to the right; any given PaO_2 will be associated with a lower oxygen saturation of arterial blood (SaO_2) [63]. Additionally, the development of microthrombi in the pulmonary vasculature may contribute to this phenomenon [64]. From this silent hypoxia, an oxygen debt can be created due to the prolonged period of hypoxemia. The ability to reverse oxygen debt is an important effect of HBO_2 therapy that has been demonstrated in severe anemia. Although the use of HBO_2 for oxygen debt associated with severe anemia likely differs from COVID-19, further research should be carried out to analyze whether repayment of oxygen debt is a key mechanism for HBO_2 on COVID-19.

Elevated blood lactate likely indicates inadequate oxygenation for which short periods of normal or even hyperoxygenation may be beneficial. On the other hand, tissue hypoxia is an uncommon cause of elevated blood lactate levels (a potential marker of oxygen debt) in sepsis, particularly after adequate initial resuscitation [66,67]. Other sepsis-related reasons for elevated lactate include impaired oxygen use due to mitochondrial

dysfunction, which would not be ameliorated by an increase in oxygen delivery [68] and stress-related increase in glucose metabolism and impaired lactate clearance [66-68], which is not likely to respond to hyperbaric hyperoxemia. Further studies are needed to assess whether the payment of oxygen debt is a key issue and potential target for therapy in the treatment of COVID-19.

Favorable mechanisms offered by hyperbaric oxygen for COVID patients

The acute restoration of adequate oxygen blood and tissue levels

Hyperbaric oxygen is frequently employed in circumstances where hypoxemia or critical organ hypoxia is encountered [1]. These circumstances include severe anemia, air embolism, decompression sickness and carbon monoxide poisoning.

A physiologic advantage of hyperbaric oxygen is enhanced delivery of O_2 not only attached to hemoglobin but also dissolved in plasma. Boerema, an early practitioner of clinical hyperbaric oxygen, demonstrated in an animal model employing piglets that dissolved oxygen in plasma was adequate to support life even when the animals were exsanguinated [69]. In COVID-19 patients the primary cause of hypoxemia is the failure to deliver adequate oxygen across a diseased respiratory membrane. If oxygen successfully crosses over the alveolocapillary membrane, the usual function of hemoglobin oxygen transport should dominate as long as the patient has no defects in hemoglobin amount or function. In two cases where co-author DD measured transcutaneous levels at pressure, their levels exceeded those that would result from 100% saturation of a normal hemoglobin (see the discussion just below) [6].

Weaver [11] has demonstrated the success of transcutaneous monitoring as a surrogate for invasive arterial blood gas sampling. Weaver and colleagues studied patients receiving hyperbaric oxygen who demonstrated a variety of lung pathologies. This study showed that this group of patients could be adequately oxygenated with hyperbaric oxygen, albeit achieving PaO_2 levels lower than patients with normal lung function [70].

Dooley and colleagues established reference values for transcutaneous measurements of oxygen tensions in normal subjects at ground level and at hyperbaric pressures [71]. In this study, an electrode was placed on the anterior chest wall 5 centimeters below the clavicle at the mid-clavicular line. On unenhanced ground-level air this value averaged 67±12mmHg. On 100% oxygen at 1.0 ATA (atmospheres absolute), this value averaged 450±54 mmHg. At 2.4 ATA, the value averaged 1,312± 112 mmHg. A co-author (DD) of this paper [6] treated a small series of patients early in the pandemic and reported excellent response. When she employed transcutaneous monitoring in two patients, she recorded values of 516mmHg and 456mmHg during treatments at 2.0 ATA. These transcutaneous values compare favorably to the ground-level measures by Dooley in normal subjects breathing air and would obviously support normal aerobic metabolism [71].

Reduction of inflammation induced by the exaggerated immune response to COVID

HBO_2 therapy in the treatment of patients is likely to attenuate the production of proinflammatory and inflammatory cytokines which are generated in response to the COVID infection (Table 2). The reduction of inflammatory stimuli by HBO_2 has been demonstrated after exercise, radiation, and surgery [72-74]. Studies have demonstrated that HBO_2 inhibits TNF-α production during intestinal ischemic reperfusion [75]. In indomethacin-induced enteropathy hyperbaric oxygen has been shown to decrease the production of both TNF-α and IL-1β [76]. A randomized pilot study found that a single preoperative HBO_2 session the day before pancreatic surgery modulated the inflammatory response for cytokines IL-6 and IL-10 and showed a decrease in postoperative pneumonia [77]. Caution should be taken, however, in equating the impact of HBO_2 in preventing inflammation with the impact of hyperbaric oxygen in reducing already-established inflammatory conditions.

Bosco and colleagues have demonstrated a persistent reduction in TNF-α and IL-6 and reduced inflammation in patients with avascular necrosis of the hip after receiving hyperbaric oxygen [78]. In an animal model of traumatic brain injury, Qian and associates reported reductions in IL-1β and the inflammasome NLRP-3 after HBO_2 therapy [79].

Evidence that hyperbaric oxygen may be useful in acute inflammation also comes from studies of acute pancreatitis, sepsis, and inflammatory bowel disease (not currently approved indications for HBO_2 treatment by the UHMS) [80-82]. In acute pancreatitis, animal studies show HBO_2 therapy reduces inflammation and improves outcomes. Similarly, HBO_2 improved sepsis outcomes in mice, perhaps by a modulation of IL-10 [83]. In a randomized trial of HBO_2 in patients with moderately severe ulcerative colitis, which like COVID-

Table 2: Likely beneficial impact of hyperbaric oxygen on COVID-19 pathogenesis [15]

Pathologic target	Specific hyperbaric effect
severe hypoxemia and tissue hypoxia	proven success in restoring or exceeding normoxic status of oxyhemoglobin and tissue oxygenation
overexuberant and harmful immune response causing inflammation	specific anti-inflammatory effects of hyperbaric oxygen on inflammasomes, proinflammatory and inflammatory cytokines and chemokines
hypercoagulation	demonstrated but not yet repeated reduction in D-dimers
oxygen debt	likely restoration of anaerobic metabolism in chronically hypoxic tissues and promotion of lactate clearance
impact on mesenchymal and possible hematopoietic stem cells	likely additional anti-inflammatory effects

19 is characterized by uncontrolled inflammation, HBO_2 seemed to improve outcomes [84]. Overall, the data suggest HBO_2 can reduce inflammation arising from several pathologic states.

Amelioration of hypercoagulopathy

In the clinical series of COVID patients receiving HBO_2 reported to date there is no definitive indication that hyperbaric oxygen interrupts or diminishes the hypercoagulable state of advanced stage SARS-CoV-2 infections. One case from the Thibodeaux, et al. series had a significant diminution in D-dimer level [4]. In the webinar sponsored by the UHMS and broadcast on June 20, 2020, Dr. Thibodeaux presented a larger group of 12 patients who had consistent decreases in D-dimer. Of note, these patients were also routinely treated with heparin drips. On the other hand, Denham did not observe a decrease in D-dimer in her series of patients cited previously [6].

Repayment of oxygen debt

No study has investigated hyperbaric oxygen's impact on "repayment" of an incurred oxygen debt as the result of COVID infection. Only a single paper was found by electronic search addressing the likelihood of oxygen debt in COVID-19 patients [57]. The prolonged and profound hypoxemia that some COVID patients experience would be expected to produce an oxygen debt by virtue of this hypoxemia. We must depend on indirect evidence to postulate a positive result by hyperbaric oxygen in the repayment of oxygen debt in COVID patients. Van Meter in several publications discusses the role of hyperbaric oxygen in addressing oxygen debt in patients with profound anemia [57,85,86]. Johnson-Arbor and Cooper also address the application of hyperbaric oxygen to treat severe anemia and its beneficial effect including reducing oxygen debt [87]. Greensmith has reported two cases of severe blood loss anemia where patients were not able to receive immediate transfusion [88]. One refused transfusion because of religious beliefs, and the second had difficulties with cross-matching because of the presence of an anti-c erythrocyte antibody. The first patient had an electrocardiogram on admission that showed ischemic changes that resolved during the first treatment and resolved permanently along with a normal troponin I level four days after admission. The second patient had a tonic-clonic seizure while waiting for her hyperbaric oxygen treatment to begin and remained unresponsive in the post-ictal phase. She received a single hyperbaric treatment with resolution of her neurologic deficits and was then able to be transfused. The first patient initially had a hemoglobin of 5.3 g/dL; the second had a hemoglobin on initial draw of 2.6 g/dL and had a lactate level of 7.4 MEq/L (normal range 0.5 to 2.2 mEq/L). It was the author's opinion that organ dysfunction (cardiac in Patient 1 and central nervous system

in Patient 2) was reversed by the hyperbaric oxygen intervention. These cases may not represent a true picture of oxygen debt since their hypoxemia was more acute than chronic. Additional study in the role of hyperbaric oxygen in eliminating oxygen debt should be pursued.

Mobilization of stem cells and impact on mesenchymal stem cells

Hyperbaric oxygen increases the mobilization of hematopoietic stem cells [89]. Schwarting et al. have given us the only report that suggests hematopoietic stem cells can reduce inflammation [90]. There is little literature addressing the effect of hyperbaric oxygen on mesenchymal stem cells (MSC). A single article by Shyu et al. shows that hyperbaric oxygen specifically increases mesenchymal stem cells in a preclinical model employing human cells in culture [91]. MSCs have strong anti-inflammatory and immune regulatory functions [92]. Mesenchymal stem cells can inhibit the abnormal activation of T lymphocytes and macrophages and induce their differentiation into regulatory T cell subsets and anti-inflammatory macrophages [93]. They are known to inhibit the secretion of proinflammatory cytokines such as IL-1, TNF-α, IL-6, IL-12, and IFN-γ, thereby reducing the occurrence of cytokine storms [93]. No clinical evidence exists at this time showing that mesenchymal stem cells are induced by hyperbaric oxygen and successfully inhibit the proinflammatory cytokines mentioned above for COVID-19 patients.

SUMMARY OF POTENTIAL MECHANISMS UNDERLYING COVID-19 PATIENT RESPONSES TO HYPERBARIC OXYGEN

Patients with COVID-19 experience acute hypoxia, a profound inflammatory response, hypercoagulability, and can incur an oxygen debt. Hyperbaric oxygen likely exerts a beneficial influence on all these problems. One publication suggests that hyperbaric oxygen may increase mesenchymal stem cell activity, which could have a beneficial impact on regulating inflammation.

A prominent feature of COVID-19 is hypoxia due to lung dysfunction. These patients are subject to severe hypoxemia and resultant tissue hypoxia. Hyperbaric oxygen is known to efficiently deliver oxygen to severely hypoxic patients. Hyperbaric oxygen has been largely successful in the three published series and several cited anecdotal unpublished reports in treating hypoxemia of severely affected COVID-19 patients. Reports demonstrate that these COVID patients frequently maintain their improved oxygen status for hours after the hyperbaric exposure. Interestingly, in those series completed to date a single daily hyperbaric exposure for as few as five treatments appears to be effective.

Those patients who become ventilator-dependent due to COVID-19 had earlier been reported to succumb to their disease in various series at rates of 50-80%. Although survival has recently improved significantly as the use of supplemental oxygen and ventilatory support have been refined, mortality rates are still in the mid- 30% range for intubated patients [95,96]. Fewer patients treated with hyperbaric oxygen have progressed to intubation, and fewer have died (Gorenstein and Thibodeaux).

The overexuberant immune response generated by COVID causes significant inflammatory and proinflammatory reactions, causing damage not only to the lung, but to the kidney, gastrointestinal tract, and other organ systems.

Anticoagulation is essential for those who develop hypercoagulability. A single report suggests that hyperbaric oxygen can reduce hypercoagulation, but this finding has not been corroborated.

Benefits predicted by our discussion of hyperbaric oxygen mechanisms, some of which are supported by only pre-clinical studies, include relief of hypoxia, possible repayment of any accrued oxygen debt, reduced inflammation, and a possible improvement in hypercoagulation. Based on our discussion of mechanisms described above, we encourage the development and conduct of well-designed clinical trials investigating hyperbaric oxygen as part of a multimodality treatment of COVID-19 patients. As experience in treating COVID patients has increased, it has become evident that a subpopulation of patients who survive the acute infection may experience persistent symptoms for weeks and even months. Indeed, some of these patients will experience permanent sequelae [97]. Future efforts will have to be directed to these long-term consequences and depending on the ultimately demonstrated causes of these sequelae, some of the beneficial effects of hyperbaric oxygen may merit study here as well.

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Conflict of interest statement

The authors have declared that no conflict of interest exists with this submission.

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