Role of Hyperbaric Oxygen Therapy (HBOT) in Recovery of Covid-19 Patients: Medical Oxygen

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Abstract: Over the past year, the COVID-19 pandemic has persisted in its global spread, yet the development and availability of consistently effective therapeutic treatments remain limited. Numerous pharmacological agents have been introduced and repurposed in the clinical management of COVID-19, their therapeutic efficacy continues to be a subject of ongoing investigation and further research. Given the potential for recurrent waves of infection, there is a sustained and pressing need to identify and implement effective treatment strategies. The burden of disease, particularly during the second wave, has led to a substantial increase in the demand for medical oxygen therapy. In many settings, access to medical oxygen has become a determinant of survival which highlighted the imbalance in healthcare resources. Availability to access to oxygen therapy is an urgent global health priority. This article explores the potential role of Hyperbaric Oxygen Therapy (HBOT) in the clinical management of COVID-19, with a particular focus on patients experiencing hypoxia resulting from severe pulmonary infection and impaired respiratory function. The physiological rationale, clinical implications, and emerging evidence surrounding HBOT in this context are discussed.

Keywords: Hyperbaric Oxygen Therapy (HBOT), Hypoxia, Medical Oxygen, Corona virus disease (COVID-19)

Introduction

A novel viral pathogen was identified and detected as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) on 11 February 2020. This virus shares genetic similarity with the corona virus responsible for the SARS outbreak of 2003, though these two differ significantly in their epidemiological and clinical characteristics. The associated disease was officially designated as Corona virus Disease 2019 (COVID-19) by the World Health Organization (WHO) on the 11th February 2020.

According to WHO data, global COVID-19 cases increased approximately forty-fold over the preceding year, while mortality rates rose eleven-fold. The scale of illness and death attributed to this pandemic represents one of the most profound public health challenges in the past century. In the field of medicine, it remains essential to derive insights from historical experiences and to contextualize new findings within established clinical frameworks [1].Beyond primary pulmonary involvement caused by direct viral infection, critically ill patients frequently develop a complex immune pathological state characterized by thrombosis and endothelial injury, which may result in multisystem failure and mortality [2].

Data from the National Clinical Registry for COVID-19 indicate a notable clinical shift during the second wave of infections given in Figure 1. Dyspnea (shortness of breath) emerged as the most prevalent symptom among hospitalized individuals, increasing from 41.7% to 47.5% of cases. In contrast, the incidence of several other symptoms declined markedly, including dry cough (5.6% to 1.5%), anosmia (7.7% to 2.2%), lethargy (24.2% to 11.5%), sore throat (16% to 7.5%), and myalgia (14.8% to 6.3%).

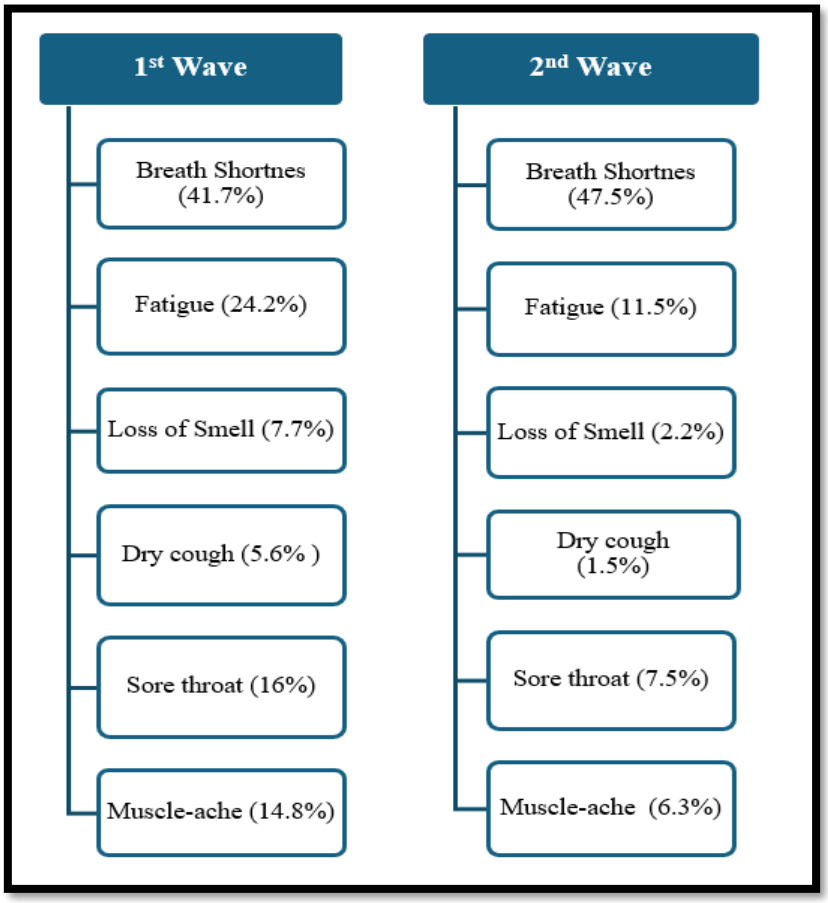

Figure1: Clinical Symptoms Comparison in COVID-19 patients (1st Wave and 2ndWave)

In India on 18 May 2021, 1.75% of Covid-19 patients were admitted to ICUs, 0.40% were on ventilators, and 4.03% required oxygen cylinder. Active cases increased to more than

20laks (20, 31, 977), the demand for oxygen supported beds has become urgent. On May 17, national Covid-19 task force members of the shared that hospital records revealed 54.5% of patients admitted during the second wave needed oxygen therapy a significant hike of 13.4% in a period of September to November and this data is based on 40 Covid-19 centres across India [4,5].

The reason for increased demand for oxygen support is unclear and require further deep investigation. Nevertheless, oxygen therapy plays a critical role in the treatment of Covid-19 patients, especially when blood oxygen (SpO_2) levels is low [6].

According to the clinical guidelines, a person is considered to have a moderate case of the disease if they have pneumonia with no symptom of severe disease. Typical symptoms include shortness of breath (dyspnoea), low oxygen levels (hypoxia), fever, and cough. Oxygen saturation levels in these cases usually fall between 90- 94% in room air [7].

For moderate cases, the main treatment is oxygen therapy, with a goal to maintain oxygen saturation level 92% - 96% and for the patients with COPD (chronic obstructive pulmonary disease) in between 88% - 92%. Depending on the patient needs oxygen can be administered through nasal prongs, face masks, or masks with reservoir bags. In some cases, patients may also be asked to lie on their stomachs (known as awake proning) to help improve oxygen levels [8].

Severe cases of COVID-19 are categorized into three principal clinical manifestations: severe pneumonia, acute respiratory distress syndrome (ARDS), and sepsis. Current clinical management guidelines recommend initiating oxygen therapy at a flow rate of 5 litres per minute. In instances where patients exhibit persistent respiratory distress or hypoxemia despite standard oxygen therapy, escalation to high-flow nasal oxygen (HFNO) therapy or non-invasive ventilation (NIV) is advised. Evidence indicates that HFNO, when compared to conventional oxygen delivery methods, significantly reduces the need for endotracheal intubation. However, this modality is contraindicated in patients presenting with hypercapnia (such as those experiencing exacerbations of obstructive pulmonary diseases), hemodynamic instability, multi-organ failure, or altered mental status, due to potential risks and limited efficacy in such clinical scenarios [9,10].

In some COVID-19 patients is silent hypoxia, a condition characterized by significant reduced arterial oxygen saturation in the absence of respiratory distress. According to the American Lung Association, individuals with silent hypoxia display blood oxygen levels lower than expected in relation to other vital parameters this is not an initial symptom of COVID-19. Affected individuals often present to emergency departments for other complaints, such as myalgia, fatigue, fever, or cough. By the time silent hypoxia is clinically diagnosed patients usually exhibit other signs of disease progression and are frequently in critical condition [11].

Since the onset of the COVID-19, ensuring equitable and sustainable access to medical oxygen has emerged as a challenge, particularly in low- and middle-income countries

(LMICs). The World Health Organization (WHO) estimates that more than 500,000 COVID-19 patients in LMICs require oxygen therapy on a daily basis. Numerous hospitals have experienced severe oxygen shortages, leading to avoidable morbidity and mortality. In many instances, the financial burden has shifted to the families of hospitalized patients, who must often pay exorbitant prices for limited oxygen supplies.
Oxygen is classified as an essential medicine by the WHO and is critical for the clinical management of severe COVID-19. Nevertheless, its availability in LMICs remains constrained due to financial, infrastructural, and logistical barriers. Health facilities frequently lack the necessary infrastructure to store and deliver oxygen at scale, contributing to preventable deaths. Current projections suggest that more than 500,000 individuals in LMICs require approximately 1.1 million oxygen cylinders per day. Twenty-five countries, predominantly located in Africa, are currently reporting surges in demand. Oxygen supply was already insufficient prior to the COVID-19 pandemic, and these deficits have been significantly exacerbated by the pandemic [12].
This constitutes a global emergency requiring a coordinated international response. It is imperative that multilateral organizations, global health partners, and donors intensify efforts to fight this issue. Therefore, a sustained and collaborative commitment is essential to scale up oxygen production and distribution, particularly in the most severely affected regions.

Discussion

Oxygen therapy remains a critical, life-saving intervention, particularly in the context of respiratory illnesses such as COVID-19. The World Health Organization (WHO) with Biomedical Consortium has facilitated coordination among clinical, technical, and procurement partners, supporting the delivery of approximately US$80 million worth of biomedical equipment to low- and middle-income countries (LMICs). Complementing these efforts, the Oxygen Taskforce is poised to accelerate scale-up through strategic innovation, expanded financing, and strengthened local capacity.
Over the past year, significant advances have been made in the clinical management of COVID-19, including the provision of oxygen therapy and other supportive treatments. However, global access to these medical advances remains highly unequal. Expanding equitable access to medical oxygen is essential to ensuring that patients-regardless of geographic location or socioeconomic status-can benefit from available therapeutic options. International cooperation is not only a practical necessity but a scientific, economic, and moral imperative in the global pandemic response [13,14].
Building on existing efforts, partners have developed an emergency response plan with four primary objectives: (1) quantifying both immediate and long-term oxygen needs in LMICs; (2) connecting national health systems with financing partners to support these needs; (3) facilitating the procurement and distribution of oxygen equipment and related consumables; and (4) implementing targeted market interventions and advocacy strategies to address systemic barriers to access.

Despite its simplicity and widespread clinical utility, oxygen remains inaccessible for many populations. The COVID-19 pandemic has worsened this issue, increasing it to the level of a global health emergency. From a clinical perspective, a subset of patients with COVID-19 experiences disease progression from mild respiratory symptoms to severe respiratory distress, necessitating oxygen support. In the most critical cases, the infection can lead to acute respiratory distress syndrome (ARDS), a life-threatening condition characterized by compromised pulmonary function and impaired gas exchange [15].

The pathophysiology of COVID-19-related hypoxemia involves direct infection of respiratory epithelial cells by SARS-CoV-2. These cells play a dual role in defending against pathogens and mediating gas exchange in the lungs. The immune response to infection, while essential, can become dysregulated, resulting in persistent inflammation and fluid accumulation in the alveolar spaces. This combination disrupts normal oxygen transfer, contributing to the development of respiratory failure. Laboratory markers often associated with this inflammatory response include elevated white blood cell and neutrophil counts [16]

Ensuring timely access to oxygen therapy, especially in resource-limited settings, is vital not only to reduce COVID-19-related mortality but also to build resilient health systems capable of managing a range of respiratory and critical care needs beyond the current pandemic.

Complications due to hypoxia in Covid-19 patients

The pathogenic elements of hypoxia may act at all systemic, organ and cellular levels, and the hypoxia triggered factors may have aggregate effects on each other Figure 2 and 3.Moreover, the potential for secondary bacterial infections during the later stages of COVID-19 may contribute to hypoxic responses through molecular mechanisms involving immune cell activation given in. Recent evidence suggests that bacterial co-infection can lead to stabilization of hypoxia-inducible factor 1-alpha (HIF1α) in macrophages via toll-like receptor 4 (TLR4) signalling and down regulation of prolyl hydroxylase mRNA expression- a pathway indirectly implicated in a study on aortic dissection, a highly inflammatory. Concurrently, local hypoxic microenvironments may arise due to leukocyte activation triggered by interferon signalling and the accumulation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), further amplifying the inflammatory response [17,18].

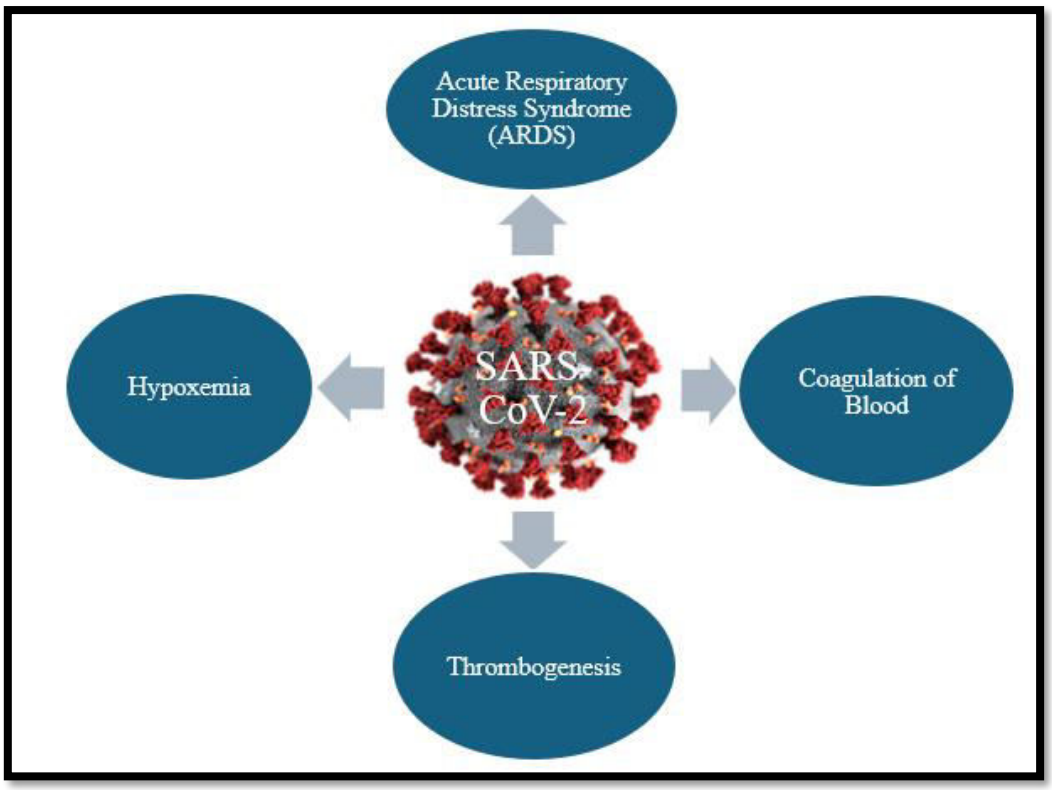

Figure 2: Complications in COVID-19 Patients

Beyond inflammation-induced disruptions to tissue oxygenation, severe hypoxemia in COVID-19 is frequently attributed to viral pneumonia characterized by bilateral interstitial infiltrates. This pathology significantly impairs the ventilation-perfusion (V/Q) ratio and may progress to severe acute respiratory distress syndrome (ARDS), thereby exacerbating oxygen desaturation [19,20]. In addition to pulmonary pathology, cardiovascular complications may also contribute to hypoxemia. Myocardial injury in COVID-19 patients may result from direct viral invasion of cardiac tissue, sustained hypoxia, hypotension, systemic inflammation, or secondary hyper inflammatory syndromes like hemophagocytic lymph histiocytosis [21]. These multifactorial mechanisms interplay between immune, respiratory, and cardiovascular systems in the pathogenesis of severe COVID-19 [22].

Hyperbaric Oxygen Therapy (HBOT)

According to the Undersea and Hyperbaric Medical Society (UHMS), hyperbaric oxygen (HBO_2) therapy is defined as a medical intervention in which a patient breathes near-100% oxygen intermittently while enclosed in a hyperbaric chamber pressurized to greater than atmospheric pressure at sea level (i.e., >1 atmosphere absolute [ATA]). For therapeutic efficacy, the chamber pressure must reach or exceed 1.4 ATA while the patient is breathing oxygen at concentrations approaching 100%.Medical-grade oxygen used in HBOT must conform to rigorous standards. The United States Pharmacopeia (USP) and Compressed Gas Association (CGA) stipulate that oxygen purity must be not

less than 99.0% by volume. Additionally, the National Fire Protection Association (NFPA) mandates the use of USP-designated medical-grade oxygen in clinical hyperbaric applications [23].

HBOT may serve as either a primary therapeutic modality or as an adjunctive intervention in conjunction with surgical or pharmacologic treatments which depends on the specific clinical indication. It can be applied to a broad range of acute and chronic conditions such as enhanced oxygen delivery to hypoxic tissues, modulation of inflammation, and promotion of neovascularisation and wound healing [24].

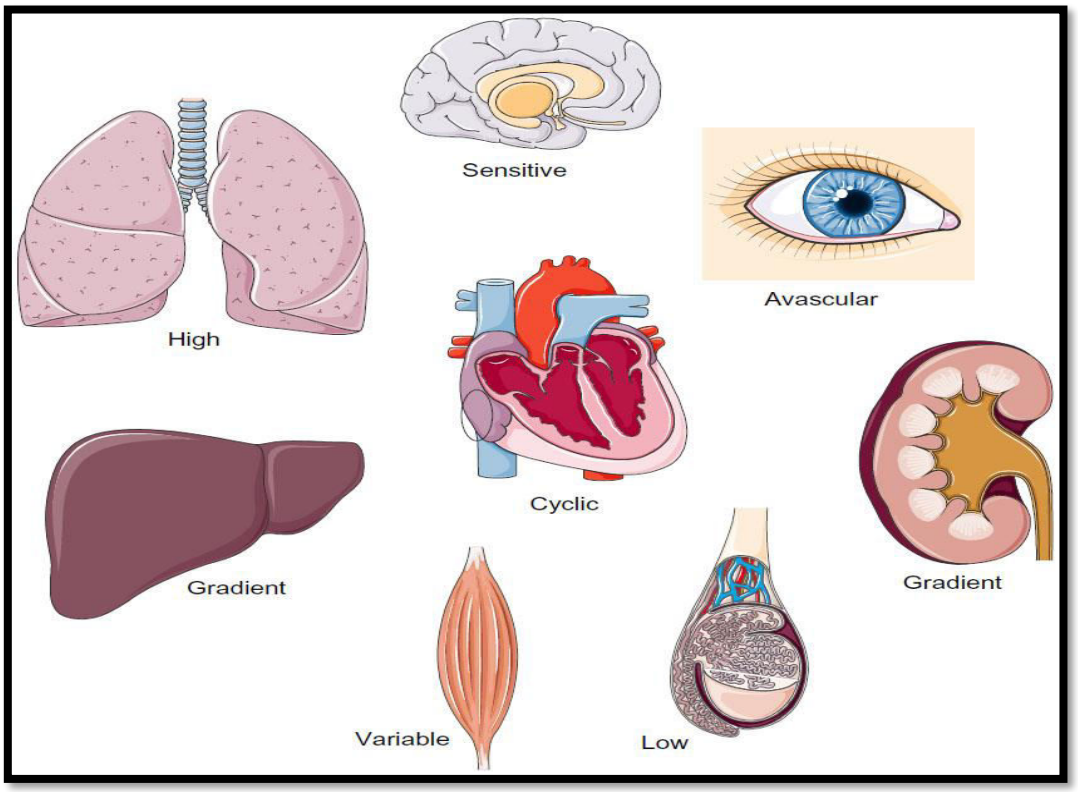

Figure 3: Impact of Hypoxia on Organs

HBOT involves the administration of near-100% oxygen at pressures exceeding atmospheric levels, delivered within a specialized hyperbaric chamber. Treatment may be delivered using either a monoplane chamber, designed for a single patient, in which the entire chamber is pressurized with oxygen, or a multiplane chamber, which accommodates multiple individuals. In the latter, the chamber is typically pressurized with compressed air and patients breathe near-100% oxygen through masks, hoods, or endotracheal tubes [25].

Inflammatory mechanisms further increase the oxygen deficits. Chronically hypoxic tissues over express pro-inflammatory cytokines, and this dysregulation can trigger or potentiate autoimmune conditions. Moreover, in critically ill COVID-19 patients, especially those with pre-existing cardiac disease, the risk of type 2 myocardial

infarction is heightened [26]. This condition results from a mismatch between myocardial oxygen supply and demand, driven by a complex interplay of hypoxia, acidosis, inflammatory cytokines (e.g., ILs, TNF-α), catecholamine surge, and hemodynamic instability [27]. Myocardial injury is associated with more severe hypoxemia and poorer clinical outcomes.

HBOT uniquely combines two physiological variables: increased atmospheric pressure and elevated oxygen concentration. Additionally, HBOT enhances mitochondrial function, promotes angiogenesis, improves tissue perfusion, and accelerates wound healing. It has demonstrated benefits in conditions involving cerebral hypo perfusion, neuro inflammation, gastrointestinal inflammatory disorders, and mitochondrial dysfunction [28,29]. This synergy significantly enhances plasma oxygen content—raising it from approximately 0.3 mL O_2/100 mL blood under normoxic conditions to up to 10–20 times that level under HBOT. This supersaturated plasma "soaks" tissues, enhancing oxygen diffusion into ischemic or inflamed regions and providing metabolic support independent of haemoglobin-bound oxygen.

HBOT has been shown to modulate immune function, particularly in hypoxic or inflamed tissues. It down regulates the expression of pro-inflammatory mediators such as IL-1, IL-6, IL-7, IL-8, TNF-α, and S100B, while upregulating anti-inflammatory cytokines including IL-4, IL-10, and IL-13. This immunomodulatory profile may be particularly beneficial in post-viral syndromes and autoimmune-mediated inflammation.

Importantly, HBOT also increases the mobilization and circulation of progenitor stem cells, contributing to regenerative processes [30].In the context of sports medicine, HBOT has gained traction as an adjunctive therapy for recovery and performance enhancement. It facilitates satellite cell proliferation, muscle fibre regeneration, and soft tissue repair. Personalized treatment protocols, guided by cytokine profiling, allow for tailored recovery and prevention strategies. Incorporating HBOT into off-season or peri-competition periods may reduce injury risk, support rapid rehabilitation, and optimize performance in both elite and recreational athletes [31,32].

A principal molecular target modulated by hyperbaric oxygen therapy (HBOT) is the hypoxia-inducible factor 1-alpha (HIF-1α), a transcription factor belonging to the basic helix-loop-helix Per/Arnt/Sim (PAS) family. HIF-1α consists of two subunits: the α subunit (approximately 120 kDa) and the β subunit (around 92 kDa) [25,26]. Under normoxic conditions, HIF-1α is rapidly degraded through the ubiquitin–proteasome pathway [33,34]. In contrast, during hypoxic conditions, HIF-1α becomes stabilized, translocates to the nucleus, and promotes the transcription of genes associated with angiogenesis, cellular metabolism, and cell survival [34].Notably, HIF-1α expression increases exponentially as oxygen tension falls below 6% [35,36]. HBOT may transiently suppress HIF-1α activity by restoring oxygenation and reversing hypoxia-driven gene expression.

Acute responses to elevated oxygen levels involve rapid post-translational modifications—such as redox changes and phosphorylation—while chronic responses involve transcriptional reprogramming over hours [37,38]. Although historically thought to exert only transient effects, systemic oxygen elevation via HBOT can lead to sustained physiological adaptations, challenging the notion that its benefits are limited to the hyperoxic exposure period [39,40].

Summary

Based on Henry's law, Hyperbaric Oxygen Therapy (HBOT) enhances oxygen delivery through several physiological mechanisms: (a) increasing oxygen dissolution across the inflamed alveolar-capillary membrane, (b) enhancing the rate of diffusion and (c) diffusion distance of oxygen, (d) significantly elevating plasma oxygen concentration, (e) optimizing haemoglobin saturation within RBCs (red blood cells), and (f) improving delivery of oxygen to the microcirculation as well as to the peripheral tissues. Hyperbaric oxygen chambers are classified as medical devices and are approved by the U.S. Food and Drug Administration (FDA) for 13 specific indications, as outlined by the Undersea and Hyperbaric Medical Society (UHMS). These are considered "on-label" uses. Any application outside these approved conditions, such as for COVID-19-associated hypoxia, is considered an "off-label" use. Despite this classification, emerging evidence suggests that HBOT may offer life-saving benefits in critically ill COVID-19 patients experiencing severe hypoxemia.

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