

Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality

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ABSTRACT

A novel virus named 2019 novel coronavirus (2019-nCoV/SARS-CoV-2) causes symptoms that are classified as coronavirus disease (COVID-19). Respiratory conditions are extensively described among more serious cases of COVID-19, and the onset of acute respiratory distress syndrome (ARDS) is one of the hallmark features of critical COVID-19 cases. ARDS can be directly life-threatening because it is associated with low blood oxygenation levels and can result in organ failure. There are no generally recognized effective treatments for COVID-19, but treatments are urgently needed. Anti-viral medications and vaccines are in the early developmental stages and may take many months or even years to fully develop. At present, management of COVID-19 with respiratory and ventilator support are standard therapeutic treatments, but unfortunately such treatments are associated with high mortality rates. Therefore, it is imperative to consider novel new therapeutic interventions to treat/ameliorate respiratory conditions associated with COVID-19. Alternate treatment strategies utilizing clinically available treatments such as hyperbaric oxygen therapy (HBOT), packed red blood cell (pRBC) transfusions, or erythropoiesis-stimulating agent (ESA) therapy were hypothesized to increase oxygenation of tissues by alternative means than standard respiratory and ventilator treatments. It was also revealed that alternative treatments currently being considered for COVID-19 such as chloroquine and hydroxychloroquine by increasing hemoglobin production and increasing hemoglobin availability for oxygen binding and acetazolamine (for the treatment of altitude sickness) by causing hyperventilation with associated increasing levels of oxygen and decreasing levels of carbon dioxide in the blood may significantly ameliorate COVID-19 respiratory symptoms. In conclusion, is recommend, given HBOT, pRBC, and ESA therapies are currently available and routinely utilized in the treatment of other conditions, that such therapies be tried among COVID-19 patients with serious respiratory conditions and that future controlled-clinical trials explore the potential usefulness of such treatments among COVID-19 patients with respiratory conditions.

Introduction

A novel virus named 2019 novel coronavirus (2019-nCoV/SARS-CoV-2) is the cause of a syndrome of symptoms that are classified as coronavirus disease (COVID-19) [1]. COVID-19 was first described among a case-series of patients that visited a local market in the Chinese city of Wuhan in December 2019 and the virus was first isolated on 7 January 2020 [2]. Since then, COVID-19 has spread around the world with the most recent estimates, as of 10 April 2020 revealing that there are currently 1,631,310 confirmed cases and 98,400 deaths [3].

A recently published *meta-analysis* examined the frequency and symptoms of COVID-19 in humans [4]. These investigators described that among the most common COVID-19 symptoms were fever (82%), cough (61%), muscle aches/fatigue (36%), dyspnea (26%), headache

(12%), sore throat (10%), and gastrointestinal symptoms (9%).

In addition to the aforementioned common clinical symptoms of COVID-19, these investigators described detailed chest imaging results [4]. Among those with chest radiologic examinations, the most common abnormalities were opacities (bilateral or unilateral, with or without pleural effusion), multiple ground-glass opacities, and infiltrate. Among those undergoing computer tomography (CT) scans, the most common abnormalities observed were ground-glass opacities (accompanied or not by septal thickening), infiltration abnormalities, and parenchymal consolidation. Only a small number of persons were observed to have normal chest radiographical or CT findings. Other investigators described that radiological examinations revealed ground-glass opacities in up to 86% of COVID-19 patients with 76% of COVID-19 patients presenting with bilateral distribution and 33% peripheral

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distribution [5]. Interestingly, COVID-19 patients were not observed to present with lung cavitations, discrete pulmonary nodules, pleural effusions, or lymphadenopathy [6]. Finally, COVID-19 patients undergoing autopsy showed bilateral diffuse alveolar damage associated with pulmonary edema, pro-inflammatory concentrates, and indications of early-phase acute respiratory distress syndrome (ARDS) [7].

Clinical examination of severe cases of COVID-19 revealed a decreased ratio of arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2:\text{FiO}_2$ ratio) with concomitant hypoxia and tachypnea [8]. In addition, investigators have described low carbon dioxide (CO_2) carbon dioxide levels in COVID-19 as the median partial pressure of carbon dioxide (PaCO_2) level was 34 mmHg [9]. In short, hypoxia and hypocapnia are seen in severe COVID-19 cases.

It was even postulated recently, based upon analyzing clinical data reported in published studies, that there was a striking similarity between high altitude pulmonary edema (HAPE) as manifested during the acute hypoxic ventilatory response and COVID-19 [10]. This researcher observed the following similarities: arterial oxygen partial pressure to fractional inspired oxygen ratio (decreased), hypoxia (present), tachypnea (increased), partial pressure of carbon dioxide level (decreased), ground glass opacities on chest CT (present), patchy infiltrates on chest x-ray (present), fibrinogen levels/fibrin formation (increased), alveolar comprise (present), and ARDS development in severe disease (present).

There are currently no generally recognized effective treatments for COVID-19, but are urgently needed given the breadth and scope of the disease. At present, anti-viral medications and vaccines are in the early developmental stages and may take many months or even years to fully develop [11]. As a result, it is imperative to consider novel new therapeutic interventions that do not necessarily cure the underlying disease, but, instead provide supportive care to help assist patients survive COVID-19, especially given its potential to induce respiratory conditions associated with significant mortality [12]. Respiratory conditions in COVID-19 are of such importance that it was described one of the hallmarks of a critical course of COVID-19 is the development of ARDS [13].

ARDS leads to low blood oxygenation levels and can be directly life-threatening because of the body's organs dependence upon adequately oxygenated blood. In order to more fully understand ARDS, it is important to consider how the lungs function. As one breathes, air is taken in through the nose and mouth and passes down the windpipe into alveoli within the lungs. It is in the capillaries that run through the alveoli that oxygen passes into the blood stream and is carried to all parts of the body. In ARDS, the capillaries within the lungs leak more fluid than normal into the alveoli and prevent the lungs from delivering enough oxygen into the blood stream. The consequence is that the body's organs work poorly or not at all. Fig. 1 summarizes the delivery of hemoglobin-based oxygen molecules to peripheral tissues in a normal patient's capillary and in a COVID-19 patient's capillary [14].

As such, supportive management of COVID-19 with respiratory and ventilator support are standard therapeutic treatments [15]. A recent meta-analysis identified that the use of supplementary oxygen therapy (38.9%), invasive ventilation (28.7%), and even extracorporeal membrane oxygenation (ECMO) (0.9%) treatments were surprisingly high among 1,876 identified patients in which any kind of pharmacological and/or supportive intervention was reported [4].

Unfortunately, regarding the standard ventilator support of COVID-19 patients, it was observed in a cohort of patients admitted to an intensive care unit (ICU) that 56% were given non-invasive ventilation at ICU admission, of whom 76% required further orotracheal intubation and invasive mechanical ventilation. The ICU mortality rate among those who required non-invasive ventilation was 79% and among those who required invasive mechanical ventilation the mortality rate was 86% [16].

The current standard respiratory treatments employed among COVID-19 patients are based upon long-established treatment protocols

for viral pneumonia. Since, the pathology observed in COVID-19 patients is very unlike other viral pneumonias, it is understandable that the currently employed therapies are highly ineffective. In the following section, it is hypothesized that a series of alternative treatment strategies for treating respiratory conditions will significantly improve tissue oxygenation among COVID-19 patients.

Alternate treatment strategies for respiratory conditions in COVID-19

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is treatment designed to increase the oxygen level in the blood. The patient either sits or lies down in an enclosed chamber. Then the pressure is raised in the chamber and 100% oxygen is administered [17]. For HBOT, pressure is expressed in multiples of the atmospheric pressure at sea level, which is 1 atmosphere (1 atmosphere = 14.7 psi, 1 Kg per cm^2 , 101.3 kPa, 760 torr, or 760 mm Hg). At sea level the blood (plasma) oxygen concentration is 0.3 mL per deciliter [18,19]. Tissues at rest extract 5 to 6 mL of oxygen per deciliter of blood, assuming normal perfusion [18,20]. Administering 100 percent oxygen at ambient pressure increases the amount of oxygen dissolved in the blood 5-fold to 1.5 mL per deciliter, and at 3 atmospheres, the dissolved-oxygen content is approximately 6 mL per deciliter. This latter level is more than adequate to meet resting cellular requirements without any contribution from oxygen bound to hemoglobin.

As such, HBOT may provide a novel means of treating/ameliorating respiratory conditions associated with COVID-19. It is theoretically possible that such therapy may have the potential to provide adequate blood oxygenation levels almost in the complete absence of lung-blood interaction. Further, it is currently estimated that more than 1,350 hospitals in the US offer HBOT services and Medicare covers HBOT for more than a dozen conditions [21]. As a result, there presently exists a large-scale infrastructure to administer HBOT to COVID-19 patients.

Packed red blood cell transfusions

It was previously described that packed red blood cell (pRBC) transfusions are a means to enhance intravascular oxygen-carrying capability, and, thus, increase the oxygenation of tissues within the body [22]. A number of previous studies demonstrated that pRBC transfusions resulted in significant increases in the oxygenation of various body tissues [23–25].

As such, pRBC transfusions may provide another novel means of treating/ameliorating respiratory conditions associated with COVID-19. It is theoretically possible that such therapy may significantly increase blood oxygenation levels. Further, pRBC transfusions are a common medical procedure, especially among patients receiving critical care [26]. Among patients not diagnosed with COVID-19, it was previously estimated that about 40% of all patients admitted to the ICU receive pRBC transfusions (with a mean of 5 units per patient) [27]. The widespread availability of pRBC provides a means to be able to rapidly and efficiently transfuse COVID-19 patients.

Erythropoiesis-stimulating agents

The kidney produces erythropoietin (EPO) a circulating hormone that stimulates erythropoiesis (the production of RBCs) by binding and activating the EPO receptors (EPOR) on erythroid progenitor cells [28]. The cloning of the EPO gene allowed for the development of treatments to stimulate erythropoiesis by erythropoiesis-stimulating agents (ESAs) [29]. ESAs given by injection were observed to significantly increase the numbers of RBCs with increased tissue perfusion and oxygenation over several weeks [30]. In addition, given the ability of ESAs to increase RBC synthesis, it was observed that the supply of iron may not be

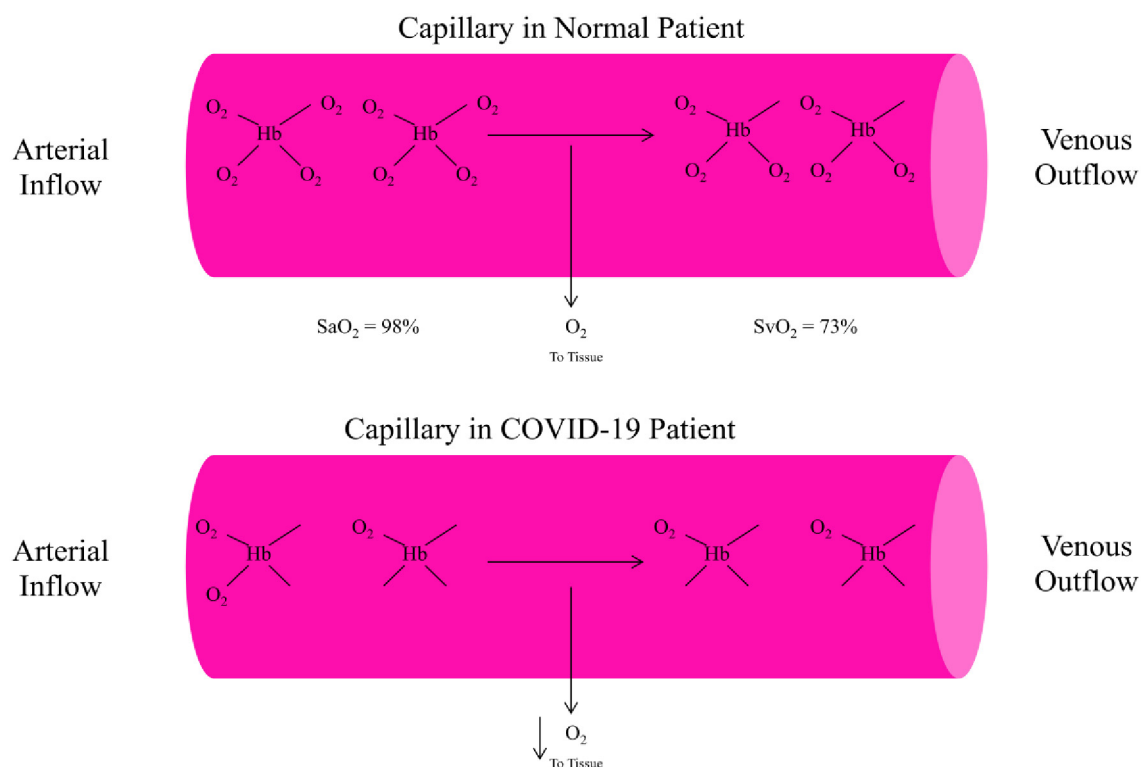


Fig. 1. A summary of hemoglobin-based delivery of oxygen molecules to peripheral tissues in a normal patient's capillary and in a COVID-19 patient's capillary. Hb = hemoglobin; O₂ = oxygen; SaO₂ = arterial oxygen saturation; SvO₂ = venous oxygen saturation. The oxygen tension of tissues will dictate whether one of several oxygen molecules will be released from oxyhemoglobin (HbO₂) and diffuse from the capillary (pink area) into the tissue. The fraction of HbO₂ relative to total Hb in arterial blood is the SaO₂, which is normally > 95%. Normal mixed SvO₂ is about 65–75%. A decrease in SvO₂ usually indicates low tissue oxygen tension, resulting in increased extraction of oxygen molecules from Hb.

able to keep pace with RBC synthesis, and, hence, it may be necessary to provide iron supplementation [31].

At present, there are multiple forms of ESA available on the US market that are defined by differences in glycosylation patterns giving rise to alpha, beta, delta, and omega forms, and ESAs are covered by Medicare [32]. The widespread availability of ESAs provides another means to be able to rapidly and efficiently treat COVID-19 patients.

Other considerations

Chloroquine/hydroxychloroquine treatments

It was recently suggested that chloroquine (CQ) and hydroxychloroquine (HCQ) may be useful in the treatment of COVID-19, but presently there is inadequate evidence to support their safe and effective treatment of COVID-19 [33]. There is emerging evidence suggesting that CQ and HCQ may directly impact coronavirus attachment to respiratory cells [34], but there is also interesting potential modes of action for these drugs with respect to respiratory conditions associated with COVID-19. Namely, it was revealed that CQ and HCQ have the ability to significantly increase cellular hemoglobin production [35] and it was suggested that such drugs may have a therapeutic potential to raise hemoglobin levels in patients [36]. In addition, a recent meta-analysis of clinical trials revealed that HCQ treatment among patients diagnosed with diabetes mellitus significantly reduced their levels of hemoglobin A1c (glycated hemoglobin decreases the oxygen carrying capacity and limits oxygen tissue delivery) [37]. As a result, CQ and HCQ treatments may help to improve respiratory conditions related to COVID-19 by a mechanism consistent with the various previously considered treatments.

Acetazolamide treatment

It was also recently suggested that acetazolamide may be useful in the treatment of respiratory conditions in COVID-19 patients [10]. Acetazolamide is a carbonic anhydrase inhibitor. Carbonic anhydrase is found in the proximal tubule of the kidney and allows for the re-absorption of bicarbonate, sodium, and chloride. Acetazolamide inhibits the re-absorption of these ions, and hence, by increasing the blood level of bicarbonate, the blood becomes acidic. This results in a compensatory hyperventilation (Kussmaul respiration) with increased blood oxygen levels and decreased blood carbon dioxide levels [38]. As a result, acetazolamide treatment may help to improve respiratory conditions related to COVID-19 by a mechanism consistent with the various previously considered treatments.

Future directions

In conclusion, it is apparent that COVID-19 is a global disease associated with significant morbidity and mortality. A significant percentage of the mortality associated with COVID-19 is related to respiratory conditions. At present, respiratory and ventilator support are standard therapeutic treatments for respiratory conditions associated with COVID-19. Unfortunately, despite such treatments of COVID-19 patients with respiratory conditions, a high mortality rate is still being observed. It is hypothesized that there are underlying pathological changes among COVID-19 patients that are compatible with ARDS. A series of alternate treatment strategies utilizing clinically available treatments such as HBOT, pRBC transfusions, or ESAs were hypothesized to deliver increased oxygen to peripheral tissues by alternative means than standard respiratory and ventilator support therapeutic treatments. Fig. 2 provides an overview of the mechanism of action for the various novel treatment strategies for respiratory conditions in

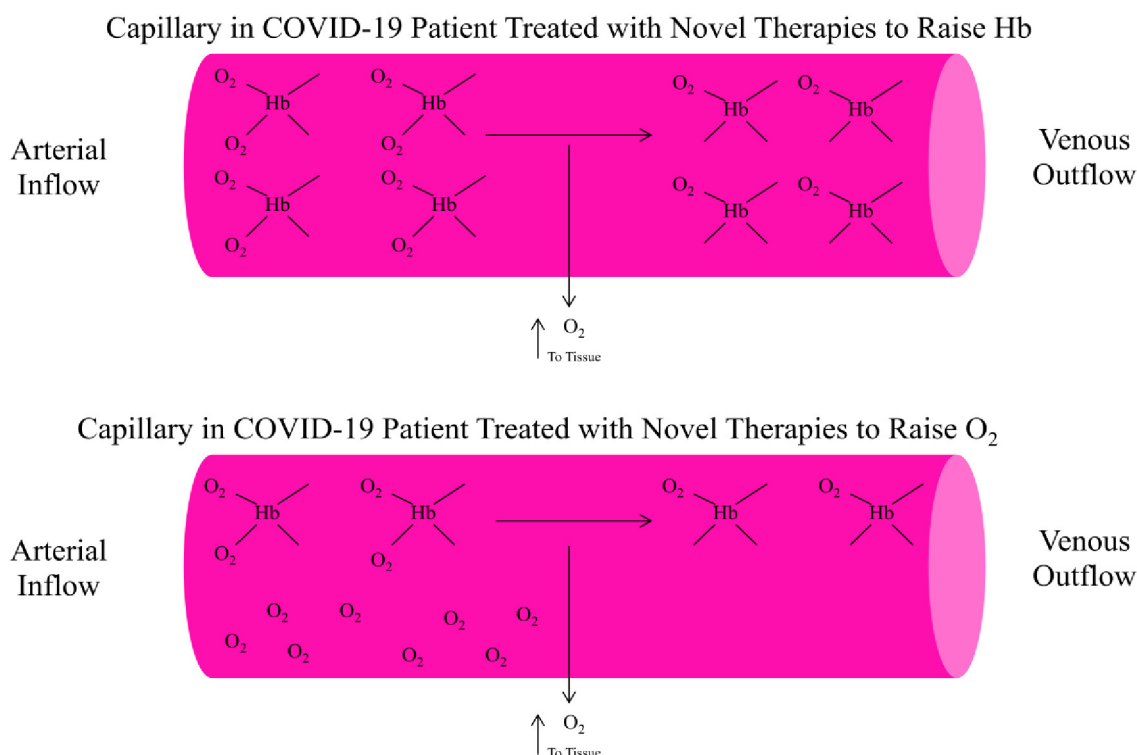


Fig. 2. A summary of novel treatments considered to improve hemoglobin-based delivery of oxygen molecules to peripheral tissues in a COVID-19 patient's capillary. Hb = hemoglobin; O₂ = oxygen. It is hypothesized that hyperbaric oxygen therapy will significantly increase O₂ levels in the blood independently of Hb levels and improve tissue oxygenation. It is also hypothesized that packed red blood cell transfusions or injected erythropoiesis-stimulating agents will significantly raise blood Hb levels by increased numbers of red blood cells and improve tissue oxygenation.

COVID-19 patients. It is recommended, given such alternative therapies are currently available and routinely utilized in the treatment of other conditions, that such therapies be tried among COVID-19 patients with serious respiratory conditions. It is also recommended that future controlled-clinical trials explore the potential usefulness of such treatments among COVID-19 patients with respiratory conditions.

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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