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REVIEW: A Mini-Review and Perspective on Anti-hypoxic Hypothesis of COVID-19

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ABSTRACT

A novel coronavirus emerged in Wuhan, China; in December 2019 and has widely affected the global community. After months of extensive effort, much remains to be understood of the pathogenesis of Coronavirus Disease 2019 (COVID-19). The available evidence raises a critical question: Is COVID-19 a lung disorder leading to circulatory problems, or a systemic disorder that leads to lung problems? If the latter scenario is correct, investigations on hypoxia conditions and the development of anti-hypoxia agents may lead to potential front-line treatments in combination with antivirals for hypoxemic COVID-19 patients. Hence, anti-hypoxic agents may become a potential part of combination therapy in hypoxemic respiratory failure and COVID-19.

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Introduction

A novel coronavirus appeared in Wuhan, China in December 2019 and has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it induces coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared the novel coronavirus outbreak as a pandemic on March 11, 2020 (1). At the time of writing SARS-CoV-2 has caused >30,000,000 infections, and >951,000 deaths worldwide. Despite intensive efforts much remains unknown of many aspects of SARS-CoV-2 infection. Many treatment approaches have been proposed with many rapid preprints and publications with conflicting results. Hence, there is much to

learn of the pathogenesis and effective treatment approaches for SARS-CoV-2 and COVID-19. Here we review the evidence for the role of hypoxia and its' potential for therapeutic targeting in COVID-19.

Virology, immunology & pathogenicity of SARS-CoV-2

Coronaviruses are enveloped positive-sense, single-stranded RNA viruses with a large genome size of 26–32 kb and are responsible for infection of a wide range of animal species and humans (2,3). Coronaviruses have been divided into four types, α, β, γ and δ, of which, human coronaviruses are classified in α (229E and NL63) and β types (Middle East respiratory syndrome (MERS)-CoV, HCoV-OC43, HCoV-HKU1, SARS-CoV and SARS-CoV-2).

The SARS-CoV-2 replication cycle starts with binding to host cell receptors that is follow by internalisation, biosynthesis, maturation, and release to infect adjacent cells. Among the different coronaviruses structural (spike (S), membrane (M), envelop (E) and nucleocapsid (N)) proteins, the S glycoprotein binds to the host angiotensin-converting enzyme 2 (ACE2) on the plasma membrane of type-*II* pneumocytes and intestinal epithelium and is the SARS-CoV-2 functional receptor (4,5). Following the binding of the virus to the host ACE2 receptor, the S protein undergoes protease cleavage at the furin cleavage site at the S1/S2 subunits (6), and other proteases such as cathepsin L and transmembrane protease serine-2 (TMPRSS2) are also involved (7,8). It is possible that the high pathogenicity of the SARS-CoV-2 stems from the broad expression of furin. After entry, antiviral immunity is activated and antigen presenting cells (APCs) interact with viral antigens to stimulate humoral and cellular immunity. Then, the host histocompatibility complex (MHC) delivers antigenic peptides to virus-specific cytotoxic T lymphocytes (CTLs) (9,10). Of humoral responses in mild COVID-19 patients, type-*I* interferon antiviral responses, as well as substantially reduced levels of $CD4^+$ Th1 and $CD8^+$ T-cells, have been observed in peripheral blood (11,12). In critical cases, after a delay in responses, there is a sudden increase in inflammatory cytokines, as well as the recruitment of neutrophils and monocytes into the lungs, leading to a cytokine storm and acute respiratory distress syndrome (ARDS), in which tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-12 play critical roles in increasing vascular permeability and respiratory failure (13).

Nevertheless, the understanding of COVID-19 pathogenicity depends on the comprehension of virus antigens interactions with the immune system and their presentation. However, there is still only incomplete evidence of this in SARS-CoV-2, and we need to extrapolate information from other well-studied coronaviruses (SARS-CoV and MERS-CoV).

Patient management

According to the WHO and Centers for Disease Control and Prevention (CDC) (14,15) there is still no established approved treatment approach, management of COVID-19 currently includes prevention and support: 1) infection prevention; 2) supportive care (e.g., ventilation, routine treatments to prevent complications); 3) self-isolation for at least two weeks in asymptomatic or mild patients, and; 4) hospital-isolation in critically ill patients for emergency treatments (e.g., respiratory failure, septic shock, hypoxia).

Potential associations of blood disorders with COVID-19

Hemoglobin is an oxygen transport metalloprotein in red blood cells, which contains four subunits including a polypeptide chain and heme group on each unit. The heme group consists of an iron ion enclosed in a heterocyclic porphyrin ring (16). Recently, a pre-print bioinformatic analysis of the role of SARS-CoV-2 proteins reports that the viral ORF8 protein and surface glycoproteins could form a complex

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that binds to porphyrin. However, hemoglobin's 1-β chain will be attacked by orf1ab, ORF10, and ORF3a proteins for iron ion dissociation to form a porphyrin. Thus, hemoglobin can no longer carry oxygen without the separated iron, which leads to the inability of lung cells to exchange CO_2 for O_2. This causes the severe inflammation that appears as ground-glass opacity (GGO) in lung radiological images in COVID-19 (17). Following this pre-print, Lansiaux *et al.* (18) hypothesized that if this concept holds true, β-thalassemic patients, who have reduced amounts or the absence of hemoglobin's β-chain should be prioritized for immunization against SARS-CoV-2 infection. These authors conducted multiple linear regression analyses on populations from three different regions of Italy with different β-thalassemia prevalence and evaluated SARS-CoV-2 infections. Surprisingly, this study indicated that a population with heterozygous β-thalassemia genotype was significantly associated with immunity against COVID-19.

This study on Italian populations, which has more than the global average of thalassemia (19), might be a possible sign of a link between blood and higher mortality rate among this ethnic group due to COVID-19 pandemic. This also might be relevant to the high rate of mortality in African Americans (20), who have a higher prevalence of inherited blood disorders namely sickle cell anemia (8-10%) compared to other populations.

Also linked to this, Mitra *et al*., (21) reported a leucoerythroblastic reaction in a COVID-19 patient that indicates that the body may attempt to compensate for the lack of hemoglobins induced by coronavirus infection. However, since it was only a case report, larger studies on the subject could help to clarify the issue. Indeed, recent investigations on hematological and biochemical parameters of COVID-19 patients show reduced hemoglobin levels, especially in severe patients admitted to the Intensive Care Unit (ICU). These patients also had significant increases in infection-associated biomarkers such as increases in procalcitonin, IL-6, erythrocyte sedimentation rate (ESR), serum ferritin and C-reactive protein (CRP) (22-24). This might also indicate increases in free heme, iron ions dissociation and increases in inflammatory cytokines elevation through lysis of red blood cells (RBC). In this case, RBCs have been found in the alveoli of patients with ARDS and cell-free hemoglobin showed a key role in exerting oxidative and endothelial injury in such patients as a pathologic mediator (25).

Notably, most COVID-19 patients (>70%) have elevated lactate dehydrogenase (LDH) levels, which might be associated with hypoxia (22). Additionally, examination of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2: FiO_2 ratio) in critical COVID-19 patients showed decreases associated with hypoxia and tachypnea (26). Studies also found low levels of the median partial pressure of carbon dioxide ($PaCO_2$) in these patients (27).

The usual clinical approaches used for ARDS apply similarly to COVID-19. Strategies such as high positive end-expiratory pressure (PEEP), prone positioning, and standard ventilator support are used. However, a cohort study showed a 79% mortality rate for non-invasive ventilation cases and 86% for invasive ventilation cases (28). It is now apparent that COVID-19 does not involve typical ARDS and currently supportive approaches are almost ineffective (29). A good analogy is with carbon monoxide poisoning. The root issue will not be addressed by ventilation because there is no problem with the lungs. The problem is that hemoglobin is occupied by carbon monoxide, which can be addressed by 100% oxygen therapy or hyperbaric oxygen therapy. However, herein, the hypothesis concludes that hemoglobin is no longer able to carry the O_2 due to iron ions dissociation. In fact, it seems that the major problem here is a hypoxia following the hypoxemia, which cannot be cured through oxygen therapy.

Hypoxia and COVID-19

Hypoxia is a generalized or local condition affecting the whole body or a region such as the lung following the reduction of available

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oxygen supply at the tissue level (30). It can result in many physiological abnormalities and lead to organ failure due to O_2 starvation (31). But, the hypoxia itself mostly occurs due to hypoxemia with low levels of O_2 or O_2 deficiency in arterial blood, which is reportedly associated with in-hospital mortality of COVID-19 patients (32). Recent evidence indicates some similarities between hypoxia/hypoxemia in COVID-19 patients and high-altitude pulmonary edema (HAPE). Decreases in PaO_2:FiO_2 ratio is observed in both disorders associated with hypoxia and tachypnea (33).

Investigations also indicated increases in fibrinogen and patchy infiltrates in both COVID-19 patients and HAPE (33-35). Besides, due to some similarities between these two entities, Solaimanzadeh *et al.* (33), recommended acetazolamide as a potential medication for COVID-19, since it demonstrated promising outcomes in reducing hypoxic pulmonary vasoconstriction and minute ventilation improvement in individuals with HAPE as well as delaying plasma lactate appearance. These authors also recommended Nifedipine and phosphodiesterase inhibitors as alternative medications as they have similar effects in HAPE.

In contrast to this recommendation, Luks and Swenson believe that, although there are some clinical similarities between two conditions such as hypoxemia, radiographic opacities and altered pulmonary compliance, they have different pathophysiological mechanisms and medications utilized for HAPE could not have benefit for COVID-19 patients, even may lead to adverse consequences.

Geier and Geier (36) also hypothesized some alternative approaches for hypoxia in COVID-19, which may be effective in improving tissue oxygenation: hyperbaric oxygen therapy, packed red blood cell transfusions and erythropoiesis-stimulating agents. Also considering the hypoxia concept, Wu *et al*., studied the effects of plasminogen supplementation on COVID-19 patients through atomization inhalation. This resulted in improved lung lesions and heart rates and increased oxygen saturation, which prevented hypoxemia after plasminogen inhalation (37). According to the Extracorporeal Life Support Organization, another approach against hypoxemia is the extracorporeal membrane oxygenation (ECMO) technique, which is employed in severe ARDS patients whose heart and lungs are not able to performed gas exchange or perfusion. This strategy has shown successful outcomes as adjunct support in COVID-19 patients in recent studies (38,39). Searching through the grey literature such as physicians' interviews identifies terms such as "happy hypoxia" or "silent hypoxemia". Studies indicate that although the COVID-19 has ARDS as a major component, lung function is usually normal in many patients and there are no apparent symptoms of respiratory distress, although oxygen saturation is low and respiratory failure progresses suddenly with severe hypoxia (40-42).

Thus, according to the evidence mentioned, the question arises: Is COVID-19 a lung disorder leading to blood problems, or a blood disorder leading to lung problems? If the latter scenario becomes a reality, along with numerous investigations on hypoxia (43-45) identify anti-hypoxia agents as potential front-line treatments in combination with antivirals for hypoxemic COVID-19 patients. Our experimental *invivo* investigation with the FDA-approved anti-oxidant medication Edaravone demonstrated excellent protective effects against hypoxia in all tested models of asphyctic, haemic, and circulatory hypoxia, as well as decreased oxidative stress levels in the brain tissue of hypoxic mice (46). Similarly, our study on magnesium sulfate ($MgSO_4$) indicated that pretreatment attenuated protein and lipid peroxidation and increased mitochondrial function in mice afflicted by different methods of induction of hypoxia (asphyctic, haemic, and circulatory). The results support the conclusion that $MgSO_4$ may increase survival time and prevent mortality associated with asphyxiation (47). Hence, the highly anti-hypoxic functions of Edaravone and $MgSO_4$ suggests that these agents may be investigated as potential treatments in hypoxemic respiratory failure

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and COVID-19.

One of the conflicting treatment choices since the emergence of the COVID-19 is dexamethasone. The preliminary report of the RECOVERY large randomized controlled trial (48) indicated a promising survival effect for dexamethasone therapy of COVID-19 patients at a dose of 6 mg q.d. for up to 10 days. The majority of the patients infected with SARS-CoV-2 are asymptomatic or only manifest a mild disease. However, the infection can lead to critical stages and cause acute hypoxemic respiratory failure requiring supplemental oxygen. Remarkably, the RECOVERY study indicated that the treatment approach was significant amongst patients with hypoxemia under the invasive/ non-invasive respiratory support, but not in mild patients without hypoxemia and breathing support. Based on this report, we improved an excellent protective effect for 10 days of dexamethasone treatment against hypoxia, especially in asphyctic and hemic models. In addition to promising dexamethasone outcomes, using propranolol as the positive control illustrated a very substantial anti-hypoxic effect even much better than dexamethasone in all models. It seems that propranolol would be a safe, potential, and prudent choice to invest in treating COVID-19 patients, too (49).

We also have recently showed good antihypoxic activities in many medicinal plants such as *Lemon Beebrush* (50), *Ferula persica* (51), *Hibiscus esculentus* (52), *Hibiscus rosa* (53), *Sambucus ebulus* and *Myrtus communis* (54), *Allium sativum* (55), *Allium ampeloprasum* (56), *Vicia cracca* (57) and *Vicia hirsute* (58). We hope that these medicinal plants will find their way in the control and treatment of COVID-19, too.

Furthermore, to avoid the toxic effects and oxidative damage induced by released iron ions, available iron-chelating agents such as deferoxamine, deferiprone and deferasirox, as well as well-known antioxidants agents like Vitamin C, A and E, nitric oxide, and foods containing quercetin and trans crocin may be effective alone or in combinations in first-line treatment.

Conclusion

We consider that there is much evidence for the hypoxic hypothesis of COVID-19, and further investigations of these concepts may lead to more effective therapies for COVID-19.

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Conflicts of interest

The authors declare that they have no conflict of interests.

Authors' contributions

All authors have intellectually contributed to the study design and process. In detail, A.Sh and D.Sh: wrote and revised the first draft of the manuscript; S.RB: illustrated the graphical abstract; MH.M and MA.E: supervised the team and contributed to the conceptualization of the facts investigated in the study. The final manuscript revised and approved by all authors.

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