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# Life Threatening Hypoxemia Associated with COVID-19 (Review)

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# Life Threatening Hypoxemia Associated with COVID-19 (Review)

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**Abstract:** COVID-19, which has become a pandemic is caused by coronavirus and led to severe acute respiratory syndrome. Its complication include respiratory incompetence, damage in the muscles of the lung and heart , problems in nervous system and kidney or death. One of the characteristic symptoms of COVID-19 is the low levels of oxygen in patients' blood, a condition known as hypoxemia. Patients with hypoxemia often show the following symptoms: coughing wheezing, difficulty in breathing, headache, feeling disoriented, cyanosis in which the skin, lips, or fingernails become blue colored, even though hypoxemia is diagnosed by some tests, such as analysis of blood gas and pulse oximetry, caution should be considered when pulse oximetry interpreted, because of shifting in the left-sided of the oxyhemoglobin dissociation curve. Hypoxemia causes acute respiratory distress syndrome, that includes inflammation and edema, leadings to impairment in the alveolar homeostasis, modification in the physiology of lung resulting in vascular thrombosis, endothelial inflammation and pulmonary fibrosis, therefore any tardiness in diagnosis and introducing proper treatment can led to mortal outcomes. In this review we present hypoxemia as one of the symptoms resulting from infection with COVID-19 infection, focusing on their types, causes and possible treatment for this condition.

***Keywords:*** *COVID-19; pulse oximetry; hypoxemia; acute respiratory distress syndrome; Plasminogen.*

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## Introduction:

In the last years a pandemic of corona virus has invaded the world, this virus belongs to the Coronaviridae family. COVID-19 is transmitted mainly by contacting with droplets holding the virus produced by talking, coughing and sneezing [1]. More than or equal to 14 days is the COVID-19 incubation period, while the disease often develops within 5 days of exposure to the virus [2]. Most effective ways for prevention are staying at home, putting a proper mask on the nose and mouth, cleaning hands with proper hand hygiene after cough or sneezing, distancing from others, and using antiseptic solutions [3]. This virus causes severe disease, most common symptom is elevation in body temperature, cough, breath shortness, fatigue, and sleeping problems commonly insomnia. Some patients of COVID-19 have acute respiratory distress syndrome as a result of cytokine storm. These patients are more susceptible to develop septic shock, blood clots, and multi-organ failure [4].

The angiotensin-converting enzyme 2 receptor (ACE- 2) is receptor that allowing virus accession to the host cells, which makes the lungs most affected organ [5]. The virus causes hemorrhage, edema, hemolysis, and destroys the alveolar-capillary tissue with super infection [6]. In advanced stages, the virus can cause hypoxemic respiratory failure. COVID-19 diagnosis is based on laboratory tests and chest computerized tomography scan, while the standard test for diagnosis is by real-time reverse transcription polymerase chain reaction using nasopharyngeal swab [4].

In spite of chest computerized tomography scan may be beneficial for diagnosing patients with a high suspicion of infection, but it is not recommended as a routine method. Earlier detection of COVID-19 by lung ultrasound can be more helpful than chest X-ray [7].

One of COVID-19 abnormalities is hypoxemia, a condition that results from respiratory system damage which is life-threatening state with low levels of blood oxygen.

## Hypoxemia:

Hypoxemia is an abnormal state in which oxygen levels in the blood are low [8] .More specifically, known as oxygen deficiency in arterial blood [9].

Hypoxemia considered as one of the most important and fatal complication of COVID-19 infection, which is caused by lung disorders [10], resulting in multiple organ failure and subsequent death. Patients with hypoxemia show $O_2$ saturation level in the range of 70 or 80%. Even in some cases, it drops below 65% of the normal level that is approximately 75 to 100 mmHg [11]. So, physicians frequently prescribe oxygen in order to diminish the risk of hypoxemia [10].

An explanation of severe hypoxemia in lungs is poor blood flow regulation and absence of hypoxic pulmonary vasoconstriction. The impairment of hypoxic pulmonary vasoconstriction in COVID-19 is due to the mitochondrial damage in the smooth muscle cells of pulmonary artery. Possible explanation for limitation in the respiratory drive and for labored breathing is due to mitochondrial injury that reducing ability of carotid bodies to sense oxygen [12].

There are two primary types of hypoxemia in COVID-19 patients: type H and L. Type L is caused by loss of hypoxic vasoconstriction and loss of respiratory regulation [13]. The Type L is characterized by low elastance, low ventilation to perfusion ratio, Low lung induct ability with very low non-aerated lung tissue and low lung weight. While the Type H is characterized by high elastance, high right to left shunt, high lung induct ability with increased amount of non-aerated lung tissue, and high lung weight. Another cause of hypoxemia in patients with COVID-19 may be due to diffuse pulmonary microvascular thrombosis [14].

## Causes of hypoxemia in COVID-19:

### Pulmonary shunting:

Ventilation (V) to perfusion (Q) contradiction is responsible for arterial hypoxemia in COVID-19 infection and thus insistence of pulmonary arterial blood flow to non-ventilated alveoli, reflected by rising in partial (alveolar–arterial) O2 gradient. The infection leads to interstitial edema [13]. Due to increased edema in the lung, surfactant deficiency and pressure, alveolar collapse appears, and a substantial portion of the cardiac output is perfusing the non-aerated lung tissue, thus causing pulmonary shunting [13].

### Loss regulation of lung perfusion:

Lang *et al*. demonstrated recently by using dual-energy computerized tomography that constriction of small intrapulmonary arteries due to alveolar hypoxia during COVID-19 infection is responsible for constancy of high pulmonary blood flow to non-aerated lung alveoli [15].

This mechanism is only triggered by the presence of endogenous vasodilator prostaglandins, bradykinin, and cytokines associated with the inflammation or by other yet unknown mechanisms [16].

### Intravascular micro-thrombi:

Endothelial damage appears as characteristics feature of COVID-19 pathogenesis, and the virus can directly infect the capillary endothelial lung cells that express angiotensin-converting enzyme 2 [17]. The intravascular micro-thrombi are the result of an imbalance between pro-coagulant and fibrinolytic

activity in the presence of endothelial injury and acute inflammatory process (18).

### Deteriorated diffusion capacity:

An elevation in partial (alveolar–arterial) O2 gradient at rest can be a result of pure diffusion defects [19]. Alveolar type 2 are cells where SARS-CoV-2 reproduce within, and large number of virus particles will be produced and released, then followed by response of immune system that destructed infected cells [20]. Hyaline membranes formed when the bared basement membrane wrapped with debris, consisting of fibrin, dead cells, and complement activation products due to the loss of alveolar epithelial cells and a pro-coagulant state [20].

In COVID-19 the absent of hypoxic vasoconstriction, a hyper-dynamic pulmonary circulation might not give enough time for RBCs to counterpoise their oxygen uptake. Therefore diffusion limitation may occur in COVID-19 infection leading to an increased partial (alveolar–arterial) O2 gradient and arterial hypoxemia that induced by exercise [19].

## Alteration in the Oxygen Dissociation Curve:

A perplexing agent is the oxygen dissociation curve shift [21]. The oxygen affinity for hemoglobin has an effect on oxygen supplementation to tissues. The oxygen affinity increases with left shift and allows for stronger binding. Reversely, the oxygen affinity decreases with a right shift and facilitates releasing oxygen to the tissues. It is clearly known that the oxygen dissociation curve shifts due to changes in potential of hydrogen, partial pressure of carbon dioxide, and 2, 3-diphosphoglycerate concentration. The "S"-shaped curve of oxyhemoglobin dissociation curve appears with left shift, due to induced respiratory alkalosis (drop in partial pressure of carbon dioxide). During hypocarbia, the hemoglobin affinity for $O_2$ and thus $O_2$ saturation increased for a specified degree of partial pressure of $O_2$. In hypoxemia, hypocarbia remarkably changes the oxygen-hemoglobin dissociation curve and recovers saturation of blood oxygen.

A biological hypothesis about direct interaction between the virus with the haem group of hemoglobin, explaining the leftward shift of the oxygen dissociation curve in COVID-19 patients. Regarding this theory, in COVID-19 increasing levels of heme serum along with injurious iron ions (Fe3+), producing inflammation and death of cells. Finally, serum ferritin is produced in large amounts and bind these free irons in order to decrease tissue deterioration [22].

## Detection of hypoxemia:

### Pulse Oximeter:

$O_2$ saturation can be determined by pulse oximetry which is a small device that clips to the finger, and it is used for hypoxemia detection. However, SpO2 should be interpreted carefully in COVID-19. Arterial SaO2 can be estimated by using a pulse oximeter through measuring the change in the optical absorption of oxyhemoglobin and reduced hemoglobin. Pulse oximetry is less precise when the SaO2 is below 80% (23). In spite of pulse oximetry is most popular for reading SaO2, it may not be a better way for detection hypoxemia depending on these readings alone (24). The diagnostic standards use 93% for judgment and take measurement error in consideration.

## Treatment of hypoxemia in COVID-19:

Supplementation of $O_2$ for Covid-19 patients is for treatment and correcting hypoxaemia and prevents low levels of oxygen in tissue, thereby preventing tissue damage. The occurrence of hypoxaemia among Covid-19 patients is associated with increased mortality and poorer survival [25]. Well-trained persons should carry out the administration of oxygen for Covid-19 patients [26]. Oxygen saturation should be identified and authenticated at the time of admission so that suitable treatment can be started in the event of unexpected clinical impairment [27]. Hyperoxia should be averted because of complications, including hyperoxic hypercapnia, absorption atelectasis, acute lung injury, toxicity of CNS, elevation in systemic vascular resistance that causes decrease in cardiac output, free radical and reactive oxygen species damage, and diminished neutrophilic function, and all of these as result of exposure to high $O_2$ concentrations [28].

## Plasminogen role in improvement hypoxemia associated with COVID-19 patients:

The lungs of COVID-19 patients have shown acute respiratory distress syndrome signs, formation of vitreous membrane that consist of fibrin, and 'ground-glass' opacity. Plasminogen has a role in fibrin degradation, healing wound and infection. ARDS patients have been shown increased levels of plasminogen. Studies suggest that during COVID-19 infections supplementary plasminogen may be effective in handling lung lesions and hypoxemia [29].

## Conclusion:

The corona virus that causes severe acute respiratory syndrome has been led to the global pandemic. Many reports demonstrate that COVID-19 patients have respiration problems and then died. The strong infectious capability for corona virus, have been contributed to the deterioration of healthcare. The base of this "peculiar phenomenon" of COVID-19 is hypoxemia, that characterized by low

levels of oxygen in the blood. The threatening hypoxemia is induced by pulmonary shunting, pulmonary vasoconstriction dysregulation, lung diffusion impairment, and intravascular micro-thrombi formation. Such serious condition could be mortal if not detected correctly, the detection can be accomplished by obvious tests using blood gas analysis and pulse oximetry. It is important to make hypoxemia associated with COVID-19 in consideration, to help physicians' attempts to minimize the risk of sudden medical complications and mortality.

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