
REVIEWS

Causes of Hypoxemia in COVID-19

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Abstract—The global pandemic of a new coronavirus disease (COVID-19) has posed challenges to public health specialists around the world associated with diagnosis, intensive study of epidemiological and clinical features of the coronavirus infection, development of preventive approaches, therapeutic strategies and rehabilitation measures. However, despite the successes achieved in the study of COVID-19 pathogenesis, many aspects that aggravate the severity of the disease and cause high mortality of patients remain unclear. The main clinical manifestation of the new variant of SARS-CoV-2 virus infection is pneumonia with massive parenchymal lesions of lung tissue, diffuse alveolar damage, thrombotic manifestations, disruption of ventilation–perfusion relationships, etc. However, symptoms in patients hospitalized with COVID pneumonia show a broad diversity: the majority has minimal manifestations, others develop severe respiratory failure complicated by acute respiratory distress syndrome (ARDS) with rapidly progressing hypoxemia that leads to high mortality. Numerous clinical data publications report that some COVID pneumonia patients without subjective signs of severe respiratory failure (dyspnea, “air hunger”) have an extremely low saturation level. As a result, there arises a paradoxical condition (called “silent hypoxia” or even “happy hypoxia”) contradicting the very basics of physiology, as it essentially represents a severe life-incompatible hypoxemia which lacks respiratory discomfort. All this raises numerous questions among professionals and has already ignited a discussion in scientific publications concerned with the pathogenesis of COVID-19. Respiratory failure is a complex clinical problem, many aspects of which remain controversial. However, according to the majority of authors, one of the first objective indicators of the clinical sign of respiratory failure are hypoxemia-associated changes in external respiration. This review addresses some possible causes of hypoxemia in COVID-19.

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INTRODUCTION

In late 2019, the People’s Republic of China experienced an outbreak of a new coronavirus infection with an epicenter in Wuhan City, Hubei

Province. On February 11, 2020, the World Health Organization (WHO) defined the official name of the infection caused by the new coronavirus as COVID-19 (“Coronavirus disease 2019”). On February 11, 2020, the International

Committee on Taxonomy of Viruses assigned the infectious agent an official name SARS-CoV-2 [1].

Coronaviruses (Coronaviridae) are a large family of RNA-containing viruses that can infect both animals and humans. In humans, coronaviruses can cause a range of diseases, from relatively mild acute respiratory infection (ARI) to severe acute respiratory distress syndrome (ARDS) [2, 3]. Large-scale studies have found that airway epithelial cells and mucosal immune cells are the first to become infected. Infected cells cause uncontrolled cascade expression of proinflammatory cytokines, chemokines and other mediators of the acute phase response, forming a “cytokine storm”, an excessive immune response to infection [4–6].

COVID-19 differs from other forms of viral infections in that this variant of coronaviruses targets mainly the lungs, which is due to its tropism to lung tissue [7, 8]. To date, it has been shown that respiratory complications owing to a high sensitivity of the lungs to SARS-CoV-2 virus are the main mortality factor in critically ill COVID-19 patients [9–11]. The reason for this sensitivity is that type II alveolar epithelial cells have a high level of expression of angiotensin-converting enzyme 2 (ACE2), which is a receptor for SARS-CoV-2, and type II transmembrane serine protease (TSP2), which promotes virus binding to ACE2 and penetration into the cell [12–14]. The available data indicate that ACE2 and TSP2 expressed on the surface of various airway, esophageal, intestinal, cardiac, adrenal, bladder, brain, and endothelial cells, as well as macrophages, may cause multiple organ failure [4, 7–12, 15–21].

As follows from the recent publications [22–25], patients admitted to an intensive care unit with severe ARDS and diagnosed with COVID-19 had a very low saturation level. However, despite the severity of life-incompatible hypoxemia, some patients had no signs of ARDS (tachypnea, dyspnea, “air hunger”). Subsequently, especially in elderly patients, there was a sharp and sudden deterioration of the condition, requiring emergency resuscitation measures. For example, a clinical observation report indicates that in a 64-year-old patient with a positive coro-

navirus 2 (SARS-CoV-2) test and ARDS progression, the saturation (SpO_2) measured by pulse oximetry was 68%, whereas the arterial oxygen tension (PaO_2) was 37 mm Hg with normocapnia ($PaCO_2$ 41 mm Hg). In another, 74-year-old, patient, also with a confirmed SARS-CoV-2 result, during face mask oxygen breathing, SpO_2 was 62%, while PaO_2 was only 36 mm Hg. However, these patients had no complaints about breathing difficulties. From this, it follows that low saturation in the absence of visible respiratory discomfort is, in many cases, typical for most patients with COVID pneumonia [22, 26].

It should be noted that pulse oximetry (SpO_2), which is usually applied in medical practice for non-invasive monitoring of hypoxemia, reflects only hemoglobin oxygen saturation ($HbO_2\%$) and thus mismatches the true partial oxygen pressure in arterial blood (PaO_2) [27]. However, according to the established ideas, the determinative factor of oxygen supply to tissues is not $HbO_2\%$, but PaO_2 in mm Hg. In compliance with the physiological principles, oxygen dissociation from hemoglobin into blood depends primarily on the position of the oxyhemoglobin dissociation curve (ODC), which has a sigmoid shape, as well as on the oxygen-carrying capacity of blood, blood flow rate, temperature factor, etc. [28]. For example, hypocapnia and respiratory alkalosis resulting from hyperventilation (tachypnea, hyperpnea) shift the dissociation curve leftward and thus increase hemoglobin affinity for oxygen, impeding its getting into blood. This accounts for a higher SpO_2 level at a very low PaO_2 [29, 30].

As seen from the above clinical examples, regardless of measurement methods—be it a non-invasive (pulse oximetry) or invasive PaO_2 determination in arterial blood, patients with COVID-19 pneumonia develop hypoxemia. Recently, in publications of many authors, the presence of hypoxia without appropriate signs of respiratory discomfort has been defined as “silent hypoxia” or “happy hypoxia” [22, 23, 31, 32]. The reports on “mysterious hypoxia” or “asymptomatic hypoxia” have risen a wide discussion in scientific publications covering in the light of the established pathophysiological mechanisms the causes of ARDS absence in severe hypoxia at the early stage of COVID-19 [31, 33, 34]. It has been

repeatedly shown in numerous studies that hypoxia progression in COVID-19 patients at the early stage of the disease occurs at the normal PaCO₂ level (normocapnia), which does not appear to be a sign of respiratory dysregulation [22, 23, 35]. However, hypoxia is known to cause hyperventilation leading to hypocapnia that inhibits central (medullary) chemoreceptors. As a result, the ventilatory response to hypoxia subsides, thus explaining the absence of respiratory discomfort (dyspnea) in hypoxia. In this case, it is a respiratory dysregulation that is concerned. However, since ARDS develops at elevated CO₂ levels (hypercapnia), the corresponding symptoms of respiratory dysfunction may apparently show up at later stages of the disease, when, against the background of hypoxia and hypercapnia, critical respiratory failure develops, i.e. impaired respiratory biomechanics, increased airway resistance, disrupted ventilation-perfusion relationships and pulmonary circulation, altered structure of the alveolar-capillary membrane, thromboembolism, etc. [22, 33, 36].

It should be noted that respiratory failure, including latent respiratory failure, is a complex clinical problem, many aspects of which remain debatable. Hypoxemia is considered to be one of the objective indicators of respiratory failure [37].

When discussing the potential mechanisms of hypoxia in COVID-19, one should consider the direct effect of SARS-CoV-2 virus on its cellular receptor (APF2), which is expressed in sensory cells of the carotid body, reducing the sensitivity of glomus cells to oxygen deficiency [38, 39]. It follows that one of the possible causes of hypoxemia in COVID-19 patients may be inhibition of peripheral chemoreception [40–42]. Here, an important practical question arises about the amount of APP2 and TSP2 in the carotid body that suffices for SARS-CoV-2 invasion into cells. The presence of APP2 in the carotid body was detected by immunoblotting [43, 44], but other authors, based on the results of immunohistochemical studies of the mouse carotid body, suggest only a minimal expression of the APP2 receptor therein, in contrast to its massive expression by epithelial cells of the lungs, intestine and kidneys [40]. Therefore, the issue of the degree of involvement of the peripheral respiratory regula-

tion in the reflex mechanisms of hypoxemia development in COVID-19 has not been solved definitively as yet. However, reflex regulation does not rule out the direct influence of humoral shifts on the respiratory center. Possible neuroinvasion of SARS-CoV-2 into the CNS is considered to be the cause of hypoxemia, although the exact localization of infected structures in the areas responsible for respiratory regulation and controlling respiratory sensations still remains largely undetermined [41, 45–47].

At the same time, the related coronaviruses SARS-CoV and MERS-CoV have been found in the brainstem respiratory neurons, leading to fatal outcomes due to the development of severe respiratory failure [48–50]. It is quite likely that similar structures and neurotropism-based infection mechanisms that were found for other coronaviruses can be applied to SARS-CoV-2 equally well [41, 42, 51–53].

Damage to the endothelium and lung microcirculatory bed is an important part of COVID-19 pathogenesis because SARS-CoV-2 infects lung endothelial cells expressing APF2 [54]. It was established that acute inflammatory process and endothelial damage caused by the imbalance between procoagulant and fibrinolytic activities, elicits intravascular microthrombosis in small-caliber pulmonary vessels [55]. Increased thrombosis has been detected in COVID-19 patients, while postmortem examination revealed massive damage to alveolar microcapillaries, edema and thickening of the alveolar-capillary membrane, pulmonary capillary occlusion, presence of large thrombi causing pulmonary artery thrombosis [56]. These data indicate that with a severe clinical course of COVID-19, thromboembolism is the most frequent complication that contributes to pulmonary vascular obstruction, disrupted ventilation-perfusion relationships, and hypoxemia development [57].

Fibrin and thrombin deposition occurs mainly in the pulmonary microvasculature bed, being a factor that promotes the development of ARDS and coagulopathy in patients dying from COVID-19. Since the transition of oxygen from alveolar air to the blood of pulmonary microvessels occurs by diffusion across the alveolar-capillary membrane, its thickening, as well as microvascular thrombi,

can lead to decreased oxygen diffusing capacity (D_{LO_2}) and the development of arterial hypoxemia. It has been shown that in severe ARDS, there occurs alveolar and interstitial edema resulting from increased permeability of endothelial and alveolar epithelial barriers of pulmonary capillaries, causing infiltration of fluid rich in protein and immune cells into the parenchyma [58]. Fluid accumulation in the alveoli, impaired surfactant synthesis promoting alveolar collapse—all these events reduce the efficiency of gas exchange between the alveoli and vasculature, leading to alveolar hypoxia and hypoxemia [59]. Therefore, microvascular endothelial damage and dysfunction of some alveoli are also the factors that positively correlate with the development of hypoxemia, particularly in severely ill patients with lower respiratory tract lesions.

Some authors consider oxidative stress as one of the possible factors of severe COVID-19 [60]. The relationship has been established between inflammation and oxidative stress [61], but many issues concerned with the degree of oxidative stress involvement in the cytokine storm have not yet been sufficiently studied. Meanwhile, it is suggested that COVID-19 may entail the dysfunction of both endothelial and platelet mitochondria, which may influence thrombosis [62].

Computer simulations have only provided tentative data on the mechanism of SARS-CoV-2 impact directly on the hemoglobin heme group [7, 63]. It is hypothesized that SARS-CoV-2 does not interact with erythrocytes directly, but affects them through an additional receptor CD147. Molecular analysis of the SARS-CoV-2 structure showed that ORF8 protein and surface glycoprotein of the virus can bind to porphyrin, while ORF1ab, ORF10 and ORF3a proteins can interact with the 1- β chain of hemoglobin resulting in dissociation of iron and porphyrin molecules. Dysfunctional hemoglobin deprived of iron atoms is unable to perform the gas-transporting function (O_2 and CO_2 transport), leading to a reduced efficiency of gas exchange and aggravated hypoxia [64, 65].

As for the causes of hypoxemia without dyspnea manifestation, not all authors mention that “silent” hypoxemia can occur not only in COVID-19, but also in patients with atelectasis,

intrapulmonary or intracardiac shunt [66]. As is known, the adequacy of gas exchange depends primarily on ventilation-perfusion relationships, i.e. the balance between capillary blood flow and pulmonary ventilation. As some authors rightly point out, the key factor of hypoxemia development at an early stage of SARS-CoV-2 infection is a mismatch between the ventilation-perfusion ratio (V/Q) and the presence of anatomic arteriovenous anastomoses or alveolar shunts in the lungs [67–71]. Right-to-left shunting implies the passage of part of venous blood through a shunt, bypassing ventilated areas of the lungs. Thus, with increased fraction of the pulmonary shunt fraction, hypoxemia results from partial discharge of unoxygenated venous blood (venous admixture) into the arterial bed [69]. An intrapulmonary right-to-left shunt has been demonstrated during contrast echocardiography in a patient with COVID-19 [72], when shunting was accompanied by hypoxia and a corresponding increase in lung ventilation. However, in the presence of a shunt, hyperventilation did not increase PaO_2 , but decreased $PaCO_2$, since CO_2 has higher diffusion capacity than O_2 . Consequently, in this case, hypocapnia can develop without an increase in ventilation, which accounts for the absence of dyspnea in hypoxemia. In the case of aggravating ARDS severity with progressing hypoxemia and increasing $PaCO_2$, dyspnea with corresponding manifestations of respiratory discomfort may probably develop.

In conclusion, it is worth mentioning that this review article was focused on the analysis of some mechanisms of hypoxemia in ARDS, caused by a new coronavirus infection SARS-CoV-2. The factors described herein are links of the same chain and are of crucial importance for the development of hypoxemia in COVID-19. Obviously, SARS-CoV-2 neuroinvasion into the peripheral and central respiratory chemoreceptors comes to the forefront. The further development of disorders results from a complex influence of the endothelial damage in the lung microcirculatory bed, massive alveolar lesion, impaired hemoglobin molecules, etc. However, according to many authors, the leading role in the development of hypoxemia in the absence of dyspnea belongs to intrapulmonary shunting. Further studies will

hopefully reveal additional mechanisms of hypoxemia development and its involvement in the pathogenesis of COVID-19.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest related to the publication of this article.

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