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Silent or 'Happy' Hypoxemia: An Urgent Dilemma for COVID-19 Patient Care

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A perplexing clinical aspect of COVID-19 is presentation of patients with pronounced hypoxemia without expected signs of respiratory distress or dyspnea, even when cyanotic. Nonetheless, these patients frequently leapfrog clinical evolution stages and suffer acute respiratory distress syndrome (ARDS), with concomitant cardiorespiratory arrest and death.[1] This phenomenon is referred to as silent or 'happy' hypoxemia.[2–5]

Silent hypoxemia Analysis of a Wuhan, China cohort of patients with serious SARS-CoV-2 infections revealed that only 19% complained of shortness of breath, while 62% of them, as well as 46% of those whose clinical progression ended in either ventilation or death, also exhibited no dyspnea.[1] In spite of low blood oxygen levels, some patients seem to be functioning without serious issues or even shortness of breath. Such serious or 'happy' hypoxemia is characterized by a significantly increased respiratory rate, as high as 38 breaths/min and deep hypoxia with low partial pressure of dissolved carbon dioxide in blood ($PaCO_2$) and no concurrent dyspnea.[2,3]

> **In spite of low blood oxygen levels, some patients seem to be functioning without serious issues or even shortness of breath**

Dyspnea pathophysiology Our interoceptive sensorial system receives the homeostatic afferent information sensing the body's physiological condition, creates awareness, and leads to conscious feelings or symptoms. That sensory information arrives at the central nervous system, and then projections from the brainstem to the cortex allow the brain to process homeostatic afferent signals. When the brain receives the signal of internal hypoxia, it gives rise to the sensation of 'air hunger' and urge to breathe, which is curiously absent in some severe COVID-19 patients. Dyspnea is a subjective symptom reported by patients and should not be confused with rapid breathing (tachypnea), excessive breathing (hyperpnea), or hyperventilation.[3]

Dyspnea: PaO_2 vs. $PaCO_2$ Hypoxemia, low partial gas pressure of dissolved oxygen (PaO_2), plays a rather limited role in the breathlessness experienced by patients with cardiopulmonary disease, contrary to the hypercapnia that generates dyspnea. Change in $PaCO_2$ is the most significant component contributing to dyspnea, triggering shifts in pH levels in both the peripheral and central chemoreceptors. Severe hypoxia elicits an effective increase in ventilation only when background $PaCO_2$ surpasses 39 mmHg.[2,3]

Pathophysiology of silent hypoxemia One pathophysiological explanation for severe hypoxemia in lungs still exhibiting a degree of compliance is impaired regulation of pulmonary blood flow and loss of hypoxic pulmonary vasoconstriction. A recent report suggests SARS-CoV-2–mediated mitochondrial damage in the pulmonary artery smooth muscle cells may explain the impairment of hypoxic pulmonary vasoconstriction. The carotid bodies' reduced ability to sense oxygen due to mitochondrial injury has been mentioned as a possible explanation for the limiting of the respiratory drive and for reduced dyspnea.[3]

Changes in oxyhemoglobin dissociation curve Pulse oximetry, which measures oxygen saturation (SpO_2), is often used to detect hypoxemia. Nevertheless, SpO_2 should be interpreted carefully in the context of COVID-19. The sigmoid-shaped oxyhemoglobin dissociation curve shifts to the left due to induced respiratory alkalosis (drop in $PaCO_2$) attributable to hypoxemia-driven tachypnea and hyperpnea. During hypocapnic periods, the affinity of hemoglobin for oxygen, and thus SpO_2, rises for a specified degree of PaO_2, explaining why SpO_2 can be well preserved in the face of a profoundly low PaO_2. Thus, physicians should not only rely on patients' self-reporting of distress, but closely monitor respiratory rates, signs of hyperventilation, oxygen saturation and, if necessary, perform invasive measurements for hypoxemia/hypocapnia at regular intervals.[2,3]

> **Possible damage to the afferent hypoxia-sensing neurons in persons with COVID-19 could be due to the intense cytokine storm or the direct effect of SARS-CoV-2**

Neural hypothesis for silent hypoxemia Such patients are often tachycardic with tachypnea and respiratory alkalosis. However, they are not aware of hypoxia. The possible damage to the afferent hypoxia-sensing neurons in persons with COVID-19 could be due to the intense cytokine storm or the direct effect of SARS-CoV-2 on either mitochondria or nerve fibers. Hypoxia activates the carotid body chemoreceptors, and the afferent signals are relayed at the nucleus tractus solitarius located in the brainstem via the glossopharyngeal nerve.[2,4,5]

The nucleus tractus solitarius communicates with, among other regions, the reticular formation, parasympathetic preganglionic neurons, hypothalamus and thalamus, forming circuits that contribute to autonomic regulation.[2,3] The virus can enter through the nasal or oral cavity and may spread along the axons of cranial nerves V, VII, IX and X. SARS-CoV-2 can therefore cause inflammation of the nucleus tractus solitarius through the axonal and synapsis routes.[2,4]

Hence, in SARS-CoV-2–mediated inflammation of nucleus tractus solitarius, the afferent hypoxia stimuli from the carotid bodies may not be effectively relayed at the nucleus tractus solitarius, resulting in impaired efferent respiratory response. This may be the reason for the COVID-19 clinical presentation of almost normal breathing despite severe hypoxemia.[1–5]

From silent hypoxemia to ARDS Silent hypoxemia may disguise severity of clinical status in COVID-19 patients, and ultimately delay their seeking medical care. Patients admitted with COVID-19 may die without ever expressing the need for supplemental oxygen. Such hypoxemia can lead to the erroneous conclusion that patients are not in serious or critical condition, with the concomitant danger that they may quickly jump clinical evolution stages and develop ARDS, resulting in cardiorespiratory arrest and death.[1,2]

It is urgent that the medical community be alert to silent hypoxemia in COVID-19, to assist physicians in their attempts to reduce the risk of sudden medical complications and death.

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