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From Happy or Silent Hypoxemia to Acute Respiratory Syndrome in Covid-19 Disease

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Abstract

One of the aspects perplexing clinicians who take care of COVID-19 patients with pronounced arterial hypoxemia yet without proportional signs of respiratory distress, with even deceiving cyanosis, is that they don't even express a sense of dyspnea. This phenomenon is referred as 'happy or silent hypoxemia". For clinicians the presence of happy or silent hypoxemia in Covid-19 patients, in spite of pronounced arterial hypoxemia, can erroneously lead to the conclusion that the patient is not in a critical condition. Those cases can quickly leapfrog clinical evolution stages and suffer ARDS, with concomitant cardio respiratory arrest and death. Pulse oximetry should be interpreted with caution, because left-sided shifting of the oxyhemoglobin dissociation curve. The pathophysiology of happy or silent hypoxemia might be explained by the following hypothesis. Hypoxia normally activates the carotid body chemoreceptors, and the afferent signals are relayed at the nucleus tractus solitarius through. This normally leads to an increase in respiratory rate and dyspnea sensation. SARS-CoV-2 infects the brain through the olfactory bulb and olfactory nerves, through trans-synaptic spread, finally reaching the brainstem, and the nucleus tractus solitarius. The inflammation of the nucleus of the tractus solitarius by the virus invasion incites that the afferent hypoxia stimuli from the carotid bodies may not be effectively relayed at the nucleus tractus solitarius, resulting in an impaired efferent respiratory response. This explains why COVID-19 patients show almost normal breathing in the presence of severe hypoxemia (Happy or silent hypoxia). Physicians should not only to trust on the patient's seeming happiness but closely monitor respiratory rate, signs of hyperventilation, oxygen saturation and invasive measurements of hypoxemia/hypocapnia at regular time intervals.

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Keywords: Happy or silent hypoxemia, Covid-19, SARS-CoV-2, Acute respiratory distress syndrome (ARDS), dyspnea, neural hypothesis

Introduction

One of the aspects perplexing clinicians who take care of COVID-19 patients with pronounced arterial hypoxemia yet without proportional signs of respiratory distress, with even deceiving cyanosis, is that they don't even express a sense of dyspnea. Nonetheless, these patients very frequently rapidly progress to acute distress respiratory syndrome (ARDS), requiring mechanical ventilation. This phenomenon is referred as 'happy or silent hypoxemia"(1-5).

For clinicians the presence of happy or silent hypoxemia in Covid-19 patients, in spite of pronounced arterial hypoxemia, can erroneously lead to the conclusion that the patient is not in a critical condition. Those cases can quickly leapfrog clinical evolution stages and suffer ARDS, with concomitant cardiorespiratory arrest and death(6,7).

Happy or Silent Hypoxemia

Analyzing a Wuhan cohort of patients severely infected with SARS-COV-2, only 19% complained of shortness of breath; 62% of those with severe disease and 46% of those who were finally ventilated or dead, did not show dyspnea(8). Guan reported dyspnea in only 18.7% of 1099 hospitalized COVID-19 patients, despite low PaO2/FiO2 ratios, abnormal CT scans (86%) and common requirement for supplemental oxygen (41%) (9).

In spite of low blood oxygen levels, some patients seem to be functioning without serious issues or even shortness of breath, but the final clinical picture is characterized by a significant increase of respiratory rate, as high as 38/mins, deep hypoxia with low $PaCO_2$ levels, but without any dyspnea until late in the clinical evolution of the disease(1,3).

There are several clinical manifestations associated with lung damage due to SARS-CoV-2 infection, and risk factors which are related to disease severity. In Covid-19 pneumonia, the lungs become filled with fluid and inflamed, leading to breathing difficulties. Pulmonary thrombosis appears to be common in COVID-19 pneumonia and takes two forms, proximal pulmonary emboli and/or distal thrombosis. SARS-CoV-2 has been shown to enter cells through binding angiotensin-converting enzyme 2 (ACE-2), found mainly on alveolar epithelium and endothelium. Activation of endothelial cells is thought to be the primary driver for the increasingly recognized complication of thrombosis(10-16).

Risk factors such as chronic obstructive pulmonary disease (COPD) or heart disease that can raise the danger for severe disease. COPD is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. Symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing. Older people are also more vulnerable for a severe case of COVID-19. Their lung tissues may be less elastic, and they may have weakened immunity because of advanced age(13,17-23).

Other important risk factor is the obstructive sleep apnea syndrome (OSAS). Risk factors for mortality in COVID-19, such as cardiovascular and cerebrovascular complications or comorbidities, for example hypertension, heart failure, coronary artery disease, cerebrovascular diseases, diabetes mellitus, and obesity

are commonly seen in OSAS patients(24-28). Fibrotic changes can also be seen after COVID-19, and fibrosis was previously shown to be a risk factor for OSAS(29).

The disengage between the severity of hypoxemia and the moderately mild respiratory discomfort reported by the COVID-19 patients, disparities with the experience of physicians regularly treating critically ill patients in respiratory failure(6,30). Happy or silent hypoxemia is not exclusively seen in COVID-19, but may also occur in patients with atelectasis, intrapulmonary shunt or right-to-left intracardiac shunt. Moreover, it has been reported in in patients with severe lesions in the glossopharyngeal or vagus nerves due to damage to the cranial nerve after neck cancer or congenital neuropathies, but these findings are unexpectedly absent in the autopsy reports that are now emerging in COVID-19 cases(3,31-34).

Pathophysiology of Dyspnea

Our interoceptive 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 to 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 a need to breathe, which is curiously absent in severe COVID-19 patients(3).

Dyspnea, also known as shortness of breath, is the conscious distressing symptom of difficulty in breathing that can be triggered by many clinical conditions. The term dyspnea designates the subjective perception of an inadequate effort to breathe, and is usually described as a sturdy constriction in the chest, air hunger, difficult breathing, breathlessness or a sensation of suffocation. Hence, dyspnea is a subjective symptom reported by patients, and should not be confused with rapid breathing (tachypnea), excessive breathing (hyperpnea), or hyperventilation(2,3,35-39).

The differential diagnosis of dyspnea is complex because there are many conditions which can lead to dyspnea in patients: anxiety disorders, asthma, pulmonary embolism, pneumothorax, hemothorax, pericardial effusion, acute heart failure, heart attacks, broken ribs, choking, etc(18). There are several clinical scales to assess dyspnea severity(40-42). The mMRC dyspnoea scale, based on a simple questionnaire, has shown its utility to assess dyspnea severity(42).

Thrombi within the pulmonary vasculature can cause severe hypoxemia, and dyspnea is related to pulmonary vascular obstruction and its consequences. Dyspnea can also arise from the release of histamine or stimulation of juxtacapillary receptors within the pulmonary vasculature. No biological mechanism exists, however, whereby thrombi in the pulmonary vasculature cause blunting of dyspnea (producing silent hypoxemia) (3,43,44).

Breathing is centrally controlled by the respiratory center in the medulla oblongata and pons regions of the brainstem that control the respiratory drive to match respiration to the metabolic demands of the body. The main input affecting the respiratory drive is derived from chemical feedback among peripheral and central chemoreceptors. The center is, however, also influenced by higher brain cortex, hypothalamic integrative nociception, feedback from mechanostretch receptors in muscle and lung, and metabolic rate. The output of the respiratory center can be divided into rhythm- (e.g. respiratory rate) and pattern generating (e.g. depth of breathing effort) signals, and these outputs may be controlled independently(45-47).

Hypoxemia produces dyspnea through the stimulation of the carotid bodies, which send signals to the respiratory center. The resulting increase in respiratory center output is transmitted down to the phrenic nerves and diaphragm, causing increased minute ventilation ($V\dot{}e$). Heightened medullary center activity is concurrently transmitted up to the cerebral cortex. It is this cortical projection (corollary discharge) that produces the unpleasant sensation of dyspnea(3,43,48,49).

Various sensory, pain and emotional stimuli affect the sensation of breathing via the cerebral cortex and hypothalamus. The abnormal sense of muscle effort is another contributor to dyspnea. Conscious awareness of the activation of respiratory muscles is not found in healthy breathing. Though, when the respiratory muscles are weary or debilitated due to altered lung mechanics (e.g. decreased thoracic compliance), breathing may be perceived as a substantial effort. Dyspnea can also be caused by input from the mechanoreceptors in the respiratory tract and the chest wall. Stimulation of vagal irritant receptors (e.g. bronchoconstriction, breathing through an external resistance) appears to intensify dyspnea. The contribution of metabolic rate in modulating sense of dyspnea in critically ill patients remains uncertain, despite its well-established role during exercise. The best-known determinants of the respiratory drive are the central and peripheral chemoreceptors(7,50).

Hypoxemia-driven tachypnea, hyperpnea and altered oxygenation predict clinical deterioration induced by either disease severity and/or host response and/or suboptimal management. Dyspnea is essential for survival as it can respond to a wide range of stimuli, including hypoxia, hypercapnia, irritants, acidosis, airway collapse, and pulmonary vascular congestion(3,28,48).

Dyspnea: PaO_2 vs. $PaCO_2$

Hypoxemia itself rather plays a limited role in the feeling of breathlessness experienced by patients with cardiopulmonary disease, contrary to hypercapnia that generates per se dyspnea. In contrast, changes in partial gas pressure of dissolved carbon dioxide in the blood ($PaCO_2$) seem the most significant component for dyspnea sense, triggering shifts in pH at the level of both the peripheral and central chemoreceptors. The ventilatory and dyspnea responses to hypoxia are heavily influenced by the prevailing $PaCO_2$. Severe hypoxia elicits an effective increase in ventilation only when background $PaCO_2$ surpasses 39 mm Hg. The respiratory centers are exquisitely sensitive to CO_2(7). Minor raises in $PaCO_2$ quickly evoke large increases in $V\dot{}e$. Consequently, an increase in $PaCO_2$ of 10 mm Hg causes an enormous respiratory discomfort which cannot be tolerated for even a few minutes(6,30).

Many patients with dyspnea are not hypoxemic, while those who are, usually experience only a slight improvement in symptoms after hypoxemia is corrected with supplemental oxygen therapy. When arterial P_aO_2 dewdrops under 40 mmHg, dyspnea frequently occurs. It is important to remark that the normal response to hypoxemia is a rise in minute ventilation, mainly by increasing tidal volume and respiratory rate. Augmented respiratory rate (tachypnea) and tidal volume (hyperpnea), cannot be confined dyspnea, and are consequently the most significant clinical signs of imminent hypoxemic respiratory failure(1-3,5-7).

It is also important to state that $PaCO_2$ serves as one of the fundamental regulators of cerebral blood flow (CBF). Hyperventilation causes decreased $PaCO_2$ which subsequently leads to arterial vasoconstriction thus dropping CBF and intracranial pressure. On the contrary, rise in $PaCO_2$ leads to augmented intracranial pressure finally leading to worsening level of consciousness, altered brainstem reflexes, and altered postural and motor responses(51-54).

The Pathophysiology of Happy or Silent Hypoxemia

One of the pathophysiological explanations for the severe hypoxemia in compliant lungs is impaired regulation of pulmonary blood flow and loss of hypoxic pulmonary vasoconstriction. It has been recently reported that SARS-CoV-2 mediated mitochondrial damage in the pulmonary artery smooth muscle cells explains the impairment of hypoxic pulmonary vasoconstriction. Reduced oxygen sensing in the carotid bodies due to mitochondrial injury has been mentioned as the main explanation for a limited respiratory drive and reduced dyspnea. Silent hypoxemia with the development of thrombi within the pulmonary vasculature often occurs. Increased thrombogenesis has been noted in patients with COVID-19(2,34,37).

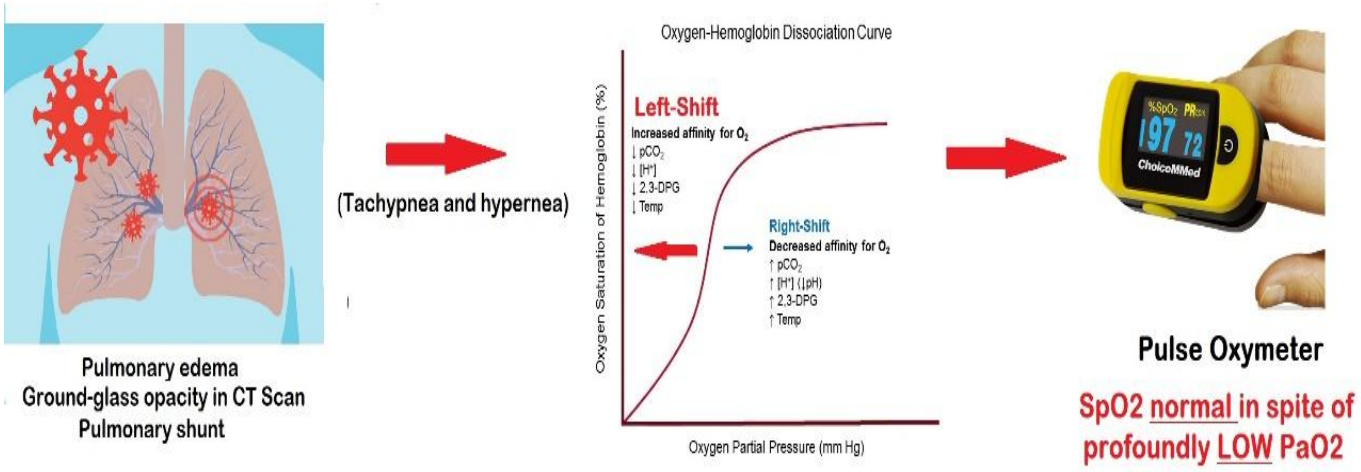
Ventilation/perfusion (V/Q) matching is determined by the balance between pulmonary ventilation and capillary blood flow assures the adequacy of gas exchange. In the initial phase of COVID-19, several mechanisms contribute to the development of arterial hypoxemia, without an associated dyspnea, although rapid clinical deterioration may occur.

Changes in Oxyhemoglobin Dissociation Curve

Pulse oximetry (PO) which measures oxygen saturation (SpO_2) is often used to detect hypoxemia. Nevertheless, SpO_2 should be carefully interpreted in COVID-19. The sigmoid shaped oxyhemoglobin dissociation curve seems to shift to the left, due to induced respiratory alkalosis (drop in $PaCO_2$) because of hypoxemia-driven tachypnea and hyperpnea. During hypocapnic periods, the affinity of hemoglobin for oxygen and thus oxygen saturation 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. In high altitude hypoxemia, hypocapnia significantly changes the oxygen-hemoglobin dissociation curve and recovers blood oxygen saturation. The alveolar gas equation also predicts that hyperventilation and the resulting drop in the alveolar partial pressure of CO_2 produces an increment in the alveolar partial pressure of oxygen and finally lead to a raise in SpO_2 (2) (Figure 1).

Liu et al. put forward a biological hypothesis about direct viral interaction with the heme group of hemoglobin, explaining the leftward shift of the curve in COVID-19. Regarding this theory, heme serum levels are increasing in COVID-19 along with harmful iron ions (Fe^{3+}), producing inflammation and cell death (ferroptosis). The last result of is the production of large amounts of serum ferritin to bind these free irons in order to decrease tissue damage(55).

Figure 1: Pulse oximetry (PO) which measures oxygen saturation ($SpO_{2)}$ is often used to detect hypoxemia. Nevertheless, PO should be carefully interpreted in COVID-19. The sigmoid shaped oxyhemoglobin dissociation curve shifts to the left, due to induced respiratory alkalosis (drop in $PaCO_2$) because of hypoxemia-driven tachypnea and hyperpnea. During hypocapnic periods, the affinity of hemoglobin for oxygen and thus oxygen saturation rises for a specified degree of PaO_2, explaining why SpO_2 can be well-preserved in spite of a profoundly low PaO_2.



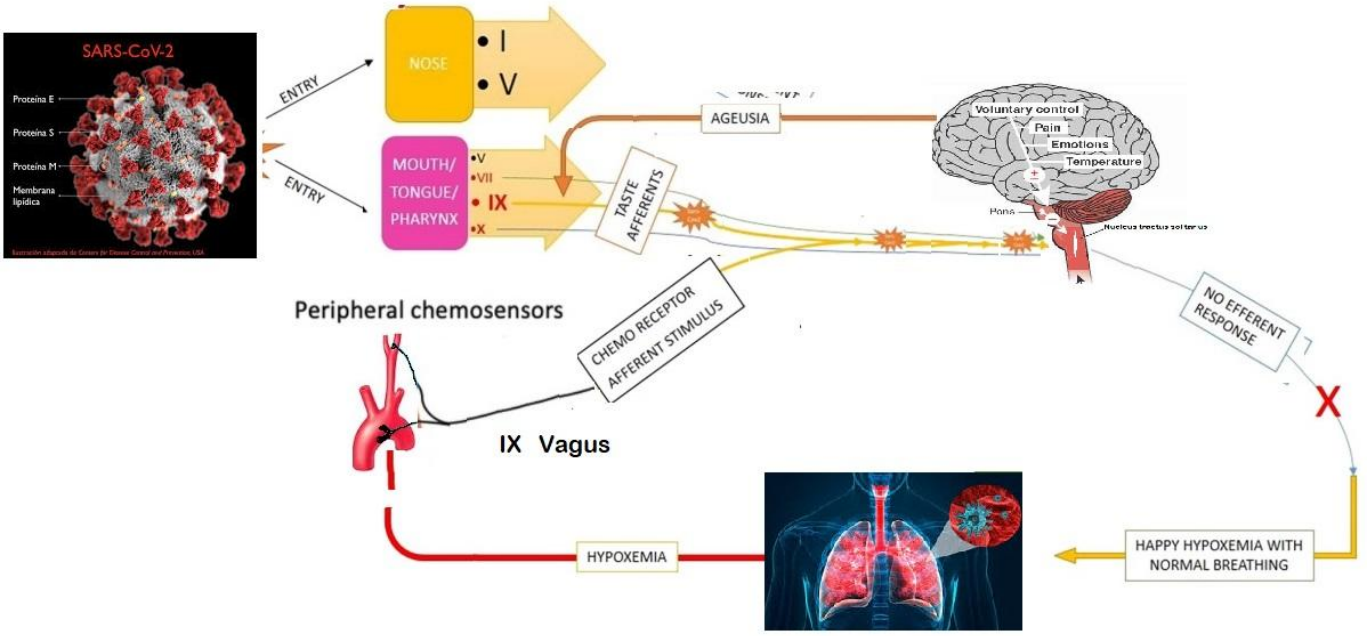
Neural Hypothesis of Happy or Silent Hypoxemia

What strikes as unusual is that those patients with happy or silent hypoxemia are tachycardic with tachypnea and respiratory alkalosis. These signs suggest that in any case some sensory information must reach the brainstem to prompt a partial compensatory reflex respiratory response enough to decrease the CO_2 level, which diffuses more speedily than oxygen across the alveoli. However, these patients have no conscious awareness of hypoxia(7).

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-COV2 on mitochondria or on the nerve fibers(1,7).

The carotid body is located at the bifurcation of the common carotid artery. The glossopharyngeal afferents which innerves the carotid body, and the vagal afferents innervating the respiratory tract, play a vital role in monitoring organ function and controlling body homeostasis through activation of the autonomic nervous system. It contains chemoreceptors that are primarily activated by a reduction in the arterial partial pressure of oxygen. Hypoxia activates the carotid body chemoreceptors, and the afferent signals are relayed at the nucleus tractus solitarius through the glossopharyngeal nerve. This normally leads to an increase in respiratory rate and vasoconstriction(7,56-59) (Figure 2).

Figure 2: The cranial nerves VII, IX, and X relay at the nucleus tractus solitarius. The carotid body is located at the bifurcation of the common carotid artery. It contains chemoreceptors that are primarily activated by a reduction in the arterial partial pressure of oxygen. Hypoxia activates the carotid body chemoreceptors, and the afferent signals are relayed at the nucleus tractus solitarius through. This normally leads to an increase in respiratory rate and dyspnea sensation. SARS-CoV-2 infects the brain through the olfactory bulb and olfactory nerves, through trans-synaptic spread, finally reaching the brainstem, and the nucleus tractus solitarius. The inflammation of the nucleus of the tractus solitarius by the virus invasion incites that the afferent hypoxia stimuli from the carotid bodies may not be effectively relayed at the nucleus tractus solitarius, resulting in an impaired efferent respiratory response. This explains why COVID-19 patients show almost normal breathing in the presence of severe hypoxemia (Happy or silent hypoxia).



These neurons are the primary sensory inputs of a series of reflex circuits that control key visceral functions, including blood pressure, swallowing, gastrointestinal motility, airway caliber, and tidal volume. They also produce the first afferents for the conscious feeling of dyspnea. Hypoxia activates the carotid body chemoreceptors, and the afferent signals are relayed at the nucleus tractus solitarius through the glossopharyngeal nerve. This normally leads to an increase in respiratory rate and vasoconstriction(7,60-62).

In the human brainstem, the solitary nucleus (SN) (nucleus of the solitary tract, nucleus solitarius, nucleus tractus solitarii) is a series of purely sensory nuclei (clusters of nerve cell bodies) forming a vertical column of grey matter embedded in the medulla oblongata. Through the center of the SN runs the solitary tract, a white bundle of nerve fibers, including fibers from the facial, glossopharyngeal and vagus nerves, that innervate the SN. The SN projects to, among other regions, the reticular formation, parasympathetic preganglionic neurons, hypothalamus and thalamus, forming circuits that contribute to autonomic regulation(62,63).

Neurons that innervate the SN mediate the gag reflex, the carotid sinus reflex, the aortic reflex, the cough reflex, the baroreceptor and chemoreceptor reflexes, several respiratory reflexes and reflexes within the gastrointestinal system regulating motility and secretion. Neurons which transmit signals about the gut wall, the stretch of the lungs, and the dryness of mucous membranes also innervate the SN. The first central neurons within the SN can participate in simple autonomic reflexes. Information goes from the solitary nucleus to a large number of other regions of the brain including the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala, as well as to other nuclei in the brainstem, such as the parabrachial area, the locus coeruleus, the dorsal raphe nucleus, and other visceral motor or respiratory networks)(7).

Mechanical or chemical stimuli of pulmonary receptors expressed on afferent vagal nerve terminals in the lung arrive in the brainstem through small-diameter myelinated (Aδ)- or unmyelinated (C)-fiber nerve axons with cell bodies in the jugular or nodose ganglia of the vagus. Both jugular and nodose pulmonary C-fiber afferents respond to inflammatory mediators and tissue acidification in a graded fashion; these can be considered nociceptive fibers as they do not react to eupneic breathing or other regular events, but are excited by noxious or potentially noxious stimuli(3).

The virus has been reported to affect both the upper and lower respiratory tract. The virus can enter through the nasal or oral cavity. From the oral cavity and pharynx, SARS-CoV-2 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 route(3,7,45).

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 an impaired efferent respiratory response. This may be the reason for the COVID-19 clinical presentation of almost normal breathing in spite of severe hypoxemia(7)

From Happy or Silent Hypoxemia to Acute Respiratory Distress Syndrome

A rising amount of evidence demonstrates that neurotropism is one shared feature of SARS-CoV-2. The infection of this virus has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected. Furthermore, some coronaviruses have been demonstrated able to spread via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways(64-70).

The most characteristic and challenging symptoms of Covid-19 are related to a ARDS.[71-74] Wang et al. reported that about 46% to 65% of the patients About 46% to 65% of the patients admitted in the intensive care unit (ICU) deteriorated in a brief period of time and died because of respiratory failure. According to these data, about 89% of the patients in ICUs could not breathe by their own in the intensive care, worsening in a short period of time and dying due to ARDS(17,75).

Reduced perception of dyspnea is finally a disorder of blood-gas interoception. It may disguise the severity of the clinical status in Covid-19 patients, and ultimately delay patients from looking for imperative medical care. Patients admitted with COVID-19 surprisingly die even without expressing the need for oxygen supplementation(2,5-7,37).

For clinicians the presence of happy or silent hypoxemia in Covid-19 patients, in spite of pronounced arterial hypoxemia, can erroneously lead to the conclusion that the patient is not in a critical condition. Those cases can quickly leapfrog clinical evolution stages and suffer ARDS, with concomitant cardiorespiratory arrest and death. It is urgent that the medical community recognizes happy or silent hypoxia in COVID-19 pandemics, which will allow physicians to provide a better patient care, reducing the risk of sudden medical complications and death.

Discussion and Conclusion

- It is crucial to recognize that several Covid-19 patients with pronounced arterial hypoxemia. yet without proportional signs of ARDS, with even deceiving cyanosis, don’t express the sensation of dyspnea.
- Physicians should not only to trust on the patient’s seeming happiness but closely monitor respiratory rate, signs of hyperventilation, oxygen saturation and invasive measurements of hypoxemia/hypocapnia at regular time intervals.
- Pulse oximetry should be interpreted with caution, because of the left-sided shifting of the oxyhemoglobin dissociation curve.

- For clinicians the presence of happy or silent hypoxemia in Covid-19 patients, in spite of pronounced arterial hypoxemia, can erroneously lead to the conclusion that the patient is not in a critical condition.

- Those cases can quickly leapfrog clinical evolution stages and suffer ARDS, with concomitant cardiorespiratory arrest and death.

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