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### Happy Hypoxemia In COVID-19

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#### ABSTRACT

The new coronavirus disease 2019 (COVID-19) pandemic is becoming a global health crisis that challenges health systems around the world. The clinical spectrum of COVID-19 varies from mild upper respiratory tract infections to severe pneumonia and acute respiratory distress syndrome, but there are also many patients present with an SpO<sub>2</sub> < 90% but without symptoms of shortness of breath. This phenomenon is called happy hypoxemia or silent hypoxemia. Shortness of breath or dyspnea is a subjective sensation resulting from inadequate breathing effort and is usually described as constriction in the chest, difficulty breathing air or difficulty breathing. Breathing is controlled centrally by the respiratory center in the medulla oblongata and the pons region which controls the "respiratory drive" and adapts respiration to the body's metabolic needs. The mechanisms that play a role in this phenomenon include the presence of intrapulmonary shunts, loss of pulmonary perfusion regulation, vascular microthrombus and impaired pulmonary diffusion capacity.

#### 1. Introduction

Coronavirus disease 2019 (COVID-19) was first discovered in Hubei province, China at the end of 2019. The virus is transmitted through human-to-human droplets and has spread widely in China and more than 190 countries in this world.<sup>1,2</sup> COVID-19 was declared a global pandemic on March 12, 2020, by the World Health Organization (WHO). The death toll from COVID-19 until February 24, 2021 reached 2,475,020 worldwide with 111,593,583 positive cases.<sup>3</sup> The clinical spectrum of COVID-19 varies from mild upper respiratory tract infections to severe pneumonia and respiratory syndrome. Many patients are hypoxaemic (SpO<sub>2</sub><80%) but do not complain of shortness of breath. This phenomenon is known as Happy Hypoxemia or Silent Hypoxemia.<sup>2,3</sup> Cases of happy hypoxia/hypoxemia in COVID-19 were first reported in April 2020, and subsequently, this phenomenon

became more common in confirmed COVID-19 patients, where patients came to the hospital with mild symptoms but rapidly worsened and ended up dying.<sup>4</sup> A cohort study in Wuhan by Guan et al found that out of 1,099 COVID-19 patients treated, only 19% of patients complained of shortness of breath, despite low PaO<sub>2</sub>/FiO<sub>2</sub>. Guan et al also reported that 86% of them had CT scan thorax, 62% with severe clinical symptoms while the other 46% require mechanical ventilation.<sup>5</sup>

The severity of hypoxemia is associated with a high mortality rate of hospitalized COVID-19 patients. This phenomenon is important to study as an effort to increase the awareness of medical personnel and take anticipatory measures to determine the need for intensive care for COVID-19 patients.<sup>6,7</sup>

## Coronavirus disease 2019

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been previously identified in humans. There are two types of coronavirus that are known to cause diseases that can cause severe symptoms, namely middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).<sup>8</sup>

SARS-Cov-2 is a virus consisting of a single chain of RNA. This virus consists of several genetic types, including alpha, beta, gamma, and delta. Among the 4 genetic types, alpha and beta are a group of viruses that can infect the human respiratory tract. SARS-Cov2 and SARS Cov1 are a group of beta coronaviruses. The naming of coronavirus occurs because of the structure of the virus that resembles a crown, this is due to the large number of proteins that surround the viral membrane making it easier for the virus to bind to the receptor.<sup>9</sup>

In general, everyone is susceptible to being infected with COVID-19. If we are exposed to the virus in large quantities at one time, it can cause disease even though the body's immune system is functioning normally. People with weak immune systems, such as the elderly, pregnant women, and other conditions, can experience faster and more severe disease progression.<sup>10</sup>

Coronaviruses can only reproduce through their host cells because viruses cannot live without host cells. The cycle of the Coronavirus begins with the attachment and entry of the virus into the host cell which is mediated by Protein S on the surface of the virus.<sup>10</sup> Protein S is the main determinant in infecting the host species as well as the determinant of tropism. In the SARS-CoV study, the S protein binds to a receptor on the host cell, the enzyme ACE-2. ACE-2 can be found in the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, large intestine, skin, and others. After the virus has successfully entered, the next process is the translation of gene replication from the viral genomic RNA. Then proceed with replication and transcription where the synthesis of

viral RNA through translation and assembly of the viral replication complex. The next stage is the assembly and release of the virus.<sup>10</sup> The life cycle of the SarsCov-2 virus is described in Figure 1.

The virus enters the upper respiratory tract and then replicates in upper respiratory epithelial cells (performing its life cycle). The virus spreads to the lower respiratory tract. The incubation period of the virus is about 3-7 days and can cause severe acute respiratory syndrome (SARS) so it was named SARSCoV-2.<sup>10</sup>

Viral infections generally trigger an innate immune response and an adaptive immune response. The innate immune response is a common mechanism against all infections characterized by the release of cytokines. The adaptive immune response is a specific reaction to infection that involves two types of white blood cells, namely T cells as a cellular and B cells as an antibody response.<sup>10</sup>

Activation of innate immunity is activated when the virus infects cells, followed by infiltration of monocytes to the site of infection. Monocytes produce inflammatory mediators such as interleukin (IL)-6, IL-1 $\beta$ , IL-2, IL-7, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1), C-reactive protein, and others. Symptoms that appear at this time in the form of fever, cough, malaise, and diarrhea. This inflammatory mediator acts as a chemoattractant that sends a signal so that leukocytes gather around the site of infection. Leukocyte levels will decrease on hematological examination. Small amounts of inflammatory mediators can enter the bloodstream, causing local blood vessel constriction, and damage leading to increased capillary permeability, so that plasma fluid enters the interstitial space, causing edema alveolar.<sup>11,12</sup>

One of the cells that can be infected by the SarsCoV-2 virus is pneumocyte type II, which causes a decrease in surfactant production, as a result, the alveoli tend to collapse. collapse coupled with edema due to inflammation causes diffusion disorders and hypoxia, so the patient requires more effort to breathe.<sup>12</sup>

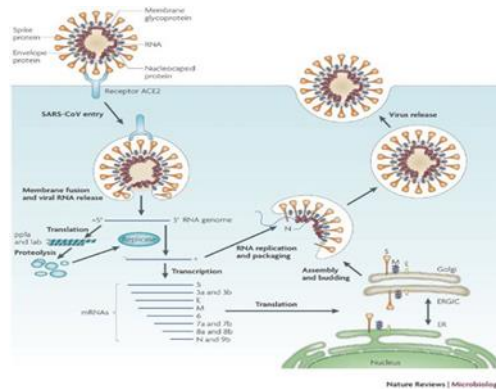


Figure 1. SARS-CoV-2 virus life cycle<sup>10</sup>

Patients with COVID-19 are clinically distinguished by asymptomatic, mild, moderate, severe, and critical conditions. The patient is asymptomatic, has no complaints, even though the results of the examination give confirmed COVID-19 results. Patients with mild clinical symptoms usually only complain of fever, cough, fatigue, anosmia, ageusia, sore throat, headache, diarrhea, nausea, and vomiting without signs of dehydration. This complaint is often reported before the symptoms of shortness of breath.<sup>13</sup>

The clinical patient was having symptoms of pneumonia in the form of fever, cough, shortness of breath with SpO<sub>2</sub> of 93% in room air. Severe clinical symptoms of pneumonia plus at least one of the following symptoms: respiratory rate >30x/min, respiratory, or SpO<sub>2</sub> <93% of room air. Critical clinical symptoms, if the patient with COVID-19 has ARDS, sepsis, and/or septic shock.<sup>13</sup>

### Pathophysiology dyspnea

Dyspnea, also known as shortness of breath, is a symptom that interferes with breathing that is consciously triggered by many clinical conditions. The term dyspnea refers to the subjective perception of inadequate breathing effort and is usually described as a feeling of tightness or heaviness in the chest, difficulty inhaling air, difficulty breathing, or shortness of breath. Dyspnea is subjective according to the symptoms reported by the patient, complaints must be distinguished from rapid breathing (tachypnea), deep breathing (hyperpnea), or hyperventilation.<sup>14</sup>

Breathing is controlled by the respiratory center in

the medulla oblongata and the pons, which control the "respiratory drive" by adjusting respiration and the body's metabolic needs.<sup>14</sup> Main input that affects breathing comes from chemical feedback, namely central and peripheral chemoreceptors. Central chemoreceptors are also affected by hypothalamic integrative nociception, feedback from *mechano-stretch* in respiratory and lung muscles, and metabolic rate. Output from the respiratory center can be divided into breathing rhythm (breathing rate) and breathing pattern (breathing depth) where these outcomes can be controlled consciously.<sup>15</sup>

Dyspnea relates to whether this sensation occurs at rest or during activity. One of the assessments to assess the severity of shortness of breath can use the Medical Research Council (MRC) modified dyspnea scale, which categorizes dyspnea from grade 0 (dyspnea only with activity) to grade 4 (severe shortness of breath to leave the house or shortness of breath when dressing). concerning subjects of the same age.<sup>16</sup> Various sensory, painful, and emotional stimuli can affect breathing via the cerebral cortex and hypothalamus.<sup>17</sup> In people with normal breathing, breathing processes, and respiratory muscle movements occur involuntarily. This is different if there is fatigue in the respiratory muscles or mechanical disturbances in the chest wall (chest wall compliance disorders) then the breathing process will require a stronger effort.<sup>14</sup>

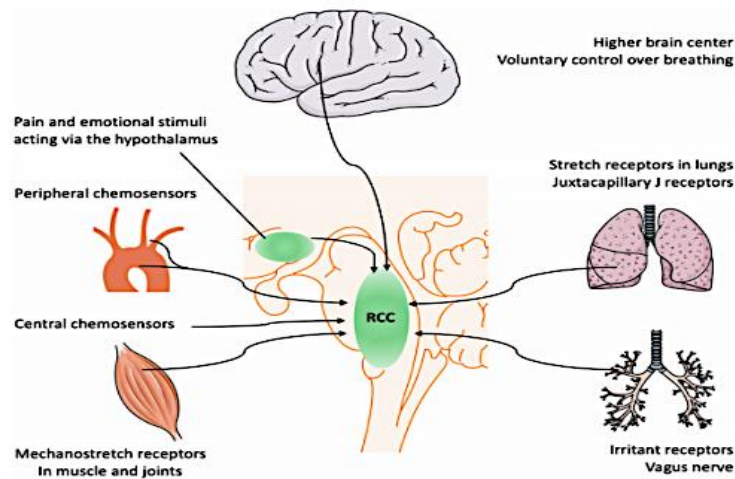


Figure 2. Respiratory input control center<sup>14</sup>

Dyspnea can also be caused by input from mechanoreceptors in the respiratory tract and chest wall. Stimulation of vagal irritant receptors (eg, bronchoconstriction, external respiratory arrest) leads to dyspnea. The increase in the body's metabolic rate also plays a role in causing dyspnea. Increased body metabolism such as during exercise can trigger dyspnea. It is also found in clinically critical patients, but the mechanism is still unclear.<sup>18</sup>

Control of the respiratory center consists of central and peripheral chemoreceptors. Changes in gas partial pressure of dissolved carbon dioxide in the blood (PaCO<sub>2</sub>) is an important component that causes a shift in pH in both peripheral and central chemoreceptors.<sup>14</sup> Under stable conditions, arterial PaCO<sub>2</sub> is determined by the equation in Figure 3:

$$PaCO_2 = \frac{K \cdot VCO_2}{V_e \cdot \left(1 - \frac{V_d}{V_t}\right)}$$

Figure 3. Arterial PaCO<sub>2</sub> equation<sup>14</sup>

Description:

- K = constant (863 mmHg)
- VCO<sub>2</sub> = production rate CO<sub>2</sub>
- V<sub>e</sub> = ventilation per minute
- V<sub>d</sub> = loss space
- V<sub>t</sub> = tidal volume

Response to hypercapnia caused by increased VCO<sub>2</sub> hypoventilation or increased is to increase the urge to breathe and the volume of ventilation per minute thereby triggering shortness of breath.<sup>19,20</sup> In contrast to hypercapnia, hypoxemia has a limited role in inducing the sensation of shortness of breath

experienced by patients with cardiopulmonary disease. Hypoxemia is inversely proportional to hypercapnia which is the main factor that can stimulate shortness of breath.<sup>14</sup> Healthy people have a respiratory drive in conditions of mild hypoxemia (PaO<sub>2</sub> 60–65 mmHg) for example when a person is at high altitudes.<sup>17</sup> Not all

dyspnea patients will experience hypoxemia, usually these patients will only experience minimal improvement with oxygen therapy <sup>14</sup>

Complaints of shortness of breath or dyspnea are often felt when the PaO<sub>2</sub> drops to 40 mmHg. The body's response to hypoxemia is an increase in minute ventilation, primarily by increasing tidal volume and respiratory rate increased respiratory rate (tachypnea) and tidal volume (hyperpnea) but not dyspnea. Tachypnea and hyperpnea are important clinical signs of respiratory hypoxemia.<sup>21</sup>

Hyperventilation causes a decrease in PaCO<sub>2</sub> which in turn causes arterial vasoconstriction thereby reducing cerebral blood flow and intracranial pressure. Conversely, an increase in PaCO<sub>2</sub> causes an increase in intracranial pressure which in turn causes a decrease in consciousness.<sup>22,23</sup> An understanding of hypoxemia can increase a more complete understanding of the clinical manifestations of COVID-19 patients so that they can be managed appropriately.<sup>20</sup>

### Changes in the oxyhemoglobin dissociation curve

Oxygen saturation as measured by pulse oximetry (SpO<sub>2</sub>) was used to detect hypoxemia. However, SpO<sub>2</sub> should be interpreted with caution in COVID-19 patients concerning hyperventilation and hypocapnia. It is advisable to check PaO<sub>2</sub> through blood gas

analysis of COVID-19 patients, the oxyhemoglobin dissociation curve changes in a sigmoid shape. The oxyhemoglobin dissociation curve appears to shift to the left as a result of respiratory alkalosis induced by low PaCO<sub>2</sub>, whereas the low PaCO<sub>2</sub> is triggered by hypoxemia. During the hypocapnic period, there is an increase in the affinity of hemoglobin for oxygen so that oxygen saturation increases to a certain degree, from PaO<sub>2</sub> and SpO<sub>2</sub> can still be normal even in a low PaO<sub>2</sub> state.<sup>24</sup>

This feature is also seen in hypoxemia at altitude, where hypocapnia significantly shifts the oxyhemoglobin dissociation curve and increases blood oxygen saturation.<sup>25</sup> The alveolar gas equation also shows that hyperventilation and a decrease in the pressure of carbon dioxide (PaCO<sub>2</sub>) cause an increase in the alveolar partial pressure of oxygen and ultimately an increase in SpO<sub>2</sub>.<sup>24</sup> Another mechanism was reported by Liu et al. Liu et al. stated the hypothesis of direct viral interaction with hemoglobin. According to this hypothesis, an increase in serum heme levels in COVID-19 together with harmful iron ions (Fe<sup>3+</sup>) causes inflammation and cell death (ferroptosis). This condition causes the production of serum ferritin to increase in large quantities to bind free iron to reduce tissue damage.<sup>26,27</sup>

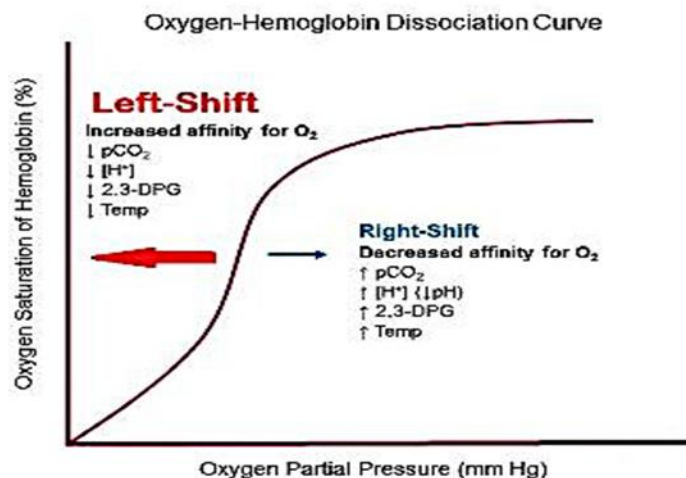


Figure 4. Shifting of the oxyhemoglobin curve<sup>5</sup>

## Hypoxemia

Hypoxemia is a condition of decreased oxygen ( $O_2$ ) levels in arterial blood. Hypoxia is a condition of inadequate supply of  $O_2$  to the tissues. Hypoxia can be caused by hypoxemia or impaired blood supply to tissues. Hypoxemia can be caused by impaired oxygenation, anemia, or decreased affinity of hemoglobin (Hb) for  $O_2$ . Impaired oxygenation is hypoxemia resulting from low  $O_2$  transfer from the lungs to the bloodstream, which is characterized by low  $O_2$  partial pressure ( $PaO_2 < 80$  mmHg). The partial pressure of arterial blood oxygen as a marker of oxygenation in arterial blood can be measured from blood gas analysis.<sup>28,29</sup>

## Pathophysiology of happy hypoxemia

The mismatch between the severity of hypoxemia and the relatively mild respiratory complaints reported by COVID-19 patients differs from that of patients with generalized respiratory failure.<sup>30</sup> One of the pathophysiological explanations for severe pulmonary hypoxemia is impaired regulation of pulmonary blood flow and loss of vasoconstriction from the hypoxic lung. SARS-CoV-2 is thought to mediate mitochondrial damage in pulmonary artery smooth muscle cells

leading to hypoxic pulmonary vasoconstriction disorders.<sup>31</sup> Another factor in the form of decreased oxygen sensing in the carotid body due to mitochondrial damage is considered to be the main cause of impaired respiratory drive, thereby reducing the appearance of symptoms of shortness of breath in COVID-19 patients.<sup>31</sup>

Happy hypoxemia or silent hypoxemia can also be caused by the formation of microthrombi in the pulmonary vessels, this is related to the increased thrombogenesis found in patients with COVID-19.<sup>14</sup> but may also occur in patients with atelectasis, intrapulmonary shunts such as arteriovenous malformations or intracardiac right-to-left shunts. Adequate gas exchange is primarily determined by the balance between pulmonary ventilation and capillary blood flow, which is called ventilation/perfusion (V/Q) matching.<sup>32</sup>

In the early phase of COVID-19, several mechanisms contribute to the development of arterial hypoxemia without an increase in the work of breathing concomitantly with a rapid deterioration in the clinical condition, this is explained by Figure 5.<sup>32</sup>

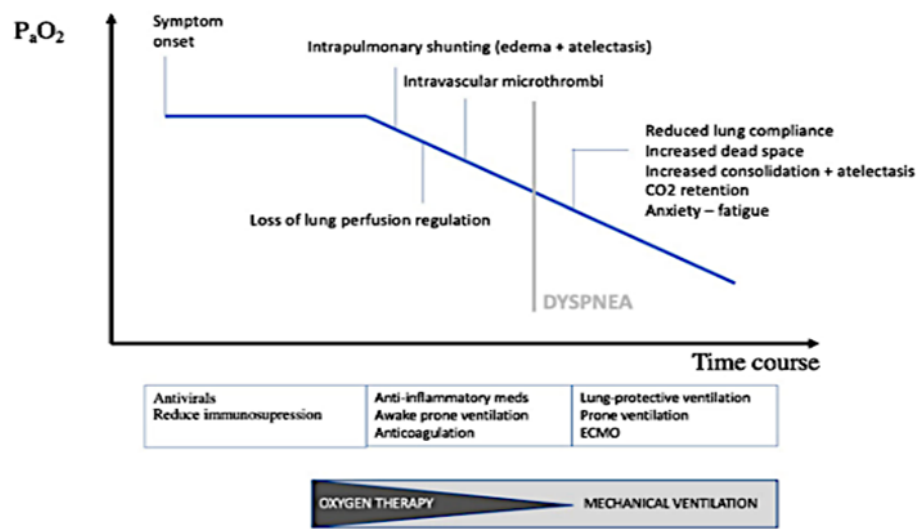


Figure 5. Mechanisms of hypoxemia in COVID-19<sup>32</sup>

## **Causes of hypoxemia covid-19**

### **Intrapulmonary pylon**

Arterial hypoxemia early in SARS-CoV-2 infection is mainly due to the V/Q imbalance and thus the persistent pulmonary arterial blood flow to the unventilated alveoli, reflected by a marked increase in the P(Aa)O<sub>2</sub> gradient. The infection leading to localized interstitial edema is simple, especially in the pulmonary interstitium with different elastic properties. Due to increased pulmonary edema (causing ground-glass opacities radiographic chest pressure superimposed, alveolar collapse, and large portions of cardiac output draining fluid into unoxygenated lung tissue, resulting in intrapulmonary shunts.<sup>21</sup>

Tidal volume increases disease-causing an increase in negative intrathoracic pressure during inspiration, coupled with increased lung permeability due to inflammation, thereby increasing the progression of edema (alveolar flooding) and lung injury due to P-SILI (patient self-inflicted lung injury). As the disease progresses, pulmonary edema increases, the alveolar collapse becomes more severe and extensive, resulting in atelectasis that further increases the area that is not getting oxygen. Consequently, this further decrease in oxygenation cannot be fully corrected by increasing the FiO<sub>2</sub>.<sup>33</sup>

### **Loss of regulation of pulmonary perfusion**

Lang et al reported high blood flow to unoxygenated alveoli in COVID-19 patients due to failure mechanisms in response to alveolar hypoxia.<sup>31</sup> This mechanism can be triggered by the release of inflammatory mediators such as endogenous vasodilator prostaglandins, bradykinins, and cytokines associated with the inflammatory process.<sup>34</sup> Vasoplegia also appears to affect the loss of pulmonary perfusion regulation, possibly due to surfactant damage resulting in disturbances in alveolar surface tension and damage to lung parenchymal structures. This is the initial stage of P-SILI (patient self-inflicted lung injury). P-SILI describes all conditions when the maintenance breathing in patients with damaged lung conditions and high respiratory drive can result in changes in lung

pressure and volume that can worsen the patient's condition.<sup>35,36</sup>

Another mechanism is dysregulation of the renin-angiotensin system (RAS) which contributes to the pathophysiology of COVID-19. ACE2 is the main receptor used by SARS-CoV-2 to enter host cells. ACE2 plays a role in converting angiotensin II (Ang II) to angiotensin 1-7 (Ang 1-7) and also degrades bradykinin. Decreased levels of ACE2 cause an increase in Ang II which mediates pulmonary vasoconstriction through agonism at Ang II receptors.<sup>37,38</sup> Liu et al showed that the increase in serum Ang II levels was proportional to viral load and lung damage in COVID-19.<sup>39</sup>

### **Intravascular microthrombus**

Endothelial injury is emerging as a key feature of the pathogenesis of COVID-19. A sars-cov2 virus can directly infect pulmonary capillary endothelial cells and bind to ACE2.<sup>29</sup> Intravascular microthrombi are the result of an imbalance between procoagulant and fibrinolytic activity in the presence of acute inflammation and endothelial injury.<sup>35</sup>

The increase in procoagulant activity in COVID-19 patients is due to activity complement system-mediated blood-clotting. Another possibility is the inhibition of plasminogen activation and fibrinolysis through increased activity of plasminogen activator inhibitors (PAI-1 and 2) induced as acute-phase proteins under the influence of IL-6. Diffuse intravascular coagulation (DIC) is also seen in patients with severe COVID-19, this is due to the release of tissue endothelial factor and activation of clotting factors VII and XI. Many patients with COVID-19 have elevated D-dimers that signal increased blood clotting. D-dimer levels can be used to predict mortality in COVID-19 in this case, it appears in a study in patients with elevated D-dimer who were hospitalized, more often had DIC (71%) with a poor prognosis, compared with patients who did not have a 0.6% increase in D-dimer.<sup>40,41,42</sup>

Pulmonary autopsy in severe and critical clinical COVID-19 shows fibrin deposition, diffuse alveolar damage, thickening of blood vessel walls, and frequent blockage of pulmonary capillaries by microthrombi and

larger thrombi causing pulmonary artery thrombosis and pulmonary embolism.<sup>43</sup> The hypercoagulable state in COVID-19 patients causes ventilation-perfusion imbalance (V/Q mismatch) and lung tissue damage. In addition, coagulation can also activate C-reactive protein (CRP) and activate subsequent complement and fibrinogen synthesis in the liver as an acute-phase protein in COVID-19.<sup>44</sup>

### **Impaired diffusion capacity**

The pulmonary diffusion capacity (DLCO) can be impaired, although pure diffusion impairment is rarely the cause of an increased P(Aa) O<sub>2</sub>.<sup>38</sup> SARS-CoV-2 spreads within type II alveolar cells, where large numbers of viral particles are produced and released, followed by an immune response that mediates the destruction of infected cells (virus-linked pyroptosis). The loss of alveolar epithelial cells and a procoagulant state causes the initially clean basement membrane to be covered by debris consisting of fibrin, dead cells, and products of complement activation known as the hyaline membrane.<sup>45</sup>

The hypoxic vasoconstriction in COVID-19 with hyperdynamic pulmonary circulation may not allow sufficient time for red blood cells to compensate for oxygen demand in the blood by balancing their oxygen uptake. As a result, the diffusion disruption that occurs in COVID-19 leads to an increase in the P(Aa) O<sub>2</sub> gradient and arterial hypoxemia.<sup>38</sup>

Xiaoneng et al, in the study, showed a decrease in diffusion capacity in COVID-19 patients. The prevalence of impaired alveolar diffusion capacity was associated with the severity of the disease, being 30.4% in mild disease, 42.4% in pneumonia, and 84.2% in severe pneumonia, respectively. Long-term studies are needed to determine whether this disorder is persistent as seen in MERS where 37% of MERS sufferers still have decreased alveolar diffusion capacity despite the recovery.<sup>45</sup>

Based on the explanation above, most of the explanations for the relationship between the severity of hypoxemia in COVID-19 and relatively normal lung mechanisms. Abnormalities of gas exchange in some COVID-19 patients can occur early When initially

infected there is no increase in airway resistance, and there is no anatomical and physiological increase in dead space so that respiratory effort has not increased because lung capacity is still normal in many patients, especially in patients who had the previous history of lung disease.<sup>46</sup>

Gattioni et al in a cohort study in which 16 clinically critical COVID-19 patients obtained a relatively normal lung compliance value of  $50.2 \pm 14.3$  ml / cmH<sub>2</sub>O, this is in line with an increase in shunt of  $0.50 \pm 0.11$ .<sup>36</sup> This is in stark contrast to most acute lung injury and ARDS disorders. The relatively large lung compliance indicates a well-maintained lung gas volume despite a concurrent increase in shunts, this explains the absence of complaints of shortness of breath during the early phase of the disease.<sup>47</sup>

Tachypnea triggered by hypoxemia, hyperpnea, and changes in oxygenation are clinical predictors of damage to the lungs caused by the severity of the disease and/or the host's response to the virus.<sup>47</sup> As the disease progresses the consolidated areas do not expand easily because they have higher transpulmonary pressures. An increase in this area reduces the total lung capacity and increases the respiratory effort.<sup>35</sup> There is evidence that the capacity of pulmonary ventilation is reduced in patients with SARS-CoV-2 pneumonia (as seen in pneumococcal pneumonia) most likely due to reduced surfactant activity, which increases the work of breathing.<sup>35</sup> Physiological dead space is also increased due to reduced blood flow caused by thrombosis. Psychological factors and anxiety experienced by COVID-19 patients also affect cortical feedback to the respiratory center so that as complaints of the disease progresses, the shortness of breath become clearer and more severe.<sup>35</sup>

### **The hypothesis of neurons in happy hypoxemia**

The carotid body is located at the branch of the common carotid artery. Glossopharyngeal afferent neurons that innervate the carotid body, and vagal afferents that innervate the respiratory tract, play important roles in monitoring organ function and controlling body homeostasis through activation of the



autonomic nervous system. The carotid bodies contain chemoreceptors that are primarily activated by a reduction in the arterial partial pressure of oxygen. Hypoxemia activates chemoreceptors in the carotid body and transmits afferent signals to the nucleus of the tractus solitarius via the glossopharyngeal nerve. This will cause an increase in respiratory rate and pulmonary artery vasoconstriction and a sensation of dyspnea.<sup>48</sup>

Patients with happy hypoxemia have tachycardia, tachypnea, and respiratory alkalosis. These signs suggest that some sensory information is reaching the brainstem to induce the respiratory reflex to compensate for the fall in CO<sub>2</sub> levels until oxygen reaches the alveoli more quickly. Damage to sensing neurons in hypoxaemic COVID-19 patients is caused by a cytokine storm that results from the inflammatory

response or the direct effect of SARS-COV2 on neuronal mitochondria.<sup>48</sup>

This virus attacks 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 can spread along the axons of cranial nerves V, VII, IX, and X. Therefore, SARS-CoV-2 can cause inflammation in the nucleus of the tractus solitarius through the axonal pathway. by SARS-CoV-2 in the nucleus tractus solitarius can interfere with afferent hypoxic stimulation from the carotid body which may not be transmitted effectively to the nucleus tractus solitarius resulting in an impaired efferent respiratory response. This mechanism is the reason for the COVID-19 clinical picture of nearly normal breathing despite severe hypoxemia.<sup>49</sup> This is explained in Figure 6.

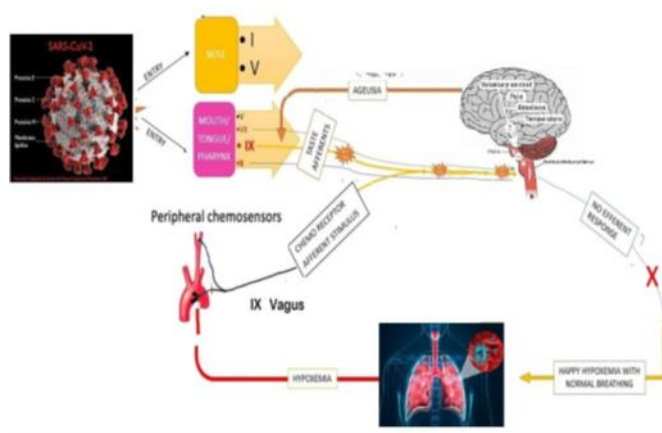


Figure 6. The hypothesis of neurons in COVID-19<sup>48</sup>

## 2. Conclusion

The phenomenon of Happy hypoxemia in COVID-19 is characterized by hypoxemia without any symptoms of shortness of breath. This is caused by several mechanisms including intrapulmonary shunts, loss of pulmonary perfusion regulation, vascular microthrombi, and impaired lung diffusion capacity as well as neuronal damage resulting in impaired hypoxemia reflexes in the carotid body.

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