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Review

Asymptomatic Hypoxemia as a Characteristic Symptom of Coronavirus Disease: A Narrative Review of Its Pathophysiology

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Abstract: Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a pandemic and caused a huge burden to healthcare systems worldwide. One of the characteristic symptoms of COVID-19 is asymptomatic hypoxemia, also called happy hypoxia, silent hypoxemia, or asymptomatic hypoxemia. Patients with asymptomatic hypoxemia often have no subjective symptoms, such as dyspnea, even though hypoxemia is judged by objective tests, such as blood gas analysis and pulse oximetry. Asymptomatic hypoxemia can lead to acute respiratory distress syndrome, and the delay in making a diagnosis and providing initial treatment can have fatal outcomes, especially during the COVID-19 pandemic. Thus far, not many studies have covered asymptomatic hypoxemia. We present a review on the human response to hypoxemia, focusing on the respiratory response to hypoxemia rather than the pathophysiology of lung injury arising from SARS-CoV-2 infection. We have also discussed whether asymptomatic hypoxemia is specific to SARS-CoV-2 infection or a common phenomenon in lung-targeted viral infections.

Keywords: COVID-19; SARS-CoV-2; silent hypoxemia; happy hypoxia; pathophysiology; narrative review

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1. Introduction

The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a pandemic since 2020 [1]. In Japan, measures are being taken to solve the problems that have arisen due to the COVID-19 pandemic, after five waves of epidemic peaks and four state of emergency declarations since February 2020 (Figure 1). Since the end of 2020, variants of SARS-CoV-2 that are known for their high transmission ability and antigenic changes have been termed as variants of concern (VOC) [2]. The incubation period of COVID-19 is ≤14 days, and the disease often develops within five days of exposure to the pathogen [2]. The proportion of asymptomatic patients is unknown, but a recent meta-analysis estimated it to be approximately 30% [3,4]. Influenza-like symptoms such as fever; respiratory symptoms including cough; sore throat; headache; and malaise are often observed in symptomatic patients, although nasal discharge and obstruction are thought to be less frequent. In a meta-analysis of 10 studies, the frequencies of olfactory and gustatory disturbances were 52% and 44%, respectively [5]. If olfactory and gustatory disorders are present in addition to influenza-like symptoms, then the probability of COVID-19 is high. Thus, there have been many pathologies during the COVID-19 pandemic that differ from those occurring during the common cold and influenza pandemic. According to an analysis of 2638 patients (enrolled by 7 July 2020) from the COVID-19 Inpatient Registry in Japan (COVIREGI-JP), the median patient age

was 56 years (interquartile range: 40–71 years), and more than half were male (58.9%, 1542/2619) [6]. The median time to hospitalization was 7 days, the median length of stay was 15 days, and the mortality rate was 7.5%. Furthermore, 62% of patients did not require oxygen, 30% required oxygen, and 9% required mechanical respiratory support including noninvasive positive pressure ventilation (NPPV) and high-flow nasal cannula (NHFC). There have been many reports of patients who were "mildly ill" and were treated at home, but then developed sudden-onset respiratory failure and died. The disease characteristics, combined with its strong infectious ability, have contributed to the collapse of healthcare. The basis of this "peculiar phenomenon" of COVID-19 is hypoxemia. Although objective tests using blood gas analysis and pulse oximetry show clinically significant hypoxemia, they are not always accompanied by subjective symptoms such as dyspnea. Silent hypoxemia syndrome, also known as happy hypoxia, has been attracting attention because it is accompanied by no subjective symptoms [7–9]. In Japan, guidelines for the diagnosis and treatment of hypoxemia have been established. The Japanese guidelines for the diagnosis and treatment of asymptomatic hypoxemia state, "Even if the disease is judged to be mild during examination, it may rapidly progress by the second week of onset, and worsening of the disease is almost always manifested as a progression of hypoxemia [10]. Therefore, measurement of SpO_2 by pulse oximetry is required whenever possible in addition to subjective symptoms" [8,10].

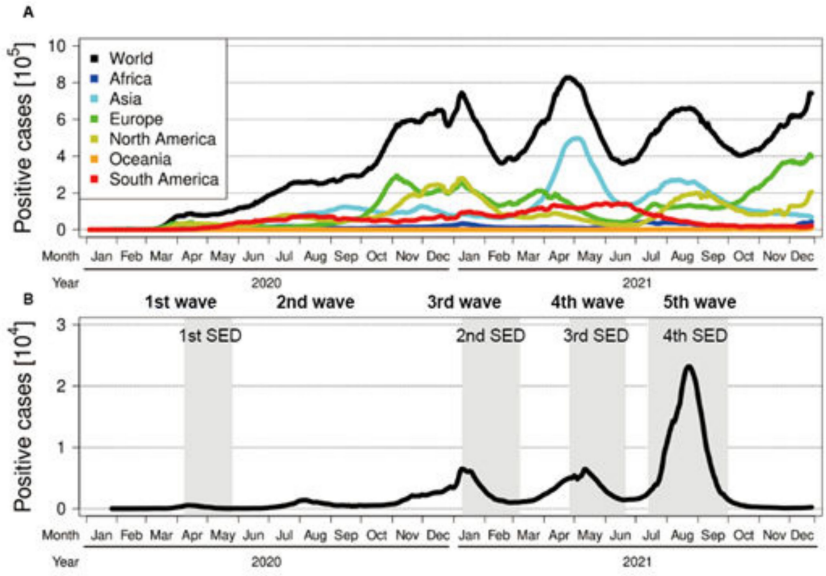

Figure 1. Trends in outbreaks of new coronavirus infection. (**A**) Cross-country data on PCR testing for SARS-CoV-2. Figure was constituted based on published data from a public GitHub repository (https://github.com/owid/covid-19-data/tree/master/public/data/testing (accessed on 28 December 2021)) [11]. (**B**) In Japan, measures are being taken to meet the needs that have arisen due to the coronavirus disease (COVID-19) pandemic, after five waves of epidemic peaks and four state of emergency declarations (half-tone dot meshing) since February 2020. SED: state of emergency declaration. Figure was constituted based on published data from Japanese Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/content/pcr_positive_daily.csv (accessed on 28 December 2021)).

Patients with "happy hypoxia" did not always complain of euphoric awareness and did not present objective symptoms; therefore, it would be more appropriate to describe this condition as "silent hypoxemia" rather than "happy hypoxia." In this discussion, we will consider this condition as "silent hypoxemia (asymptomatic hypoxemia)" (Table 1).

Table 1. Principal elements of asymptomatic or silent hypoxemia.

Elements of Silent Hypoxemia
hypoxemia: $PaO_2\downarrow$, $SaO_2\downarrow$
dyspnea (-)
air hunger (-)
breathing effort (-)

A survey was conducted on a social network to know how many doctors have experienced "happy hypoxia." The results of the survey on the social network service revealed the existence of "happy hypoxia" was denied by 7.1% of responders [12].

Anesthesiologists and intensivists need to be aware of two points: (1) hypoxemia is often not accompanied by dyspnea; (2) cardiopulmonary response as a compensation for hypoxemia may be abruptly lost. The response to hypoxemia is greatly influenced by differences in respiratory drive related to an individual's age, concomitant illnesses, medications taken, and genetic background. Furthermore, not many published studies have covered asymptomatic hypoxemia. Therefore, the present review discusses the respiratory responsiveness and pathophysiology of the asymptomatic hypoxemia "syndrome" from the viewpoint of SARS-CoV-2 infection.

2. Hypoxia and Hypoxemia

Hypoxia can be conceptually defined as a state of inadequate oxygen supply to the whole body or to specific tissues or organs, wherein oxygen metabolism is suppressed. In clinical medicine, hypoxia or tissue hypoxia is often considered to be a negative mismatch between oxygen supply and demand at the organ, tissue, or cellular level [13–16].

Hypoxemia is defined as "a condition in which arterial blood oxygenation is not normal under non-anoxic conditions." Hypoxemia refers to a condition in which the oxygen concentration in the blood is low. On the contrary, hypoxia can be defined as a condition in which the oxygen concentration in tissues, organs, or the entire body is low [13,14,16].

Arterial blood gas analysis and pulse oximetry can be used to objectively determine the amount of oxygen in arterial blood if the measurements are performed correctly. As emphasized in the Guide to the Treatment of Coronavirus Infections of Infectious Diseases of the New Type (COVID-19), 5th Edition [10], the measurement and evaluation of arterial blood oxygen saturation using pulse oximetry (SpO_2) or arterial blood gas analysis (PaO_2 and SaO_2) are important for determining the severity of COVID-19 [17,18].

According to the guidelines, $SpO_2 \leq 93\%$ before receiving oxygen therapy is used as the criterion for classification. An SpO_2 value of 93% is used as the clinical criterion with a margin, but in reality it is assumed to be $\leq 90\%$. In other words, some patients had no subjective complaints of respiratory distress, even when the PaO_2 was below 60 mmHg in terms of partial pressure in arterial blood, indicating that hypoxemia is objectively evident.

Silent hypoxemia is a finding based on clinical observation. Below, we present a few cases of silent or asymptomatic hypoxemia.

Case 1

The patient was a 66-year-old man who was positive for SARS-CoV-2 infection and was diagnosed with COVID-19. Ten days before his visit to the emergency room (ER), he had headache, malaise, and cough; he visited his local physician, who prescribed medication for common cold. Later, he had difficulty while eating and was referred to our ER on foot. His blood pressure (BP) was 82/56 mmHg, and his heart rate (HR) was 70 bpm. Under room-air conditions, oxygen saturation by pulse oximetry (SpO_2) was 70–75%, and the partial pressure of oxygen by arterial blood gas analysis (PaO_2) was 42 mmHg. Although he had marked fatigue, he did not complain of respiratory distress but had marked cyanosis. The patient was admitted to the hospital, and treatment with mechanical ventilation was initiated.

Case 2

The patient was a 63-year-old man with hypertension, right-sided paralysis due to cerebral hemorrhage, and a history of pulmonary tuberculosis at 25 years of age. He had fever with varying body temperature (38 °C four days before his visit to the hospital and 37 °C two days before his visit). His BP was 124/69 mmHg, HR was 120 beats/min, and respiratory rate (RR) was 24 bpm. The patient was positive for SARS-CoV-2 and was diagnosed with COVID-19. His SpO_2 was 83% under room-air conditions, and oxygen (8 L/min) was administered using a mask. His SpO_2 was 93% and PaO_2 was 83.6 mmHg. However, he had no complaints of respiratory distress.

Case 3

A 66-year-old man, who was positive for SARS-CoV-2, was transferred to the ER due to COVID-19 pneumonia. Arterial blood gas analysis showed PaO_2 of 33.4 mmHg, $PaCO_2$ of 39.6 mmHg, and SaO_2 of 60.3%. Although there was general malaise, he did not have dyspnea or tachypnea. The patient was started on a 2 L/min nasal cannula for hypoxemia, and his SpO_2 was 90–93%. He received medication for hypertension.

Case 4

An 82-year-old woman presented to the ER with dysphagia and anorexia. Her SpO_2 was 81% and her RR was 20 bpm without tachypnea, although she had breathlessness, to some extent. Arterial blood gas analysis showed PaO_2 of 34.6 mmHg, $PaCO_2$ of 35.6 mmHg, and SaO_2 of 60.2%. Oxygen (3 L/min) was administered through a nasal cannula, and her SpO_2 improved to the upper limit of the 90% range. Her medical history included hypertension and diabetes mellitus. She was positive for SARS-CoV-2 and was diagnosed with COVID-19.

The common features of these four patients were severe hypoxemia, a lack of awareness of dyspnea, and no symptoms of tachypnea. In addition, $PaCO_2$, which reflects ventilation status, was maintained within the normal range as in cases 3 and 4.

3. Hypoxemia in COVID-19 Patients

3.1. Mechanisms of Hypoxemia

The main gas exchange abnormalities caused by SARS-CoV-2 infection are intrapulmonary shunting and ventilation/blood flow (V/Q) mismatch, similar to those seen in other viral pneumonias and bacterial pneumonias [7]. The infection leads to localized interstitial edema, which gradually increases the intrapulmonary shunt rate and causes a further decrease in oxygenation that cannot be completely corrected by increasing FiO_2, as in the case of acute respiratory distress syndrome (ARDS) [19] (Figure 2).

The hypoxic pulmonary vasoconstrictor mechanism may be dysfunctional during SARS-CoV-2 infection; although this mechanism is unclear, it may be related to the release of prostaglandins, bradykinin, and cytokines associated with inflammatory processes [20,21]. Serum angiotensin II levels are also linearly related to the viral load and lung injury severity in COVID-19 patients [22].

There is a consensus that endothelial cell injury is a central phenomenon in the pathogenesis of COVID-19. SARS-CoV-2 infects the vascular endothelium, resulting in the formation of intravascular microthrombi due to an imbalance between procoagulant and fibrinolytic activities in the presence of acute inflammation and endothelial injury [23,24]. Thus, SARS-CoV-2 infection causes swelling and damage to endothelial cells (endotheliitis); microthrombi (microthrombosis), which affects the microcirculation and leads to capillary congestion; damage to pericytes essential for capillary integrity and barrier function; tissue repair (angiogenesis); and scar formation [25]. Many patients with COVID-19 have elevated D-dimer levels and increased thrombus formation [26,27]. Fibrin deposition; diffuse alveolar damage; thickening of the vessel wall; and presence of complement-rich microthrombi, which occlude pulmonary capillaries; and large thrombi causing pulmonary artery thrombosis and embolism have been identified. The hypercoagulable state leads to further exacerbation of the V/Q mismatch and damage to the lung tissue.

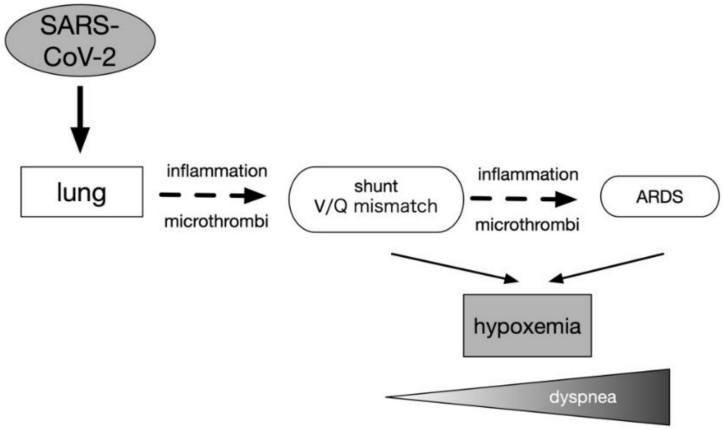

Figure 2. SARS-CoV-2 infection and hypoxemia. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the lung causes inflammation of the alveoli and blood vessels, resulting in tissue and cellular damage, and the consequent inflammation and microthrombi promote the formation of pulmonary vascular shunts, resulting in V/Q mismatch and impaired oxygen exchange, leading to hypoxemia. If this process progresses, then it will lead to a final pathological picture, such as acute respiratory distress syndrome. In this process, if carbon dioxide retention is suppressed, the ventilatory drive is not activated. Fewer patients complain of subjective symptoms, including dyspnea, when the ventilatory drive is weak. In this situation, COVID-19 is characterized by the fact that the pathology progresses without complaint of dyspnea, and the pathology progresses without subjective symptoms to a condition that requires ventilation [7].

3.2. Changes in the Oxygen Dissociation Curve

Another confounding factor is the shift in the oxygen dissociation curve (ODC) [28]. The oxygen affinity for hemoglobin has a significant impact on the supply of oxygen to tissues. A left shift increases the oxygen affinity and allows for tighter binding. On the contrary, a right shift decreases the oxygen affinity and facilitates oxygen release to the tissues. It is well known that the ODC shifts in response to changes in pH, pCO_2, and the concentration of 2,3-diphosphoglycerate (2,3-DPG). Heat generation shifts the curve to the right: at 37 °C, the SaO_2 is 91.1% when the PaO_2 is 60 mmHg (normal pH and $PaCO_2$), but when the temperature increases to 40 °C, the SaO_2 is 85.8% (an absolute decrease of 5.3%). At a PaO_2 of 40 mmHg, SaO_2 is 74.1% at 37 °C and 64.2% at 40 °C (an absolute decrease of 9.9%) [29].

3.3. Accuracy and Limitations of Pulse Oximeter

Using a pulse oximeter, we can estimate arterial SaO_2 by measuring the change in the optical absorption of oxyhemoglobin and reduced hemoglobin. The saturation (SpO_2) estimated by pulse oximetry is thought to be different from the SaO_2 measured by CO oximetry by approximately ±4%. Pulse oximetry is much less accurate when the SaO_2 is less than 80% [30–32]. Although pulse oximetry is a good and common screening approach, it may not be a good basis for judging hypoxemia based on these readings alone [33,34]. The diagnostic criteria introduced above use 93% as the threshold for judgment, and take measurement error into account.

4. Dyspnea

Dyspnea is an uncomfortable breathing sensation that occurs when a person has a disease affecting the respiratory tract, such as the common cold or influenza, or when the intensity of exercise is high, even under normal conditions [35–38]. Thus, dyspnea is a subjective symptom of "breathlessness" that refers to "an unpleasant sensation" during breathing. Medical practitioners commonly equate physical signs (tachypnea, tachycardia, and facial expression) with dyspnea, but these objective symptoms should be disconnected

from the patient's subjective complaints [39]. When considering dyspnea as a "sensation" from a physiological standpoint, the information obtained from the receptors associated with dyspnea is transmitted to the cerebral cortex through afferent pathways to elicit the associated sensation. Any disturbance in the signaling from hypoxia to the central nervous system may lead to asymptomatic hypoxemia [35,36,40].

We have described some important physiological and pathophysiological issues that may be helpful in considering this problem (Figure 3).

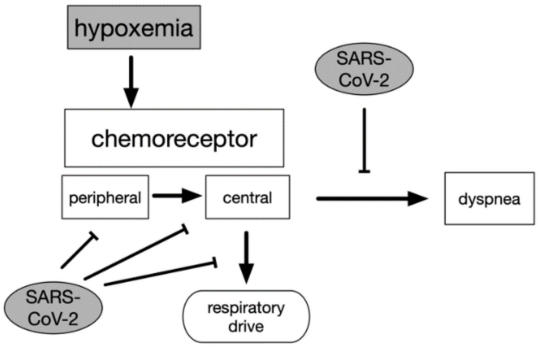

Figure 3. Impact of SARS-CoV-2 on hypoxia signaling. The body has specialized sensors to detect hypoxia: peripheral sensors such as the carotid body and central sensors in the brainstem to detect partial pressures of oxygen and carbon dioxide, and the detected hypoxia may cause respiratory drive or may be transmitted to higher levels to induce dyspnea [41,42]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may act to inhibit hypoxia signaling through various mechanisms, including inducing inflammatory responses in sensor cells and the nervous system [43].

4.1. Chemoreceptors of Arterial Oxygen Tension

Chemoreceptors are classified as central or peripheral chemoreceptors. Central chemoreceptors, which are located in the brainstem (medulla oblongata), are stimulated by elevated blood CO_2 ($PaCO_2$) [44]. Thus, the respiratory center in the brainstem is susceptible to changes in CO_2, and a slight increase in $PaCO_2$ can rapidly lead to a significant increase in ventilation. A 10 mmHg increase in $PaCO_2$ causes unbearable respiratory discomfort, even for a few minutes [44]. On the contrary, the carotid body, which is located at the bifurcation of the common carotid artery, is a well-known peripheral chemoreceptor in humans. Like central chemoreceptors, peripheral chemoreceptors are stimulated by CO_2 in the blood, but the stimulatory effect is weaker, and the most characteristic feature is that they are strongly stimulated by hypoxia. Central respiratory excitation is transmitted to the diaphragm through the diaphragmatic nerve, causing an increase in ventilation. At the same time, signals from the medulla oblongata are transmitted to the cortex and may induce respiratory distress [36,40]. Pulmonary irritant receptors, pulmonary stretch receptors, and C-fiber receptors are representative of these receptors, which are stimulated by biological substances such as histamine, bradykinin, and prostaglandin, in addition to mechanical stimulation. Inflammatory mediators, for which is stimulated by viral infection, elicit dyspnea through the vagus nerve [45,46].

4.2. Information Transmission and Processing from Peripheral Receptors to the Central Receptors

It is thought that information from these sensory receptors is transmitted to the medulla oblongata through afferent pathways, finally reaching the cerebral cortex through the thalamus [36]. The cerebral cortex also projects extensively to the limbic system and forebrain, not just the somatosensory cortex. There are two major neural pathways through which information is transmitted from the sensory receptors to higher centers; one of which is the vagus nerve, which carries information about the lungs and airways from the thalamus to the limbic regions, especially the cingulate gyrus and insula. By contrast, information from respiratory muscles and tendons converges in the primary and secondary

somatosensory cortices and has been suggested to play a role in discriminating the type and intensity of dyspnea [47].

4.3. Pathogenesis of Dyspnea

The most popular theory regarding the mechanism of dyspnea is called the central–peripheral mismatch theory or the output–reinput mismatch theory, which states that dyspnea occurs when there is a discrepancy or mismatch between the motor output from the respiratory center and the afferent input from the nerve receptors [35,36,39]. For example, when respiratory activity increases due to hypercapnia or hypoxemia, the output from the respiratory center is transmitted to the respiratory muscles, and ventilation is increased. As ventilation increases, respiratory muscle activity increases and, at the same time, passive movement of the lungs occurs. This excites mechanical receptors in the respiratory muscles, tendons, joints, and lungs. Simultaneously, a copy of the motor output from the respiratory center is transmitted to the sensory receptors in the cerebral cortex. In the sensory receptors, the motor output from the respiratory center is compared with the afferent input from respiratory muscles and lung receptors, and dyspnea occurs when there is a discrepancy or mismatch between the output from the respiratory center and the afferent input from peripheral nerve receptors.

It is important to note that dyspnea is not a single sensation, but that different peripheral receptors produce different qualities of dyspnea [37,38,48,49]. At least three different qualities of dyspnea have been identified and classified as air hunger, chest tightness, and effort/work sensation [36,50]. Air hunger is caused by abnormal chemoreceptor activity, chest tightness is caused by abnormal vagal receptor activity, and effort/work sensation is caused by abnormal respiratory drive [36]. In addition, it is important for the sensory center not only to receive information from the sensory receptors to cause dyspnea, but also to recognize the information after receiving it and to have an emotional processing mechanism to cause feelings of discomfort.

4.4. Relationship between Partial Pressure of Arterial Blood Oxygen and Respiratory Response

Viral infections of the respiratory tract induce inflammatory changes at the site of infection, and the inflammation, as well as cytokines and chemokines produced by the infection, stimulates peripheral sensory receptors and induces the transmission of afferent impulses to the respiratory center. Thus, viral infections can induce dyspnea [51]. On the other hand, in a situation where the respiratory center would have been stimulated by hypoxemia, the air hunger response is not observed and the detection and awareness of hypoxemia are delayed. On the other hand, in situations where hypoxemia would have stimulated the respiratory center, there may be no air hunger response and the detection and awareness of hypoxemia may be delayed [52].

The ventilatory response to hypoxia is not linear: there is little change in the ventilatory output when PaO_2 decreases from 90 mmHg to 60 mmHg; only when PaO_2 decreases further does ventilatory output increase exponentially (Figure 4) [53,54]. Even when the end-expiratory oxygen partial pressure fell below 60 mmHg, only half of the subjects experienced dyspnea. Ventilatory and dyspnea responses to hypoxia were strongly influenced by $PaCO_2$. Hypoxemia induces an effective increase in ventilation only when the $PaCO_2$ is greater than 40 mmHg [55]. One of the reasons why COVID-19 patients do not complain of severe dyspnea may be the involvement of shunts in gas exchange abnormalities. Intrapulmonary shunts and V/Q mismatch have only a smaller effect on the gas exchange efficiency of carbon dioxide excretion than on oxygen uptake. Thus, mild hyperventilation can reduce arterial carbon dioxide and decrease both carotid- and central chemoreceptor-mediated respiratory drive. Breathlessness in pulmonary disease is more strongly correlated with carbon dioxide retention than with hypoxemia; therefore, patients for whom the arterial partial pressure of carbon dioxide can be reduced by increasing respiration are less likely to experience dyspnea [56]. The response to hypoxemic conditions appears to be variable. Some patients with an oxygen saturation of less than 70% may have

panic attacks with dyspnea, while others remain calm. Intrapulmonary shunts caused by viral infections do not necessarily reduce lung compliance or produce dyspnea [57]. Thus, even if a patient with hypoxemia has an oxygen saturation of less than 70%, there may be only moderate transient changes in other signs and symptoms, including consciousness, and many patients do not have urgent dyspnea as their chief complaint.

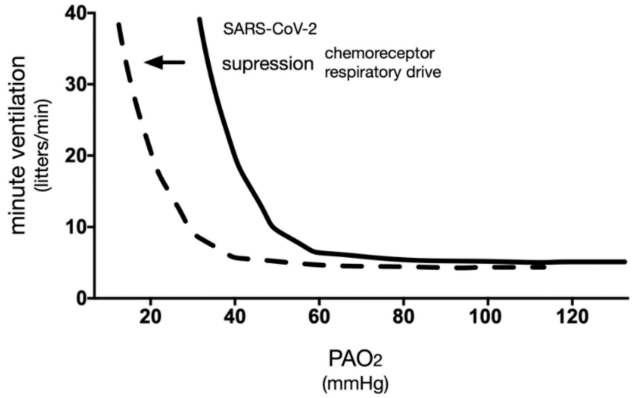

Figure 4. Relationship between alveolar oxygen partial pressure and ventilatory response under constant blood carbon dioxide. When the alveolar oxygen partial pressure (PAO_2) decreases, the ventilatory response is triggered, and the minute ventilation rate increases. However, this relationship is not linear, and the data from healthy subjects show a curve with an inflection point of approximately 60 mmHg. If such a shift occurs in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, then it may partly explain the pathogenesis of asymptomatic hypoxemia.

Therefore, it is possible that patients with and without COVID-19 may present with asymptomatic hypoxemia.

5. COVID-19 and Asymptomatic Hypoxemia

It has been shown that a severe inflammatory response can develop in the central nervous system of COVID-19 patients involving different immune cells around the vascular system and in the brain tissue [58,59]. SARS-CoV-2 affects the neural control of respiration [60,61].

Compared to other inflammatory brain diseases, the inflammatory responses triggered by COVID-19 are unique and indicate a severe disturbance in the brain's immune response. In particular, the essential defense cells of the brain, known as microglial cells, are strongly activated, together with the migration of killer T cells and the development of pronounced neuroinflammation in the brain stem [62]. Immune changes are particularly detectable near small brain vessels [63]. Because these vessels express the viral receptor angiotensin-converting enzyme 2 (ACE2), and SARS-CoV-2 binds to these receptors, the virus was also directly detectable. It seems possible that the immune cells recognize infected cells and that inflammation then spreads to the nerve tissues, causing symptoms. Thus, it is possible that early immunomodulatory or immunosuppressive treatment could reduce inflammation.

5.1. Possible Neuroinvasion by SARS-CoV-2

Considering the effects of SARS-CoV-2 infection on the neural control of asymptomatic hypoxemic respiration and/or respiratory sensory mechanisms in COVID-19, SARS-CoV-2 infection of central respiratory control cells has been noted [64]. Infection of peripheral chemoreceptor carotid bodies may disrupt hypoxia-sensing mechanisms and allow asymptomatic hypoxemia to develop. In fact, the carotid body is a major source of the proteins required SARS-CoV-2 infection, namely ACE2, which is the receptor for SARS-CoV-2 cell entry, and the transmembrane protease TMPRSS2, which is a serine protease that cleaves the viral S protein to allow host cell entry [65,66]. The coronaviruses SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) infect brainstem respiratory neurons

and cause death due to respiratory failure. Therefore, detailed anatomical information on the targets of SARS-CoV-2 infection in key regions that control respiration and respiratory sensation, such as vagal sensory receptors, peripheral chemoreceptors, and brainstem neurons important for respiratory rhythm and patterning, will be important. Importantly, the loss of these critical neural elements can lead to ventilatory failure and death. Recently, SARS-CoV-2 was detected by immunostaining and reverse transcriptase-polymerase chain reaction in the carotid arteries of a patient who died due to COVID-19-related ARDS despite receiving intensive care, including ventilation [66]. Although there was no indication that this patient had asymptomatic hypoxemia syndrome, infection of the carotid body with SARS-CoV-2 may explain the cause of asymptomatic hypoxemia and contribute to the increased morbidity and mortality in COVID-19 patients; however, the details are unknown.

5.2. Anosmia or Absence of the Sense of Smell

SARS-CoV-2 infection induces loss of olfactory sensation (anosmia), which is thought to be a diagnostic trigger in the early stages of COVID-19 [67]. It is likely that olfactory-derived respiration-related signals projecting to the hippocampus, prefrontal cortex, and other areas are affected, which may influence the sensation of dyspnea. Recent RNA-seq and single-cell RNA-seq analyses suggest that non-neuronal cells in the olfactory system that express transcripts and proteins associated with SARS-CoV-2 entry contribute to COVID-19 apnea. Diffuse edematous areas of the olfactory bulb, inflammatory cell infiltration, severe neurodegeneration, and neuronal necrosis (necrotizing olfactory bulbitis) were observed [68]. SARS-CoV-2 may enter the brain through the olfactory pathway and cause olfactory dysfunction of sensory nerve origin.

Therefore, it might be interesting to test for anosmia in COVID-19 patients and to evaluate olfaction in relation to asymptomatic hypoxemia.

5.3. Inflammatory Responses

Humans use the innate immune system in the early stages of viral infection and the acquired immune system in the later stages to fight viruses. Among the innate immune responses, the response mediated by humoral factor-1 interferons (type I IFNs), including IFN-γ, plays a central role. When viral infection occurs, type I IFNs secreted by some infected cells exert an activity that limits viral replication in themselves and surrounding cells, leading to an antiviral state and elimination of the virus from infected cells. In fact, it has been reported that mice genetically deficient in type I IFN receptors show increased viral replication and die earlier than wild-type mice. It has also been proposed that when viral exposure is low, interferon is produced early and the virus is eliminated, but when exposure is high, interferon production is relatively insufficient and the virus causes persistent inflammation, leading to severe disease. The systemic cytokine profile observed in patients with severe COVID-19 is similar to that observed in cytokine release syndrome. interleukin (IL)-7, tumor necrosis factor (TNF), and inflammatory chemokines, including CC-chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 10 (CXCL10), as well as the soluble form of the alpha chain of the IL-2 receptor, are activated. IL-6 levels are often elevated in the serum of critically ill patients, and vascular endothelial growth factor (VEGF) and reduced E-cadherin expression contribute to the pathophysiology of hypotension and pulmonary dysfunction in ARDS. VEGF and reduced E-cadherin expression may contribute to the vascular permeability and leakage involved in the pathophysiology of hypotension and pulmonary dysfunction in ARDS.

A neuroinflammatory response to acute lung injury may be associated with dyspnea in patients with COVID-19. Acute lung injury induces inflammation in the body. This change increases the expression of pro-inflammatory cytokines in brainstem regions, which are important for respiratory control, and this circuit may induce tachypnea associated with acute lung injury. In fact, studies have reported that the local infusion of interleukin-1β into the nucleus tractus solitarius induces tachypnea, even in the absence of hypoxemia and hyperventilation [69]. However, even in this case, inflammatory cytokines act in a direction

that promotes the respiratory response, and it is unclear whether cytokine effects on the CNS lead to dyspnea; therefore, it would be worthwhile to study the role of circulating cytokines in altering the degree of hypoxemia and whether these patterns distinguish COVID-19 patients.

6. Is Asymptomatic Hypoxemia a "Paradoxical" Phenomenon?

Hypoxemia without dyspnea observed in COVID-19 patients focuses on the question of whether the lack of dyspnea is truly paradoxical and characteristic of COVID-19, or whether it is a somewhat common phenomenon observed in the course of severe pulmonary-targeted viral infections. The initial symptoms of COVID-19 are similar to those of influenza and the common cold, which makes it challenging to distinguish COVID-19 from conventional respiratory viral infections such as the common cold and influenza. However, it may currently be easier, i.e., during the COVID-19 pandemic, owing to the low incidence of influenza. A retrospective cohort study indicated that among 270 COVID-19 patients at a large tertiary care hospital between 31 January and 31 August 2020, 3.0% of patients met the criteria for "silent hypoxia" [70]. According to an analysis of 2600 cases in the registry of COVID-19 cases in Japan (COVIREGI-JP) [6], the median time to hospitalization was 7 days, and the most frequent symptoms were fever, cough, malaise, and dyspnea. The frequency of taste disorders (17.1%) and olfactory disorders (15.1%) seemed to be lower than those reported in foreign countries. Another study reported that about 30% of patients with asymptomatic hypoxemia do not complain of dyspnea when mild COVID-19 cases are included [71]. On the other hand, in a study of severe cases, 60–70% of patients complained of dyspnea. COVID-19 leading to bilateral pneumonia is often associated with dyspnea [72]. In addition, it is necessary not to rely on respiratory symptoms alone, but to consider that if there is a worsening of respiratory rate or SpO_2, attention should be paid to the development of pneumonia and respiratory failure.

It is recognized that old age, chronic obstructive pulmonary disease, diabetes, and obesity confer a patient at risk of severe COVID-19. Patients with these comorbidities are thought to have reduced hypoxic response, which may explain the phenomenon of fewer complaints of dyspnea. Chest computed tomography shows multiple ground-glass opacities in the bilateral lung fields, mainly distributed around the bronchi and just below the pleura, and a crazy-paving appearance, which is also observed in fibrous microthrombi in small pulmonary arteries. These findings may serve as the basis for hypoxemia without subjective dyspnea.

Patients with asymptomatic hypoxemia develop dyspnea during disease progression. First, sustained hypoxemia causes respiratory drive due to increased chemosensitivity of the carotid artery, and the sensory information from the chemoreceptor is transmitted to the central receptors. These signals are involved in the development of dyspnea. Further lung inflammation may develop, and the stimulation of C-fibers distributed in the lungs may drive tachypnea. However, the course of these events will vary among COVID-19 patients, and there will be marked differences among individuals, including the presence or absence of asymptomatic hypoxemia.

There is a limitation to this review. It has been more than a year and a half since the first report of COVID-19, and mutations in the SARS-CoV-2 state have also been reported. Currently, the reported studies do not clearly distinguish between the clinical characters of VOCs. Thus, the position of COVID-19 in the severity of the condition of asymptomatic hypoxemia may also change.

7. Conclusions

Although asymptomatic or silent hypoxemia has been observed in COVID-19 patients, there is no epidemiological information that can help in determining whether hypoxemia is symptom-specific to COVID-19. Asymptomatic hypoxemia can be observed in patients who are supported by ventilation and have no major problems in the airway system. SARS-CoV-2 infects peripheral and central nerve organs, and asymptomatic hypoxemia may be

caused by the direct influence of hypoxia sensing and its receptor pathways. The spread of SARS-CoV-2 infection is mediated by asymptomatic carriers. However, it is important to keep in mind that even SARS-CoV-2 carriers without symptoms may develop hypoxemia, depending on the patient's attributes.

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