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# Modulation of Respiratory Neural Drive by Physiological Loads in COVID-19 Patients with Dyspnea

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## Abstract

COVID-19 patients often experience dyspnea due to several factors. The underlying unique pathophysiology of dyspnea in COVID-19 is not yet fully understood, but it is believed to be related to a combination of respiratory, cardiovascular, and neuromuscular factors. Hypoxemia is considered one of the key symptoms of COVID-19. This affects the respiratory drive, which determines the rate, depth, and pattern of breathing. The relationship between increased ventilatory neural drive and abnormal gas exchange, particularly in the context of ventilation/perfusion (V/Q) mismatches and chemosensitivity, has gained significant attention following the COVID-19 pandemic. The ACE2 receptors allow viral entry into the lungs, leading to the loss of surfactant, hypoxic vasoconstriction, and intrapulmonary shunting that may result in a V/Q mismatch. Additionally, acidosis, hypercapnia, elevated 2,3-diphosphoglycerate levels and fever may shift the oxygen diffusion curve rightward, lowering arterial oxygen saturation levels and triggering ventilatory responses. This paper examines how physio pathological factors such as altered gas diffusion, chemosensory feedback, V/Q ratios, altered compliance, arterial blood gases, and respiratory muscle dysfunction in these patients affect ventilatory drive. A review of the published literature was also conducted to determine the mechanism of dyspnea. To ensure appropriate gas exchange, individuals need to augment their minute ventilation (VE) when physiological dead space is elevated. This serves as a compensatory mechanism to counteract the effects of compromised gas exchange and keep adequate oxygenation throughout the body. The respiratory centers may experience dysregulation due to the impact of the virus on the respiratory system, which could affect the rhythm-generating and pattern-generating signals that are vital for regulating the respiratory rate and depth of breathing effort. The cerebral cortex, in conjunction with the brain stem centers, plays a crucial role in regulating ventilation dur-

ing prolonged hypoxemia. This interaction between these two components may help elucidate the conscious respiratory sensation (or dyspnea) experienced by patients. It is hypothesized that neuroventilatory decoupling acts as a mechanism to prevent sensory signals from translating into mechanical or ventilatory responses. This decoupling phenomenon is believed to have a notable impact on the intensity of breathlessness. By understanding the relationship between increased ventilatory neural drive and abnormal gas exchange, particularly in the context of ventilation/perfusion (V/Q) mismatches and altered chemosensitivity, healthcare professionals can develop strategies to optimize respiratory support for COVID-19 patients.

## Keywords

Hypoxemia, Ventilatory Drive, Dyspnea in COVID-19, Neuroventilatory Uncoupling

## 1. Introduction

It is known that physiological changes in arterial blood gases and pH are controlled by the respiratory feedback mechanisms, and this is achieved through altering the respiratory drive [1] [2]. Dyspnea is attributed to disengaged respiratory drives in people with COVID-19, which may be caused by the virus directly affecting the respiratory center in the brainstem and the host inflammatory response [3] [4]. In December 2019, a cluster of novel human pneumonia cases spread in Wuhan, China [5]. Most patients with this viral infection experience mild symptoms, while others experience severe respiratory distress. Despite severe pathophysiological changes, most COVID-19 patients with severe hypoxemia had minimal complaints during the early phases of the pandemic [6] [7] [8]. This is a highly unpredictable disease condition characterized by its non-uniformity. It surprised many clinicians since one of the most confusing aspects of pneumonia management is the presentation of patients with extremely low blood oxygen levels without symptoms of dyspnea or respiratory distress. As a result of this phenomenon, the term "happy hypoxemia" originated [9] [10] [11].

Studying the physiological loads (summarized in **Table 1**) on the respiratory system and its impact on the ventilatory drive will be useful for developing effective treatments for COVID-19. In addition to improving patient outcomes, clinicians can reduce respiratory failure risks by modulating respiratory drive.

## 2. Hypoxemia and Hypercapnia in COVID-19 Patients and Its Genesis

Hypoxemia is one of the key symptoms of COVID-19 [12]. The current target for oxygen saturation range for patients with COVID-19 recommended by the National Institutes of Health is 92% - 96% [13], which results in having a low

**Table 1.** The implications of various physiological loads and their possible mechanisms of action contributing to rapid breathing and ventilatory drive.

| Physiological loads | COVID-induced physiological changes | Ventilatory drive modulation |
|---|---|---|
| Hypoxemia | In early infection, arterial hypoxemia is primarily caused by V/Q mismatches and increases in $P(A\text{-}a)O_2$ gradients. As a result of local interstitial edema, acute inflammation, endothelial injury, and intrapulmonary shunting, oxygen diffusion is decreased [20]. | In mild hypoxemia ($PaO_2$ between 60 - 70 mmHg), the respiratory drive is typically unaffected, often presenting as "happy hypoxemia" without dyspnea. Due to hypoxemia worsening as $PaO_2$ decreases, respiratory drive increases gradually. |
| Hypercapnia and acidosis | Peripheral chemoreceptors sense changes in arterial blood directly, while central chemoreceptors sense changes in chronic hypercapnia through the pH of CSF [1]. | Respiratory rate and arterial $pCO_2$ have inverse associations [81]. |
| Intrapulmonary shunting and V/Q mismatching | Dead space can be caused by thrombosis in hypercoagulable states (an elevated level of D-dimer, fibrinogen, or interleukin-6 markers) [82]. | The ratio of dead space to tidal volume ($V_D/V_T$) may cause endothelial injury and microvascular coagulation [30] [83]. |
| Decreased respiratory compliance | An index of rapid shallow breathing (Respiratory rate divided by tidal volume). Ventilatory demand may not be met by excessive drive [84]. | When drive increases, respiratory rate increases, resulting in a decrease in respiratory time. |
| Anemia | An infection with this virus can result in a greater production of immature RBCs, followed by their release into the bloodstream and a consequent drop in Hb levels [85]. | A greater respiratory drive is induced when hypoxemia occurs due to chemoreceptor sensitivity to $PaCO_2$. |
| Impairment in respiratory muscle strength (muscle fatigue) | The reduction of forced vital capacity (FVC) and lung diffusing capacity in survivors of COVID-19 [5]. | Resulting in a reduced tidal volume and an increased work of breathing due to neuromechanical dissociation. |
| Pulmonary vasoconstriction | Hypertension is etiologically linked to RAAS dysfunction. The cellular receptor for COVID-19 is ACE2. ACE converts angiotensin I into Ang II and degrades bradykinin. When ACE2 levels are low, RAAS is activated, resulting in pulmonary vasoconstriction [86]. | ACE2 plays a role in neuroinvasion, as it is expressed in the brain on neurons and glial cells, particularly in the brainstem, in the paraventricular nucleus, and in the rostral ventrolateral medulla [7]. The drive may be blunted. |
| Decreased diffusion capacity and rise in $P(A–a)\ O_2$ gradient | An infection results in moderate interstitial edema and surfactant loss. Alveolar collapse results in intrapulmonary shunting, resulting in non-aerated alveoli being perfused [32] [87]. | Carotid body chemoreceptors are stimulated by low $PO_2$ resulting in increased drive |
| Shift in oxygen dissociation curve or increased $P_{50}$ values | An oxygen dissociation curve shift caused by fever may result in lower arterial oxygen saturation levels. | Silent hypoxemia is believed to occur due to this phenomenon, combined with the carotid bodies' response to decreased $PaO_2$ rather than $SaO_2$ [18]. |
| Autonomic dysfunction | The neuro-vagal anti-inflammatory reflex may be impaired by hypoxemia-induced reductions in parasympathetic activity and sympatho-excitation. There is a possibility that this impairment could contribute to the emergence of a cytokine storm [4]. | Tachypnea may be caused by pro-inflammatory cytokines in the brainstem [57]. |

$PaO_2$ (normal $PaO_2$ is 80 to 100 mmHg). An indicator of pneumonia severity derived from arterial oxygen and carbon dioxide pressures can be used to predict

clinical outcomes in hospitalized patients [14]. Even though $SpO_2$ measures tissue oxygenation accurately, it does not indicate ventilatory drive or oxygen uptake efficiency. When the ventilation drive is reduced, pulmonary arterial blood flow is shunted to non-ventilated alveoli, resulting in an increase in $P(A\text{-}a)O_2$. Furthermore, when ventilation decreases, some local interstitial edema develops, especially where the elastic properties of lung structures differ. Increasing the $P(A\text{-}a)\ O_2$ gradient along with edema contributes to hypoxia [15].

In hypoxemia, the ventilatory response is mediated primarily by the carotid body and respiratory centers in the brain stem [16]. Hypoxemia causes a rise in tidal volume and an increase in breathing frequency when oxygen delivery is reduced by less than 25%, which is considered a critical threshold [17]. When there is severe hypoxemia present, tachypnea is one of the most important clinical indicators of respiratory distress. Interestingly, tachypnea in COVID-19 patients is more likely to be induced by lung inflammation than by hypoxic stimulation since lung receptors are stimulated by inflammation [18]. A COVID-19 patient has elevated minute ventilation due to dead space ventilation. There are three factors involved: $CO_2$ production, decreased $V_D/V_T$ (relationship between physiological dead space and tidal volume), and increased $PaCO_2$ [19]. Development of a precapillary shunt occurs when blood flow is redirected away from the capillaries, which are responsible for gas exchange, to other blood vessels. As a result, oxygen-rich blood bypasses the capillaries and does not participate in the exchange of gases. This leads to a decrease in oxygen levels in the blood and the development of hypoxemia [20]. Hypoxemia can also result from alterations in blood vessel diameter or alterations in lung tissue compliance, in addition to dead space and precapillary shunts.

## 3. Right Shift of Oxygen Dissociation Curve (ODC)

A COVID-19 infection reduces oxygen delivery to the consuming tissues by at least two mechanisms which include a compromised saturation of hemoglobin in the injured lung, as well as anemia in the tissues [21].

When fever is present, such a condition can significantly impact oxygen delivery to tissues. Patients with COVID-19 commonly experience fever, which shifts the ODC to the right (or $P_{50}$ increases), meaning that the saturation of oxygen ($SaO_2$) is lower. Apart from this, curve shifts may occur due to decreased pH, higher $PCO_2$ and higher 2,3 diphosphoglycerate (2,3-BPG) levels. Recent research has found that COVID-19 inhibits heme metabolism by targeting hemoglobin's 1-Beta chain and capturing porphyrin leading to anemia [22].

In cases of anemia caused by a decrease in cell production or hemolysis, the ODC shifts to the right. This may be attributed to an increase in the concentration of 2,3-BPG. Hypoxia and anemia are associated with COVID-19 usually decrease oxygen affinity due to a rise in 2,3-BPG. The ODC in COVID-19 has only been addressed in a limited number of publications. According to Böning and colleagues [21], the $P_{50}$ decreased from 26.7 mmHg in healthy subjects to 23.4 mmHg. However, because of 2,3-BPG synthesis, the $P_{50}$ increased by 4 mmHg in

patients with both lung injury and anemia in this study. As a result of methemoglobin formation, the oxygen affinity of remaining undamaged Hb monomers increases in patients with COVID-19 compared with routine anemia patients [21]. In addition, there may be unknown factors that increase oxygen affinity in patients with COVID-19. As a result of these changes, oxygen is loaded into the compromised lung more effectively during COVID-19 [22]. Early dyspnea seen in these patients may not have been severe enough due to this reason.

## 4. Increased Dead Space Caused by Damaged Cellular Biology

When COVID-19 invades the lungs, it causes shunting and diffuse microvascular thrombus formation, leading to dead space in the alveoli [20]. The virus binds to epithelial cells in the nasal cavity and replicates [23]. By binding to the angiotensin-converting enzyme 2 (ACE2) receptor in the epithelial cells of the lungs, this virus can spread. As the virus replicates in the cells, it damages the respiratory epithelium.

Acute respiratory distress syndrome and acute lung injury can result from viral entry through ACE2 receptors in the lungs [24]. As reported in a rat model, ACE2 is expressed in the carotid body chemoreceptors that detect oxygen levels in the blood [25]. It is estimated that two-thirds of patients with COVID-19 have anosmia-hyposmia caused by ACE2 expression in the nasal mucosa [26]. A significant increase in lung permeability can result in edema, alveolar flooding, and patient-self-inflicted lung injury (P-SILI) [27].

## 5. Loss of Surfactant, V/Q Mismatch & Intrapulmonary Shunting

As a result of the infection, severe pneumonia has been characterized by inflammatory lung injury, progressive parenchymal stiffness and consolidation, collapse of the airways and alveoli, altered vascular permeability, and diffuse alveolar damage [28]. Acute respiratory distress syndrome (ARDS) is also caused by COVID-19 in addition to pneumonia. ARDS caused by COVID-19 is characterized by severe hypoxemia and high mortality. Consequently, a significant amount of cardiac output is used to perfuse non-aerated lung tissue, resulting in intrapulmonary shunting. In patients with lung disease, ventilation-perfusion inequality is by far the most common cause of impaired gas exchange [29]. Multiple hypotheses suggest that intrapulmonary shunts and mismatches in ventilation/perfusion (V/Q) ratios may influence endothelial injury, microvascular coagulation, and host inflammatory responses [30]. Low V/Q ratios caused by hypoxic vasoconstriction from coagulopathy divert lung perfusion to other alveoli [31]. An increase in pulmonary artery resistance results from hypoxic vasoconstriction as a physiological homeostatic response. High inflation pressures may cause excessive alveolar stretching, resulting in leaky and wet lungs [31]. A cohort of COVID-19 patients suffering from ARDS was studied by Gattinoni *et al.*, and

the average V/Q ratio was found to be approximately 0.5 (normal: 0.8 - 1). Additionally, the hypoxic vasoconstriction exacerbated the $PAO_2$-$PaO_2$ gradient [32].

## 6. Chemosensory Feedback for Ventilatory Drive in Hypoxia and Hypercapnia

As depicted in **Figure 1**, the respiratory center in the medulla oblongata and pons regions of the brainstem receives input from peripheral and central chemoreceptors. These chemoreceptors are responsible for detecting changes in oxygen, carbon dioxide, and pH levels in the blood and cerebrospinal fluid. The input from these chemoreceptors is the primary factor that influences the drive of respiration, ensuring that the metabolic demands of the body are met [1]. The respiratory center produces two types of output signals: rhythm-generating signals and pattern-generating signals [33]. These signals are responsible for regulating the respiratory rate and depth of breathing effort, respectively. The ability to independently control these signals allows for precise and coordinated regulation of respiration [34].

The respiratory drive can be significantly affected by hypoxemia. However, the relationship between hypoxemia and the stimulation of carotid chemoreceptors is nonlinear and not necessarily proportional to the severity of low oxygen levels [35]. The examination of carotid body sensitivity to hypoxia during ventilatory acclimatization has shed light on the involvement of neuromodulators and the delicate balance between excitatory and inhibitory modulation. Understanding these mechanisms is crucial for comprehending the respiratory adaptations that occur in response to reduced oxygen levels [36].

The increase in respiratory drive caused by hypoxemia is primarily mediated by the stimulation of peripheral chemoreceptors, rather than the central respiratory drive [37]. This means that the body's response to low oxygen levels is mainly driven by the detection of hypoxemia in the periphery, rather than by the central respiratory centers in the brain stem. Viruses can also inhibit this respiratory drive by disrupting the normal functioning of chemoreceptors, decreasing breathing rates and depths. The result can be respiratory depression due to damage to the respiratory-related neurons [38].

The medulla's central chemoreceptors sense a decrease in pH in brain extracellular fluid and adjust ventilation accordingly [39] [40]. The central chemoreceptors account for around 80% of $CO_2$ chemosensitivity [41]. When $PaCO_2$ reaches 45 mmHg, central chemoreceptors are activated, while when $PaCO_2$ reaches 39 mmHg, peripheral chemoreceptors are activated, and ventilation increases linearly [40]. There is a stronger relationship between carbon dioxide retention and breathlessness in lung disease than between hypoxemia and breathlessness [42].

It has been shown that hypercapnia can lead to excessive respiratory drive, which is caused by an increase in the dead space fraction of the lungs [43] and by stimulation of lung and chest wall receptors. These potential mechanisms should

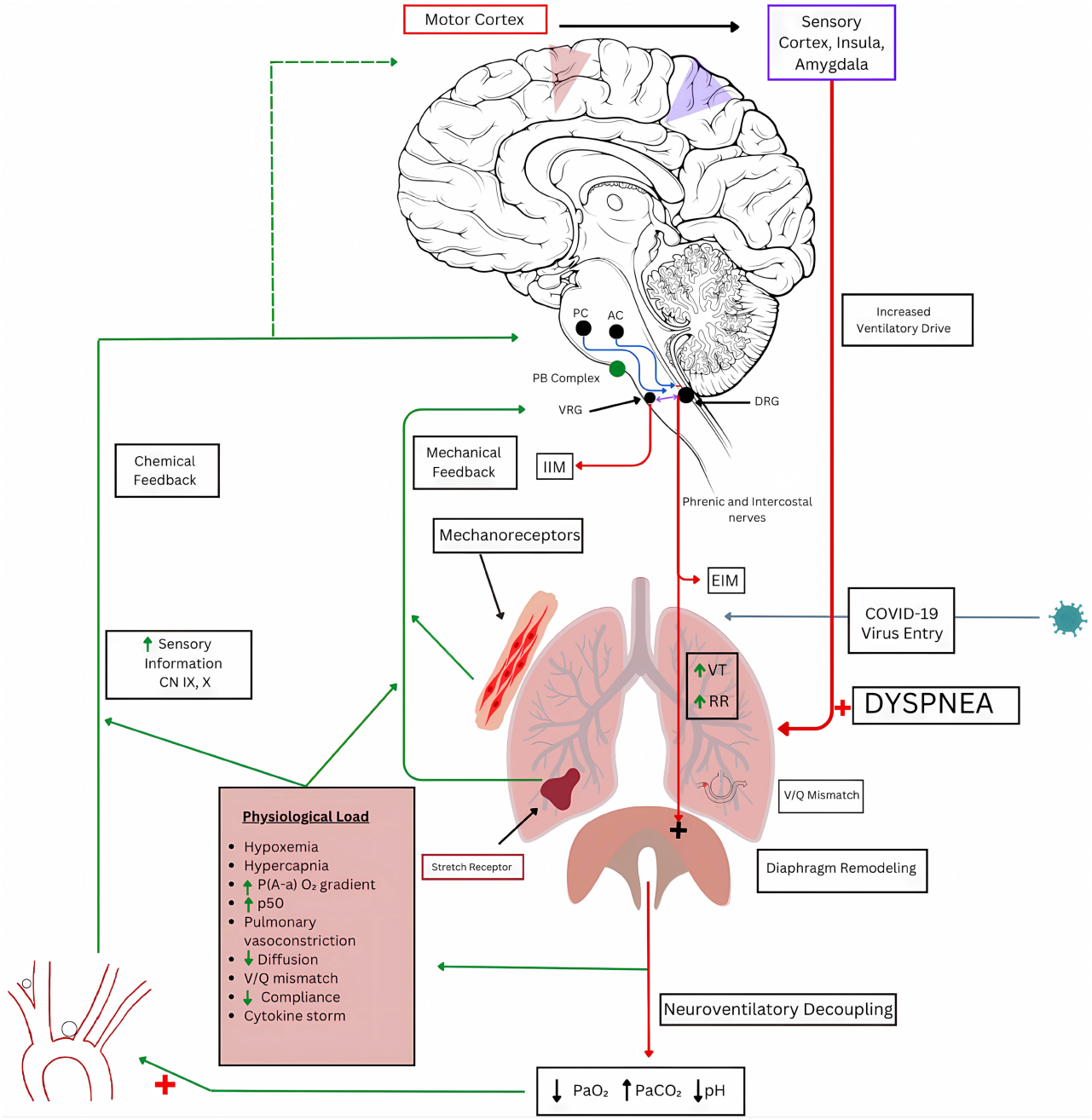


**Figure 1.** The diagram illustrates how physiological loads lead to central-peripheral mismatches, resulting in dyspnea in patients with COVID-19. Arrows in green are afferent and arrows in red are efferent. (PBC = preBötzinger complex; PC = Pneumotaxic center: AC = Apneustic center; DRG = Dorsal respiratory group; VRG = Ventral respiratory group; VT = Tidal volume; RR = Respiratory rate; IIM = Internal intercostal muscle; EIM = External intercostal muscle) An imbalance in the feedback loop could result in an increase in the drive of the medullary respiratory center, resulting in an increase in breathing rate as well as minute ventilation of the lungs. There may be a dissemblance between the respiratory drive and the ventilatory apparatus due to physiological host responses, resulting in neuroventilatory uncoupling. The increased respiratory drive caused by a physiological load contributes to neuromechanical dissociation.

be considered when evaluating patients with excessive respiratory drive, since they may require specific interventions [44].

As shown in the illustration (**Figure 1**), breathing is controlled and generated

by a complex network of neurons arranged in specific patterns within the ventrolateral medulla and lateral pons. A variety of phases of the breathing cycle are produced by the pre-Bötzinger complex, lateral parafacial region, and post-inspiratory complex, whereas a combination of the Kölliker-Fuse nucleus and parabrachial complex regulates and coordinates breathing [45]. Brainstems contain longitudinal respiratory columns (LRCs), aligned dorsally from the caudal medulla to the rostral pons. Anatomically, this structure is crucial to the production of eupnea, or normal breathing. Rhythm and depth of breathing are controlled by the respiratory pattern generator based on the LRC [46] [47]. According to a recent report, children with cerebral palsy have difficulties breathing because of impaired diaphragm muscle pressure generation, failure rate, and rhythm center impairments [48].

## 7. Dominant Sympathovagal Response in COVID-19

Vagal afferents in the lung are a heterogeneous group of fast-conducting myelinated A fibers and slow-conducting unmyelinated C fibers. Besides controlling respiration, this nerve also controls cardiovascular, immune, and digestive functions. To regulate respiration, part of the autonomic nervous system (ANS) must be functioning normally. COVID-19 can disrupt the functioning of this system. A reduced parasympathetic function may be associated with early clinical symptoms of COVID-19. In COVID-19, early clinical symptoms may be associated with sympathetic dominance and reduced parasympathetic function [49]. There has been some evidence that heart rate variability, which depends on autonomic or sympathovagal balance, may be related to infections of the central nervous system (CNS) caused by viruses [50]. According to Giannitsi and colleagues, psychological stress generated by the pandemic is activated in the brain-heart axis, possibly exacerbating disease conditions [51]. The sympathetic nervous system may be activated by emotional stress via a network of cortical regions. Most of the regions involved in respiratory rhythm and pattern formation in the brain step and spinal cord have been discovered through electrophysiological analyses and optical imaging studies.

An excessive amount of sympathetic activity can also be caused by pre-existing illnesses such as diabetes and cardiovascular disease, in addition to hypoxemia caused by viral-associated pneumonia and ARDS. Psychological isolation following hospitalization may also result in more sympatho-excitation, which puts additional pressure on the lungs, leading to tachypnea [52] [53]. Sympatho-vagal reciprocal inhibition in patients with COVID-19 enhances parasympathetic withdrawal [53]. According to this report, during the infection, there is a decreased parasympathetic activity coupled with sympatho-excitation that may blunt the neuro-vagal anti-inflammatory reflex, contributing to massive cytokine release has been documented. According to a study conducted by Fara *et al.*, vagus nerve stimulation has been found to be effective in reducing levels of pro-inflammatory cytokines in patients with ischemic heart disease. Also, a study conducted

by De Ferrari by vagal stimulation as a treatment option in the cardiac patients. In both studies, this intervention has demonstrated promising results in managing the host response associated with ANS dysfunction by restoring autonomic balance [4] [54].

Additionally, forceful breathing damages the endothelium-epithelium barrier, eventually causing pulmonary damage [55]. The Herring-Breuer vagal reflex normally protects against overdistension of the lungs. Due to the absence of this reflex in COVID-19 infection, elastic fibers of the lungs become strained and damaged due to enlarged lung volumes. As a result of injury, alveolar micromechanics and barrier functions may be disrupted in patients, resulting in ARDS [56] [57].

## 8. Blunting Hypoxic Ventilatory Response

A patient who has blunted reactivity to hypoxia or has experienced recurrent hypoxia episodes before becoming infected with COVID-19 will be more likely to progress to severe and critical stages of the infection [58]. Such patients usually experience an asymptomatic or mild course, and those who deteriorate usually do so by the eighth day after symptoms arise. "Happy hypoxia" is common among patients suffering from COVID-19, particularly in older populations [59]. Despite the lack of explanation, it has been proposed that these patients encounter this phenomenon when their $SpO_2$ drops by 3% - 5% which could be due to infection-independent blunted sensitivity of the respiratory system to hypoxia and hypercapnia [60].

The mortality rate for some individuals with COVID-19 varies greatly depending on whether they have pre-existing health conditions that may blunt their hypoxic sensitivity to chemoreceptors. It is more likely that host factors, rather than viral factors, determine mortality. Some authors believe symptoms are due to an inadequate respiratory response to hypoxia [61]. Additionally, dysfunction of the vascular endothelium may contribute to neurologic changes, cause swelling and edema, and result in insufficient chemoreceptors for detecting changes in interstitial fluid pH [62].

The cerebral cortex also plays a role in modulating ventilation during prolonged hypoxemia. It receives input from the brainstem and helps to regulate the breathing rate and depth in response to changes in oxygen levels [63]. When a patient with COVID-19 presents with hypoxemia, a hypoxic ventilatory decline occurs within 15 minutes. This decline is caused by a decrease in the sensitivity of the chemoreceptors to low oxygen levels. A healthy individual can overcome this decline through adaptations to hypoxia [63], seen in those ascending to a high altitude. Acute hypoxemic respiratory failure is a condition where there is a significant increase in respiratory effort and drive. It is often seen in patients with COVID-19 [64].

Frizzelli and colleagues analyzed the breathing pattern using the ratio of inspiratory time ($T_I$) to the total breath duration ($T_I/T_{TOT}$) during the tidal volume

($V_T$) and by determining the $V_T/T_I$ ratio, the underlying mechanisms of unexplained dyspnea in COVID-19. Based on the $T_I/T_{TOT}$ and $V_T/T_I$, the breathing pattern of individuals with unexplained dyspnea is more prone to diaphragmatic fatigue, and it is less efficient than those in the control group [65]. A high respiratory drive can lead to an increase in respiratory rate accompanied by a low $T_I$, which indicates an unsatisfied ventilatory demand. This means that the body's need for ventilation is not being met adequately. When the respiratory drive is high, the body tries to compensate by increasing the number of breaths taken per minute, resulting in a higher respiratory rate.

## 9. Inspiratory Neural Drive (IND) and Neuro-Mechanical Uncoupling

Dyspnea is an incredibly multifactorial condition, and it is not one symptom, but a group of symptoms related to a wide range of factors. As mentioned earlier, the angiotensin-mediated physiological effects of COVID-19 on the carotid bodies expressed with ACE2 receptors may result in more complex brainstem-level respiratory control independent of hypoxia and changes in lung mechanics [66]. These relationships may become even more complex over time as lung mechanics, ventilation requirements, and neural sensitivity change. Electromyography (EMG) of the diaphragm measures neural drive [67] [68] and can be used to investigate the pathophysiology of neuromechanical dissociation. EMG recordings can be made using either surface electrodes intramuscular needles or wire electrodes. Muscle electrical signals indicate the muscle's response to action potentials fired from groups of Dorsal root ganglion (DRG) neurons via the phrenic and intercostal nerves. The intrathoracic pressure does not necessarily reflect changes in neural drive in severe respiratory mechanical impairment, despite such studies for understanding dyspnea. Therefore, intrathoracic pressure may not be an accurate determinant of neural drive. As such, for the purposes of this review, we would only cover the activity of the diaphragm to measure the amount of IND. The relationship between diaphragm function and central voluntary activation in patients with COVID-19 suggests that impaired diaphragm function and reduced central voluntary activation may contribute to the development of dyspnea [69]. As a result of increased motor command output to the respiratory muscles and increased central corollary discharges from the respiratory motor centers to the somatosensory cortex, perceived breathing effort increases [70] [71].

According to Hopkinson et.al, the motor cortex's intracortical circuits correlate strongly with inspiratory muscle strength and hypercapnia [72]. This observation was limited to COPD patients as their research was conducted prior to the COVID-19 pandemic. Since then, neuromechanical and neuroventilatory decoupling has been hypothesized to prevent electrical signals from being converted into mechanical or ventilatory responses in respiratory disorders such as COPD and respiratory infections. As such, it is possible that these observations in motor cortex intracortical circuitry may be applicable to COVID-19 patients.

Dissociations occur when diaphragmatic electromyography (EMGdi) does not translate into mechanical or ventilatory responses in these patients when they are suffering from diseased conditions [73]. When the normal relationship between neural respiratory drive and ventilation is disrupted, neuroventilatory uncoupling occurs. Breathing difficulties can occur as a result. According to recent research, IND increases occur due to acute elastic loading of functionally weakened inspiratory muscles [74] [75].

A recent report reveals many COVID-19 patients who were admitted had persistent dyspnea, with six cases (2.4%) experiencing de-novo diaphragm dysfunction [75]. Additionally, patients who have recovered from COVID-19 may suffer from persistent dyspnea due to diaphragm dysfunction. In critically ill patients with novel Coronavirus disease, diaphragm dysfunction may occur due to critical illness myopathy or ventilator-induced diaphragm damage due to blunted ventilation [76] [77]. Also, the significance of corticospinal input to the respiratory centers has been highlighted for contributing to neural drive during the waking state [78]. The corticospinal pathway regulates diaphragm movement directly via neural inputs. The reticular formation provides most of this drive [79] [80].

## 10. Conclusion

The cause of dyspnea in COVID-19 patients is complex and multifactorial. An inflammatory host response might increase respiratory afferent signals in response to metabolic demands induced by the physiological load. Consequently, rhythmic, and pattern-making signals are generated by the respiratory center modifies breathing rate and depth. In the case of persistent hypoxemia, the cerebral cortex may be involved in modulating ventilation. A disruption of the normal relationship between neural respiratory drive and ventilatory apparatus results in neuroventilatory uncoupling. As a result, the severity of breathlessness may be significantly affected. A person with elevated levels of chemosensitivity has an enhanced ability to respond to physiological loads, which increases IND and eventually minute ventilation.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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