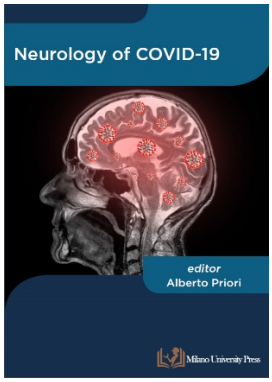

Neurology of COVID-19
Editor Alberto Priori
DOI: https://doi.org/10.54103/milanoup.57

Published by: Milano University Press
Via Festa del Perdono 7 - 20122 Milano
URL: https://milanoup.unimi.it/
E-mail: redazione.milanoup@unimi.it

Chapter 3. **Does the COVID-19 related respiratory failure have a neurogenic component?**

DOI: https://doi.org/10.54103/milanoup.57.5

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Chapter 3. Does the COVID-19 related respiratory failure have a neurogenic component?

Davide Chiumello, Matteo Bonifazi

Pathological pathways

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has pushed the response of health systems to maximum capacity. Worldwide the surge of cases has overwhelmed the facilities and human resources available[1-4]. Intensive care units have found themselves with no available beds due to the huge influx of severe cases over just a few weeks, with acute respiratory distress syndrome (ARDS) as the main reason for admission[1-4]. Indeed, its structure and mechanism of transmission and replication make SARS-CoV-2 highly infectious[5-9].

One widely reported phenomenon is the presence of a profoundly hypoxemic patient with the slightest, or no, dyspnea, out of proportion to the extent of radiographic abnormalities and changes in lung compliance. This clinical manifestation has been called "happy hypoxemia or hypoxia" but has been better described as "silent hypoxemia". This has led to speculation that there are underlying pathophysiologic differences between lung injury due to COVID-19 and ARDS from other causes[10-14].

Histological SARS-CoV-2 has been established as a cause of severe alveolar damage and pneumonia. The consolidation of lung parenchyma precipitates the alterations in blood gases in COVID-19 patients that are known to complicate and cause hypoxemic respiratory failure[15,16]. Indeed, the damage caused by SARS-CoV-2 at the level of gaseous exchange in the lungs causes exudative and organized diffuse alveolar damage. It has been reported that severely hypoxemic COVID-19 patients may present quite different characteristics: 1) normal breathing ("silent" hypoxemia) or remarkably dyspneic; 2) quite responsive to nitric oxide or unresponsive; 3) deeply hypocapnic or normo/hypercapnic; and 4) responsive to a prone position or not responsive. Therefore, the same disease presents itself with notable heterogeneity. The ongoing exudation and fibrosis in the terminal bronchioles and alveolar walls thicken the gaseous barrier leading

to profound hypoxia and the risk of hypoxemic-respiratory failure. Many patients with a severe drop in partial alveolar (pa)O_2 remain asymptomatic, initially due to possible compensation by an increase in the rate of breathing that comes into play through the neurogenic mechanism against hypoxia resulting from a poor diffusion of O_2 across the alveolar barrier[15-17]. A possible explanation for such severe hypoxemia occurring in a compliant lung is the possible loss of lung perfusion and hypoxic vasoconstriction[10-13].

However, the alteration of paO_2 and $paCO_2$ in COVID-19 is complex and difficult to understand when compared to conventional viral cases of pneumonia. The reason for this added complexity is the concurrent renal, gastrointestinal, and adrenal damage, coagulation abnormalities, and metabolic derangements like lactate production from cellular damage that are known contributors to the maintenance of blood pH and blood gases, and act as buffers to combat any alteration that may occur in these parameters.

An alarming but yet unexplored component in COVID-19 is the damage to the neurons in the central nervous system (CNS) that has been reported to start during the disease course in some patients. Emerging data on COVID-19 cases from hospitals and autopsies in the last few months have helped in understanding the pathogenesis of respiratory failures in COVID-19[18-21]. Recent reports have provided overwhelming evidence of the occurrence of acute respiratory failure in COVID-19 due to neurotropism of the brainstem by SARS-CoV-2[22-26]. It is easy to compute the complexity that ongoing damage to respiratory regulating neurons in CNS would add to the pulmonary damage in COVID-19. Knowledge of the circuit of neural projections and synapses that regulate the breathing process is essential to understanding respiratory failure in general and that seen in COVID-19.

The breathing process carried forward by the CNS under physiological conditions is an involuntary (autonomous) process enforced by pacemaker cells in the pre-Bötzinger complex (pre-BÖTC) on either side of the medulla oblongata in the brainstem. These neurons produce rhythmic discharges that reach the phrenic nerve motor neurons. In addition, dorsal (DRG) and ventral (VRG) groups of respiratory neurons are present in the medulla, and they are known to project to the pre-BÖTC pacemaker neurons. The rhythmic discharges of the pre-BÖTC pacemaker neurons are modified by a pneumotaxic center (nucleus parabrachialis), which may play a role in switching between inspiration and expiration in the pons and afferents in the vagus nerve from receptors in the airways and lungs.

A rise in the $paCO_2$ or H+ ion concentration of arterial blood or a drop in its paO_2 increases the rhythmic discharge in the medulla oblongata and vice versa[22-28].

The effects of variations in serum chemistry on the rhythmic discharge of pre-BÖTC are mediated via respiratory chemoreceptors: the carotid and aortic

bodies and the central chemoreceptor area in the medulla[29]. Each carotid and aortic body contains isles of two types of cells, glomus type I and glomus type II cells (supporting cells), surrounded by fenestrated sinusoidal capillaries. The glomus type I is closely associated with glossopharyngeal nerve afferent nerve (CN-IX) endings and is stimulated by hypoxia-induced inhibition of O_2-sensitive potassium K+ channels. The transmitter involved appears to be dopamine, which stimulates the nerve endings by way of D2 dopaminergic receptors. The glomus type I receptors in the carotid/aortic bodies are stimulated, with increased afferent nerve discharges, by a rise in the $paCO_2$ or H+ concentration of arterial blood or a decline in its paO_2 below 55-60 mmHg. Therefore, the stimulatory effects of hypoxia on ventilation are not manifested until they become strong enough. In addition, even though spontaneous breathing is not usually a conscious phenomenon, both inspiration and expiration are under voluntary control. The pathways for voluntary control pass from the neocortex (Brodman's area 4 neurons) to the motor neurons innervating the respiratory muscles, without influencing the medullary neurons[20-30].

Invasion of the CNS by SARS-CoV-2 has recently been shown in areas such as the brainstem that control the normal breathing process with nuclei like the pre-BÖTC. This may explain why some of the patients with COVID-19 who have been reported to have recovered from pneumonia could not be weaned off invasive mechanical ventilation, and the occurrence of acute respiratory arrests seen in COVID-19. This debate is important for many reasons, one of which is the fact that permanent damage to the medullary respiratory centers by SARS-CoV-2 would not benefit from mechanical ventilators, something which could be happening during the management of COVID-19 patients[20-31]. Moreover, there have been reports of acute respiratory failure in 45-65% of cases of COVID-19 in which the patients lost spontaneous breathing, required mechanical ventilation, and then later died. Some of the patients with COVID-19 that have been reported to recover from pneumonia but could not be weaned off invasive mechanical ventilation need to be investigated for deteriorating SARS-CoV-2 neurotropism that can prove fatal. The occurrence of these spontaneous (autonomic) breathing control failures early in COVID-19 is alarming and possibly reflects the damaging effect of SARS-CoV-2 on the CNS nuclei that control normal involuntary breathing mechanics[18-30].

SARS-CoV-2 probably invades the brain via axonal transport and transneuronal spread from the olfactory nerves on to the rhinencephalon, ultimately reaching the brainstem and causing the irreversible respiratory failure seen in severe COVID-19, typically characterized by lack of dyspnea. Additionally, SARS-CoV-2 has been isolated from the cerebrospinal fluid (CSF) of COVID-19 patients and the hematogenous or lymphatic routes have been proposed as ways through which the virus may gain entry to the CNS[20-30].

It is more likely that the virus invades the brainstem in the early phases of COVID-19. Therefore, respiratory failure due to damage in respiratory regulating centers can occur long before the hypoxemic influence comes into effect, as has been reported recently, since severe respiratory distress is observed 8-14 days after symptoms develop. In fact, even partial damage to the pacemaker neurons in the pre-BÖTC area can lead to intervals of loss of autonomic breathing and lead to the neurological manifestations reported in COVID-19. Moreover, the spinal motor neurons that act as a nuclear group for phrenic nerve, emerging as nerve roots, are located at cervical nerves 3, 4, and 5 (C3, C4, and C5) and could be involved, as has recently been reported, in affecting the diaphragm and thoracic muscles, completely interrupting respiratory function[21-31].

Clinical features and possible treatments

Correlating the pulmonary sign and symptoms of patients with COVID-19 and the ongoing neurological deficits can help identify the possible regions of the CNS where SARS-CoV-2 impacts the breathing process. The ability of COVID-19 patients to retain control over voluntary breathing suggests that the neocortical projections of the brain to the spinal motor neurons are spared. Moreover, the damage to both the pneumotaxic center and vagus nerves is also expected to result in inspiratory spasms as if the patient was holding their breath in the inspiratory phase of breathing (apneusis), as has been reported. Damage to the central chemoreceptor can strongly affect breathing rate and depth. Partial neurotoxicity of the neurons in the pre-BÖTC region which normally generates pacemaker impulses for autonomic breathing appears to be the most likely explanation for the patient having a sensation of losing the ability to breathe spontaneously, while a complete or substantial loss of the neurons in this region would induce neurogenic acute respiratory arrest despite the presence of moderate hypoxia and hypocapnia.

The question of survival in COVID-19 patients could also be best explained by the degree of the quantitative loss of neurons in the pre-BÖTC region and the ability of the neurons to compensate for a partial loss in those patients who survive the episode of medullary neurotoxicity in COVID-19. Paralysis of the diaphragm and damage to spinal motor neurons below C5 segments, or a combination of these, can contribute to syndromic respiratory failure[21-33].

All these signs could, therefore, be explained by the concept of central neurogenic respiratory failure. Given this, it is important to mention that, in a severe case of COVID-19, distinguishing hypoxemic respiratory failure from exclusive respiratory arrest due to damage to the brainstem pre-BÖTC and phrenic nerve nuclear group at C3-C5 is difficult if not impossible. A respiratory arrest that cannot be explained by the extent of lung damage in early onset COVID-19

and abnormal breathing patterns should undergo thorough clinical investigation, since, as previously mentioned, neuro-invasiveness by SARS-CoV-2 can occur early during COVID-19 and could be missed.

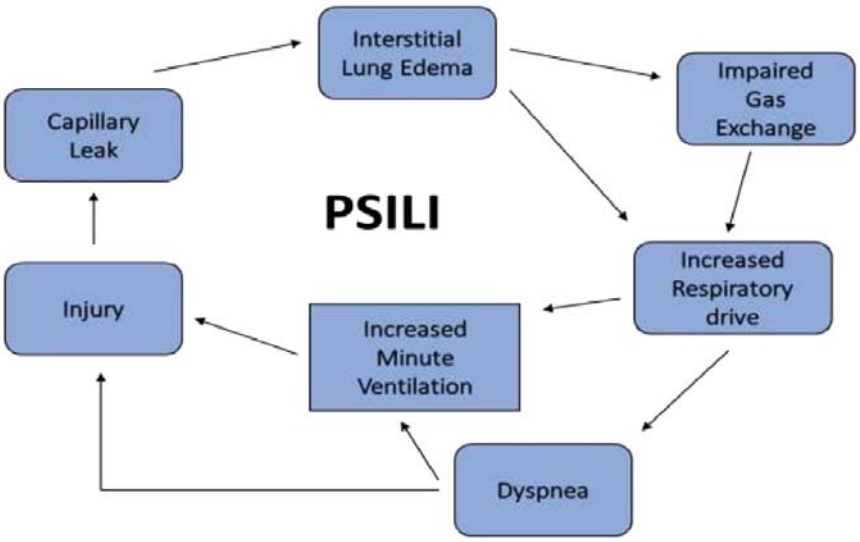
Moreover, the decline in arterial O_2 tension is normally detected by O_2-sensing cells in the carotid body (CB), the main arterial chemoreceptor, which rapidly activates sensory fibers impinging on neurons in the brainstem to induce compensatory hyperventilation and increase the heart rate. In this way, both O_2 uptake and its distribution to the tissues are enhanced. Indeed, bilateral removal of the CB in humans leaves individuals unaware of hypoxemia, with complete abolition of the hypoxic ventilatory response. Therefore, inhibition of CB responsiveness to hypoxia could be a plausible explanation for the impaired respiratory drive and reduced dyspnea that characterizes the "silent hypoxemia" observed in COVID-19 patients. The CB parenchyma is organized into clusters of cells called glomeruli. Each glomerulus is composed of 4-8 neuron-like glomus or Type I cells, which are in close contact with a network of fenestrated capillaries and are richly innervated by afferent sensory fibers of the petrosal ganglion. Glomus cells, the O_2-sensing elements in the CB, contain abundant synaptic vesicles with neurotransmitters that are rapidly released in response to hypoxia to activate the sensory fibers that connect the brainstem respiratory and autonomic centers. In addition, the CB glomeruli also contain a smaller number of glial-like, Type II or sustentacular cells with interdigitating processes that envelop the glomus cells. Type II cells are multipotent stem cells that can differentiate into O_2 sensitive glomus cells to support CB growth under sustained hypoxia. Although acute O_2-sensing is an intrinsic property of CB glomus cells, the functional responses of these cells are modulated by numerous auto- and paracrine signals generated within the organ. In this regard, a local renin-angiotensin system (RAS) and its principal components (angiotensinogen, angiotensin-converting enzyme, and angiotensin receptors) have been described in the CB. Indeed angiotensin-converting enzyme 2 (ACE2) has an important regulatory role in the RAS and it has been identified as the functional receptor by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells.

Based on the high ACE2 expression found in human CB, it is plausible that infection of chemosensory glomus cells by SARS-CoV-2 could alter their ability to detect changes in arterial O_2 tension. This could mask the hypoxemia, as occurs in cases of "silent hypoxemia" in COVID-19 patients. Several studies show a highly individual variability of ACE2 expression in human CB tissue, which could explain why there appears to be no explanation as to why any particular COVID-19 patient should experience "silent hypoxemia".

Therefore, ventilation dysregulation and dyspnea add to an already injured lung, exacerbating the damage. In fact, breathing produces a phenomenon of continuous cyclic strain deformation, where the applied pressure is inspiratory

pressure. The overall strain for the whole lung can be defined as the ratio between the tidal volume (Vt) and a reference volume, usually the volume of air at the end of passive expiration, and the functional residual capacity (FRC). Stress, the force acting on a surface unit, produces its deformation. Transpulmonary pressure corresponds to the stress in the lung. Strain and stress in the lung tissue are closely related to each other through a constitutive relation (stress = tissue elastance*strain)[34-44]. Both play an important role in the onset and development of ventilator-induced lung injury (VILI) and patient self-inflicted lung injury (P-SILI).

Figure 3.1: Patient self-inflicted lung injury cycle (PSILI)



High values of strain are known to be harmful to the lung and to increase mortality[34-42].

Assisting ventilation both with non-invasive support and invasive mechanical ventilation can be used to minimize stress and strain when impending respiratory failure is recognized.

Continuous positive airway pressure (CPAP) helmets and non-invasive ventilation (NIV) can prevent excessive respiratory effort. The latter can be assessed through monitoring esophageal pressure swings, a surrogate of the transpulmonary pressure in spontaneously breathing patients[43-46].

CPAP potentially modulates drive by improving oxygenation by means of positive airway pressure, optimized oxygen delivery, and improvement of lung mechanics, while NIV may reduce respiratory drive by several mechanisms: 1) unloading respiratory muscles from inspiratory effort, which also reduces CO_2 production; and 2) improving oxygenation and lung mechanics through increases in positive end-expiratory pressure (PEEP)[43-46].

Despite respiratory support, the neurological involvement of SARS-COV-2 requires an additional strategy to control dyspnea in these patients. In fact,

respiratory drive and respiratory rate could be controlled through sedation to prevent and treat high respiratory frequencies along with respiratory support. Sedation also plays an important role in making patients comfortable and helping them to cope with what could be several days of non-invasive ventilation as compliance to treatment is fundamental given the lengthy course of the disease. Indeed, measuring respiratory drive in patients with COVID-19 acute distress syndrome (CARDS) could be important when selecting the initial ventilatory support and in deciding when to wean the patient off mechanical ventilation. Indeed, vigorous breathing efforts can amplify the severity of lung injury, which in turn can influence the duration of mechanical ventilation and impact patient outcome.

The prone position has been widely adopted in COVID-19 patients to treat hypoxemia[45]. However, its role has been fundamental not only to restore gas exchange in both awake and sedated patients, but in particular to homogenize the lung and reduce unprotective lung ventilation, thus reducing lung injury[48-50].

Despite this, some patients will remain dyspneic, breathing spontaneously, with or without respiratory support. Vigorous and dysregulated respiratory effort, even if under control in terms of respiratory rate, may promote P-SILI, with generation of high stress and strain, as shown by a high swing in esophageal, thus transpulmonary, pressure.

Ultimately, this phenomenon worsens the respiratory failure; the patient must be intubated and mechanical ventilation is required in up to 20-30% of cases. When invasive mechanical ventilation is instituted, there is often an initial phase of deep sedation, which may decrease the respiratory drive and, occasionally, a period of neuromuscular blockade, which eliminates breathing effort. Once assisted breathing is restored, uncontrolled high respiratory drive may also resume.

SARS-CoV-2 neurological involvement could also be seen during mechanical ventilation; an alteration of the central nervous system with dyspnea and delirium can promote the development of asynchronies and VILI[51,52].

Ventilator asynchronies have been associated with longer duration of mechanical ventilation and increased mortality. In particular, reverse trigger is defined as a dyssynchrony in which the patient starts to activate the inspiratory muscle during a passive insufflation of the lung (i.e., in non-triggered breaths). The inspiratory muscle causes an increase in the inspiratory effort with larger Vt and double cycling (breath stacking) with increased stress and strain, leading to unprotective ventilation[52-53].

Thus, in these patients, early detection of the possible presence of asynchrony and reverse trigger is fundamental. Moreover, impaired respiratory drive and excessive inspiratory efforts represent a challenge during the weaning process from mechanical ventilation, leading to increased mortality and fewer days off mechanical ventilation.

As has been said, pharmacological intervention with opioids, drugs modulating agitation and anxiety like dexmedetomidine, as suggested in a recent study, and partial muscular paralysis by low-dose neuromuscular blocking agents could achieve protective Vts and inspiratory pressures in CARDS patients exhibiting uncontrolled high respiratory drive during assisted ventilation[54,55]. Non-pharmacological techniques, such as extracorporeal carbon dioxide removal ($ECCO_2R$) or venous-venous extracorporeal membrane oxygenation (ECMO), could also be applied in selected severe cases of CARDS and refractory hypercapnia[56-58].

Conclusions

With a rapid rise in mortality in patients with COVID-19 exhibiting extrapulmonary manifestations, there is an urgent need to understand and diagnose the neurological symptoms early in the course of this disease. Future research is needed to understand the route of virus entry (neural or through the bloodstream), the neuronal damage and the affected areas in the brain, including pathological assessment of the respiratory center in the brainstem.

Take-home message

- COVID-19 is a systemic disease with multiple organ involvement, especially the lung.
- Respiratory failure is not only due to direct damage to the lung but is a consequence of neurological involvement.
- Respiratory effort and its neurological control play an important role in causing acure respiratory distress and lung damage.
- Sedation together with lung ventilatory strategies to prevent VILI should be tailored based on pathophysiology assessment.
- Understanding neural patterns can help identify phenotypes of respiratory efforts in COVID-19 patients.

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