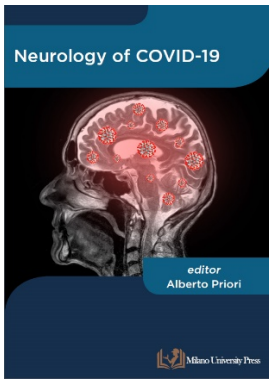

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Chapter 2. **The lung-brain axis**

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Chapter 2. The lung-brain axis

Giuseppe Francesco Sferrazza Papa, Giulia Michela Pellegrino, Stefano Centanni

Introduction

There is an intrinsic connection between neurological and respiratory functions both in conditions of health and of disease. Over the past decades, it has become increasingly acknowledged that lung and brain represent an integrated physiological *ensemble* such that insults involving one organ will necessarily affect the other. For instance, it has been shown that neurological conditions such as brain death[1], traumatic brain injury[2], or status epilepticus[3] may cause pulmonary edema and lung injury, thus further worsening clinical outcomes[4,5]. On the other hand, severe respiratory disorders such as acute respiratory distress syndrome (ARDS) may be responsible for poor neurocognitive outcomes[6].

After a brief overview of neurobiology and physiology, this chapter will introduce the concepts of dyspnea and respiratory failure in COVID-19, and then focus on post-COVID sequelae with a special focus on the respiratory and neurological aspects. Finally, we will provide some practical recommendations for the clinician caring for patients post COVID. Further insights into the neurogenic component of COVID-19-related respiratory failure are discussed elsewhere in the book.

Neurobiology and pathophysiology

Breathing is a key homeostatic function that regulates gas exchanges of oxygen (O_2) and carbon dioxide (CO_2) in the lung in order to stabilize pH and support metabolism. Ventilation is the result of the integrated actions between the mechanical properties of the airways, lungs, respiratory muscles, and the chest wall, while gas exchanges are due to the capacity of the lung to exchange gases across the alveolar–capillary membrane.

Respiratory movements occur automatically and continuously, and are driven by the rhythmic motor activity generated within neural circuits in the brainstem and spinal cord[7]. The underlying neural machinery is not a simple trigger, but rather a complex flexible system that provides physiological and behavioral

integration. Recent research showed that the brainstem respiratory network works at multiple hierarchical levels, which allows flexible expression of different rhythmogenic mechanisms under different physiological conditions and enables a wide repertoire of respiratory patterns[8]. The core circuit components of the neural machinery that generates the rhythm and shapes the inspiratory and expiratory motor patterns are located within three adjacent structural compartments in the ventrolateral medulla: the Bötzinger complex (BötC), pre-Bötzinger complex (pre-BötC), and rostral ventral respiratory group (rVRG)[8]. Recent experiments showed that, in adult mammals, the rhythm is dominated by the pre-BötC[9] which seems to work as a self-organized group-pacemaker[10].

The respiratory rhythm should then be modulated to satisfy the body's metabolic demand and transformed into an efficient pattern of movement. To regulate this task, the brain links sensory information to the motor output, the respiratory muscles. To provide this regulation, carotid bodies and brainstem chemosensory organs monitor blood O_2 and CO_2 levels. The carotid bodies are located at the bifurcation of the carotid arteries and produce signals that relate mostly to O_2 levels in arterial blood[10,11]. Although lung and cardiac diseases are the main causes of breathing disorders, dysfunctions of the neural control of breathing may play a role in some diseases such as sudden infant death syndrome (SIDS)[12,13]. Several genetic disorders cause abnormal respiration, including Rett syndrome[14] and congenital central hypoventilation syndrome (also known as Ondine's curse)[15]. Death due to progressive respiratory failure occurs in neurodegenerative diseases such as amyotrophic lateral sclerosis, and may play a role in some cases of Parkinson's disease[16] and multiple system atrophy (MSA).

Respiratory dysfunction and brainstem viral infections

The relationship between respiratory alterations and brainstem viral infections has long been studied and appears to stem from both primary respiratory and brainstem affections.

A) *Primary respiratory affections* - changes in primary afferent neurosensors subsequent to respiratory viral infections may alter the synaptic integration of peripheral inputs at the brainstem level. The most frequent consequence is cough hypersensitivity following an acute respiratory viral infection. Studies employing capsaicin inhalation challenge to measure cough reflex sensitivity have documented a transient tussive hyper-responsiveness induced by upper respiratory infections (URI) that reverts to normal values by 4-8 weeks post infection. An underlying hypersensitivity of the cough reflex potentiates the effect of the exogenous stimulus, resulting in refractory, chronic cough in a particular subgroup of individuals[17].

Numerous mechanisms have been proposed to explain the transient cough and enhancement of cough reflex sensitivity associated with acute viral URI. Direct effects of the viral infection on airway epithelium include inflammation and cytokine release which stimulate sensory afferent nerves. Other airway effects of URI include increase in neurotransmitter levels, such as Substance P, reduced activity of neutral endopeptidases, increased neural receptor levels (NK-1), and transient modulation of airway neural activity. Increased leukotriene production and mucus hypersecretion are likely additional contributors to cough induction. Many patients experience cough during acute COVID-19 pneumonia, and less frequently report cough as a symptom of long COVID. The latter might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways similar to that of the cough hypersensitivity syndrome.

B) *Brainstem affections* - brainstem viral infections can cause respiratory complications, both by direct pulmonary involvement and respiratory muscle failure.

Most tumoral and infectious causes of brainstem encephalitis (BE) determine ventilatory failure by compromising the central ventilatory control, as is the case of Listeria Monocitogenes, herpes simplex virus (HSV) 1 and 2, and human herpes virus 6 (HHV6); some may affect respiratory muscles as well, such as the Epstein-Barr virus (EBV)-related overlapping of BE and Guillain-Barré syndrome, while others primarily determine bulbar muscle impairment and subsequent respiratory failure, such as the progressive multifocal leukoencephalopathy (PML) caused by the JC polyomavirus[18].

Brain stem encephalitis caused by enterovirus 71 determines a release of cytokines and chemokines which may induce secondary pulmonary edema (PE). The disease is a hyperinflammatory syndrome resulting from hypercytokinemia and central nervous system inflammation of various inflammatory mediators. Some studies have shown that proinflammatory cytokines (interleukin [IL]-6, tumor necrosis factor [TNF]-α, and IL-1β) are associated with brainstem encephalitis that is complicated by PE[19].

Recent reports have provided some evidence of the occurrence of acute respiratory failure in COVID-19 due to neurotropism of the brainstem by SARS-CoV-2, which may contribute to the pulmonary damage. SARS-CoV-2 probably invades the brain via axonal transport and transneuronal spread from the olfactory nerves on to the rhinencephalon, finally reaching the brainstem and causing the irreversible respiratory failure seen in severe COVID-19, typically characterized by lack of dyspnea[20].

Patients with COVID-19 often develop respiratory failure 8-14 days after symptom onset, with "silent hypoxemia" and a high respiratory rate, resulting in hypocapnia. The hypoxia in COVID-19 leading to stimulation of the pre-BÖTC via the chemoreceptor area is expected to cause an increased respiratory

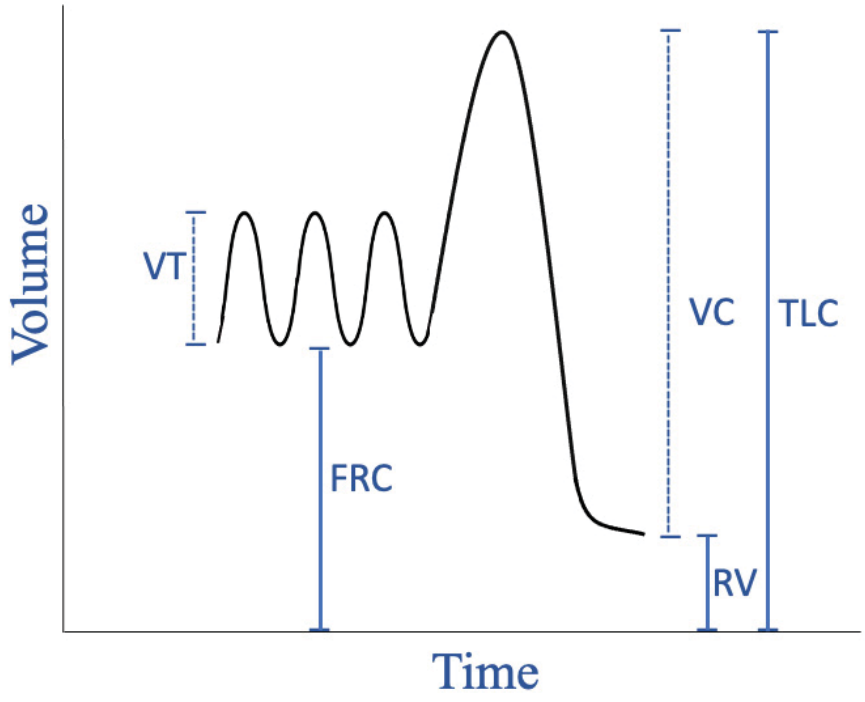
rate and depth that has often been reported in COVID-19 patients. On the contrary, the patients with profound hypoxia seemingly appear to be asymptomatic, though respiratory failure is expected to occur quite soon. Damage to vagal receptors of the lungs, and perhaps mechanoreceptors of the respiratory muscles, might explain the lack of dyspnea, along with a possible defective central neural system processing of the respiratory signals[21].

Respiratory clinical physiology

Patients with persistent respiratory symptoms after COVID-19 need to be thoroughly examined to assess the presence of disease sequelae. Outside the emergency setting, pulmonary function testing (PFTs) is part of the key investigations, and this must be performed before any invasive or second-line imaging tests such as computed tomography.

As the COVID-19 infection quite often affects lung parenchyma, spirometry and lung volume measurements may be of help to detect the lung disease. This is strongly suggested by a decrease in total lung capacity (TLC), forced vital capacity (FVC), and the forced expiratory volume in 1 s (FEV1) below the threshold of natural variability[22] (Figure 2.1).

Figure 2.1: Lung volumes



VT: tidal volume; RV: residual volume; FRC: functional residual capacity; VC: expiratory vital capacity; TLC: total lung capacity.

Measurement of lung gas exchange is also part of the clinical evaluation of the patients affected by COVID-19 infection. For instance, a decrease in diffusing capacity for carbon monoxide is an index of alveolar inflammation or pulmonary fibrosis. Similarly, a decrease in arterial oxygen tension will indicate an important gas exchange impairment[22]. In contrast, an increase in arterial CO_2 tension is consistent with an impairment in ventilation as a result of the inability of the inspiratory muscles to maintain the minute ventilation required to satisfy metabolic requirements. Under these conditions, measuring the inspiratory muscle force and diaphragm activity with ultrasound will help estimate the severity of the respiratory muscle defect.

Dyspnea: a complex symptom

The American Thoracic Society defines dyspnea as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses"[23]. There are numerous sensory receptors located throughout the respiratory system that send afferent information to the central nervous system. It is widely accepted that there are at least three main dyspnea components, depending on quality of the symptom, the generating stimuli, and the pathways involved: 1) air hunger; 2) work/effort; and 3) chest tightness.

1) Air hunger is a primordial sensation that signals the urgency to breathe and correlates with the failure of pulmonary ventilation in maintaining gas exchanges. It is strongly linked to the development of hypercapnia, and, to a lesser extent, of hypoxia. To the best of our practical daily experience, this is the principal component of the dyspnea experienced during COVID-19.

2) Respiratory effort arises when the work of breathing or the required motor command is increased by high minute ventilation, by impedance to inspiration, by weakness of respiratory muscles, or by placing inspiratory muscles at a disadvantageous length.

3) Chest tightness appears to be specific to bronchoconstriction and is the earliest symptom of asthma. It arises from the activation of rapidly adapting stretch receptors (RARs) and C-fiber receptors in the lungs.

Given the different mechanisms underlying dyspnea, it is of practical help to assess not only the presence and intensity, but also the different qualitative components. The widely used one-dimensional scales (such as the BORG scale[24], the Visual Analog Scale [VAS][25], or the Medical Research Council [MRC] scale[26]) adequately measure the intensity of the perceived dyspnea but cannot characterize its different components. In the past years, there has been great interest in the development of novel tools that capture the different, multidimensional

qualities of dyspnea such as the Multidimensional Dyspnea Profile (MDP) and the Dyspnea-12 Questionnaire (D12)[27].

Respiratory failure in COVID-19

The clinical spectrum of COVID-19 is quite heterogeneous. In a recent study, severity of the respiratory infection, older age, and renal impairment, and absence of any comorbidities were predictors of 28-day mortality in patients affected by COVID-19[28]. Respiratory failure due to interstitial pneumonia, decreased lung compliance, and hypoxemia are the most critical features of the disease[28,29]. Examining a series of ventilatory features such as lung elastance, ventilation-to-perfusion ratio, lung weight and lung volume recruitability, Gattinoni et al. were able to identify patterns with different combinations of the lung function/imaging parameters possibly explaining the changes in the severity of the disease over time and its susceptibility to different treatments[30].

In addition, disproportionate endothelial damage may disrupt pulmonary vasoregulation, thus promoting ventilation-perfusion mismatch and fostering thrombogenesis. Finally, remarkably increased respiratory drive could potentially increase tidal strain and energy loads to highly vulnerable tissue, thus adding patient self-inflicted lung injury[31] to the mix of the lung's inflammatory assault[32].

Mechanical ventilation support keeps patients alive until their own biological mechanisms are able to outwit the coronavirus[33]. The best way to minimize ventilator-associated complications is to avoid intubation unless it is absolutely necessary[34,35]. In a cohort of 64 patients, Brusasco et al.[36] reported successful treatment of severe COVID-19 pneumonia by CPAP ventilation in 83% of the cases, with only four deaths and seven patients requiring subsequent intubation. In a multicenter study performed on 175 patients, Aliberti et al.[37] reported only a 55% efficacy of helmet CPAP in treating severe COVID-19 pneumonia, with higher rates of CPAP failure occurring in patients with more severe pneumonia upon admission and higher IL6 levels.

Even though there is no consensus as to the best length of time for mechanical ventilation, most of the studies agree on the concept of stopping the treatment as soon as possible to avoid risks of infection and death[38].

It has been documented that, whereas the most severe and critical COVID-19 patients have no significant long-term sequelae, a substantial proportion suffers from long-lasting symptoms and respiratory impairment. In a study performed on severe and critical COVID-19 patients, about 25% of patients complained of persistent fatigue at the 3-month follow-up. Twenty percent of the patients exhibited signs of fibrosis on lung HRCT, and this was somewhat correlated with length of stay in the intensive care unit (ICU) and mechanical ventilation.

Post-COVID clinical *sequelae*

COVID-19 infection has been shown to frequently cause complications that last weeks to months after recovery. This has been named Long COVID and defined as a post-viral illness that can affect survivors of COVID-19 regardless of the initial disease severity or patient age, with a prevalence in the female sex and in those patients exhibiting more than five early COVID-19 symptoms or early dyspnea[39].

Clinical manifestations are quite heterogenous and fluctuate over time, with the most common symptoms being fatigue and dyspnea that can last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairment, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and heart problems. Possible pathophysiologic mechanisms are persisting tissue damage within the lung, brain, and heart, and/or exaggerated inflammatory processes as a result of viral persistence, immune dysregulation, or autoimmunity.

Interestingly, many of the above mentioned respiratory, cardiovascular, gastrointestinal, and neurological problems that follow the COVID-19 infection have also been reported in other chronic diseases involving the neural system, such as chronic pain, migraine and myalgic encephalomyelitis or chronic fatigue syndrome. Whether this could be explained by neural mechanisms activated independently of the underlying diseases is an interesting hypothesis that, however, still has to be demonstrated.

Practical recommendations for the clinician

Patients recovering from COVID-19 pneumonia frequently report symptoms such as dyspnea, cough, asthenia, and general malaise even some time after the initial infection.

In view of possible further pharmacological or physical treatments, the patient should be carefully evaluated according to different criteria (Table 2.1). In chronological order, there has been a tentative suggestion to first review the clinical history of the patient along with the time course and duration of the COVID-19 disease and consider any other associated diseases that could potentially interfere with recovery. Measuring dyspnea with the VAS scale should be performed with current scales such as the MRC or multidimensional tools. Measuring oxygen saturation at rest and during walking is another simple and effective way of evaluating the patient's clinical condition and excluding severe diseases such as persistence of pulmonary thromboembolism. Routine blood tests are then recommended along with pulmonary function testing inclusive of spirometry, measurement of lung volumes, DLCO, assessment of the respiratory muscle force, and blood gas analysis. Based on these findings, CT scans

will then be recommended to provide support to steroid therapy in case of persistence of interstitial lung disease.

Finally, a cardiopulmonary exercise test could be indicated in case the dyspnea cannot be explained on the grounds of the above mentioned clinical, functional, and radiological tests. This can identify the presence of anomalous respiratory or cardiovascular adaptations to exercise and/or locomotor muscle deconditioning. In the opposite case, the hypothesis of psychogenic dyspnea could find substantial support[40].

Table 2.1: Practical issues in managing patients after COVID-19 pneumonia or post-COVID syndrome

Assessment	Treatment
SYMPTOMS AND LUNG FUNCTION	
• Assess dyspnea (exertional), cough and fatigue *(consider referral to neurologist)* • Spirometry and DLCO • Consider ABG if SpO2<92% in room air or suspected chronic respiratory failure *In selected patients*:* • full PFTs with body plethysmography • respiratory muscle testing *(e.g., MIP/MEP, SNIP)* • Perform CPET	• Check adherence to therapy and other coexisting medical conditions • Avoid empiric use of bronchodilators (*indicated only for obstructive pulmonary diseases*) • Vaccines (SARS-CoV-2, pneumococcal, flu) • Rehabilitation for selected patients • Consider enrolling in clinical trials
IMAGING	
• Follow up ground glass areas/lung nodules *(e.g., high-risk patients such as smokers)* • Avoid unjustified use of CT scan • Consider use of lung and diaphragm ultrasound	

ABG: arterial blood gas; COPD: chronic obstructive pulmonary disease; CT: computed tomography; PFT: pulmonary function tests; CPET: cardiopulmonary exercise testing; DLCO: diffusing capacity of the carbon monoxide; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; SNIP: sniff nasal inspiratory pressure. * Particularly for patients who underwent long term invasive ventilation.

Take-home message

- SARS-CoV-2 induces a wide spectrum of neurological and respiratory manifestations that may co-exist with and complicate the clinical course of the disease.
- Respiratory failure due to interstitial pneumonia is the dominant clinical issue and the main determinant for the prognosis in the acute care setting; assessing and monitoring its severity and minimizing invasive support may help to improve treatment efficacy.
- Post-COVID syndrome is an intriguing clinical entity that is currently the subject of much debate. Many survivors have been affected, with heterogenous clinical presentation often requiring a multidisciplinary diagnostic approach.
- Given the complex interactions between lung, muscles, and brain after acute respiratory failure, not only due to SARS-CoV-2, clinical physiology should guide the physician in detecting respiratory alterations and provide appropriate treatment.

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