

# Silent Hypoxia in COVID-19 Pneumonia: State of Knowledge, Pathophysiology, Mechanisms, and Management

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## ABSTRACT

Patients with COVID-19 often present with life-threatening hypoxemia without dyspnea or signs of respiratory distress. Termed *silent* or *happy hypoxia*, it has puzzled clinicians and challenged and defied our understanding of normal respiratory physiology. A range of host- and pathogen-related factors appears to contribute to its development, including SARS-CoV-2's ability to produce different COVID-19 phenotypes; induce endothelial damage and elicit a vascular distress response; invade cells of the central nervous system and disrupt normal interoception and response; and modulate transcription factors involved in hypoxic

responses. Because hypoxemia in COVID-19 is associated with increased mortality risk and poorer survival, early detection and prompt treatment is essential to prevent potential complications. Interventions to prevent hypoxemia and improve oxygen delivery to the blood and the tissues include home pulse-oximetry monitoring, optimization of patient positioning, judicious use of supplemental oxygen, breathing control exercises, and timely and appropriate use of ventilatory modalities and adjuncts.

**Key words:** coronavirus disease 2019, COVID-19, hypoxemia, hypoxia, nursing, pathophysiology, SARS-CoV-2

Patients with COVID-19 often present with pronounced severe arterial hypoxemia without manifesting dyspnea or signs of respiratory distress. This presentation has been termed *happy hypoxia*, *silent hypoxia*, or *nondyspneic hypoxia* in the medical literature because patients may exhibit profound hypoxemia to a level incompatible with life but without accompanying clinical manifestations associated with a dangerously low arterial saturation such as restlessness, anxiety, tachypnea, diaphoresis, shortness of breath, hypotension, and cyanosis.<sup>1-3</sup>

This baffling presentation was first highlighted by Richard Levitan,<sup>1</sup> an emergency medicine physician working at Bellevue Hospital in New York City, who, writing in the *New York Times*, noted the occurrence of a

significant number of patients who were admitted in the emergency department with profound hypoxemia but remained completely asymptomatic. Unlike normal pneumonia, in which hypoxemia is associated with shortness of breath and chest pain, the pneumonia associated with COVID-19 causes oxygen deprivation, which may occur in the absence of breathing difficulty, hence the term *silent hypoxia*.<sup>4-6</sup> Incidentally, the diagnosis of COVID-19

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pneumonia is made on the basis of findings on routine chest radiographs or on computed tomography scans performed as part of investigations for other presenting complaints or conditions such as orthopedic injuries, intoxication, trauma, or fall.<sup>1</sup> By the time patients feel severely short of breath, their oxygen levels have dropped profoundly low and the lung damage has progressed to the point that most of these patients are already in critical condition and requiring ventilatory support.

In contrast to the exudative and proliferative damage associated with other non-COVID-19 pneumonia, wherein the alveoli are completely filled with fluids or pus, the pneumonia in COVID-19 is initially associated with normally compliant lungs but a significantly deranged ventilation-perfusion ( $V/Q$ ) ratio mismatch.<sup>7,8</sup> Over time, the cumulative injury from alveolar inflammation and pulmonary vascular damage, complicated by a dysregulation in interoceptive and neural responses, contribute toward the development of hypoxemia and the associated blunting of dyspnea. Accumulated evidence has shown that among patients with COVID-19, dyspnea and hypoxemia are associated with increased hospital mortality rates and worse survival,<sup>9</sup> and this is brought about by the hypoxic damage to vital body organs as a result of direct oxygen starvation and the associated inflammation.<sup>10</sup> The great number of patients with COVID-19 who are reported to have silent hypoxia is concerning, given that these individuals reflect the subset of patients who may benefit from early aggressive interventions that have the potential to prevent catastrophic complications. A thorough understanding of the pathophysiology of silent hypoxia is crucial if we are to develop effective treatment strategies that are aimed at addressing this complex and devastating physiologic phenomenon.

## Review of Relevant Pathophysiology

### Dyspnea: Definition, Regulation, and Neurobiology

Dyspnea refers to one or several different sensations characterized by shortness of breath, breathing difficulty, or breathlessness that are felt, experienced, and reported by an awake, conscious individual.<sup>11,12</sup> The American Thoracic Society defines *dyspnea* as the “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in

intensity”<sup>13</sup> and is derived “from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses.”<sup>14</sup> Dyspnea can be caused by a wide and diverse range of medical conditions and is a common feature of pathologies affecting the cardiovascular and respiratory system, including COVID-19,<sup>15</sup> but other conditions affecting the neurologic, musculoskeletal, endocrine, immunologic, and hematologic systems, as well as some psychiatric and psychologic disorders, have also been implicated as important causes of dyspnea.

Our current understanding of the pathophysiology of dyspnea is derived from a neurobiologic model in which the sensation of shortness of breath occurs when the brain perceives an imbalance between the need or demand to breathe that is unmet by the corresponding mechanical or neuromuscular response of the respiratory system.<sup>11,13</sup> The physiology and experience of breathing are part of a complex process and are based on an intact and coordinated action of 3 interrelated components: afferent receptors and impulses, central information processing, and efferent impulses and responses. An activation in 1 or more of the sensory receptors (ie, chemoreceptors, mechanoreceptors, metaboreceptors, pulmonary fibers) triggers the release of afferent impulses, which travel to the brainstem, thalamus, limbic system, and cerebral cortex for processing and integration. This information is processed and incorporated in the medulla, the insula, and the cortical network, where an appropriate neuronal output is generated. Efferent signals are then sent downstream via the phrenic and thoracic spinal nerves to the diaphragm and intercostal muscles, stimulating the mechanical response of breathing.<sup>12</sup> Any dysfunction or perturbation in any part of that physiological pathway can contribute to the experience of dyspnea. Dyspnea appears to occur when the demand for ventilation or airflow exceeds the body’s capacity to provide it. A state of imbalance develops, which triggers the sensation of distress, unpleasantness, or discomfort, which is then perceived by the individual.<sup>11,13</sup>

Dyspnea is multidimensional and has a cognitive and affective dimension that is partly separate from its sensory intensity or perceptual experience.<sup>13</sup> The experience of dyspnea activates several important structures

in the brain that are linked with emotions, anxiety, mood, attention, pain, and learning. Cognitive and affective states strongly influence respiratory perception, and they play an important role in the modulation, treatment, and control of this distressing symptom.<sup>16</sup>

### Hypoxia and Hypoxemia: Etiology, Determinants, and Mechanisms

Although they are used interchangeably, the terms *hypoxia* and *hypoxemia* are not synonymous. Hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood (ie, partial pressure of arterial oxygen [ $\text{PaO}_2$ ] below normal [ie, <80-100 mm Hg (10.6-13.3 kPa)]), whereas hypoxia is defined as the failure of oxygenation at the tissue or cellular level.<sup>17,18</sup>

Hypoxemia can be directly determined by measuring the  $\text{PaO}_2$  levels in an arterial blood specimen or the percentage of total hemoglobin saturated with oxygen (<88%-92%), or indirectly determined by measuring peripheral oxygen saturation levels.<sup>19</sup> *Tissue hypoxia*, which is defined biochemically by low levels of adenosine triphosphate, high levels of reduced nicotinamide adenine dinucleotide, or decreased levels of oxidized cytochrome aa3, is very difficult to quantify clinically, apart from surrogate markers and clinical indicators that reflect poor tissue oxygenation at the cellular level.<sup>20</sup> The 2 most commonly used clinical biomarkers of tissue hypoxia include blood pH and blood lactate level, the derangement of which is based on the understanding that tissue hypoxia associated with anaerobic metabolism leads to the production of lactic acid and a drop in blood pH. However, given that blood pH and lactate values reflect global or systemic disturbance and are only crude measures of tissue anaerobiosis, isolated pH and lactate readings cannot be reliably used to determine or identify the source of hypoxia in an acidotic gas. In addition, other metabolic derangements can cause acidosis in the presence of normoxemia or normal cellular oxygenation (eg, diabetic ketoacidosis; methanol, salicylate, toluene, biguanide, ethylene glycol poisoning; hyperchloremic acidosis) and can also be iatrogenic (eg, result of transfusion of large volumes of intravenous fluids containing lactate, chloride, or bicarbonate).

Hypoxemia is one of the main causes of tissue hypoxia; however, any process that leads to reduced or defective delivery of oxygen to

cells or an impaired extraction or use of oxygen by the tissues can lead to tissue hypoxia.<sup>19</sup> Maintaining adequate blood oxygenation depends on several factors, the most important of which include the fraction of inspired oxygen; the adequacy of alveolar ventilation; matching of alveolar blood flow to the alveolar gas in the alveolar-capillary units (ie,  $\dot{V}/\dot{Q}$  ratio matching); effective diffusion of oxygen through the alveolar-capillary interface and from the plasma to the red blood cells; and the adequacy of amount of hemoglobin in the blood and its binding to oxygen.<sup>19</sup> Cellular oxygen uptake and extraction are determined by the metabolic demands of the tissues, degree of dissociation of oxygen from hemoglobin in accordance with the hemoglobin-oxygen dissociation curve, the size of the partial pressure of oxygen gradient between capillary blood and mitochondria, and the diffusion distance from capillary to cell.<sup>21</sup> Last, cellular use of oxygen in the cells depends on the rate of cellular metabolism, which is affected by, for example, temperature regulation, fever, sepsis, trauma, sympathetic activation, pain, shivering, catecholamine, and stimulant drugs; and the presence of drugs, toxins, or poisons that can uncouple oxidative phosphorylation or lead to inhibition of oxygen cellular metabolism (eg, cyanide, oligomycin, rotenone, endotoxins in sepsis, other cytokines).

### Body's Response and Adaptation to Hypoxia

The ability of cells to sense, detect, and respond to hypoxia is crucial in maintaining tissue homeostasis, differentiation, growth, and survival. Cells respond to tissue hypoxia by increasing oxygen extraction from surrounding tissues, using "hibernation" or survival strategies to reduce metabolic rate, downregulating high-energy-requiring cellular functions such as protein production and ion transport, and shifting to anaerobic metabolism.<sup>22</sup> Several transcription factors play an important role in sensing and responding to tissue hypoxia, the most understood of which is hypoxia inducible factor (HIF)-1, which is a constitutionally expressed transcriptional activator whose activity is strictly regulated by lowered cellular oxygen tension.<sup>23</sup>

In oxygen-deplete environments, HIF-1 upregulates the transcription of vascular endothelial growth factor to promote endothelial

cell migration and accelerate angiogenesis to form new blood vessels to supply the hypoxic area with oxygenated blood.<sup>24</sup> HIF-1 also decreases cellular mitochondrial oxygen consumption by shifting to anaerobic metabolism for cellular energy production. Finally, HIF-1 plays a role in activating genes involved in erythropoiesis and hemoglobin biosynthesis, modulating inflammatory responses by accentuating bactericidal responses by myeloid cells,<sup>25</sup> and protecting cardiac cells from damage caused by ischemia.<sup>26</sup>

### Pathophysiologic Mechanisms of Silent Hypoxia in COVID-19

Although our knowledge of the pathogenesis of COVID-19 infection is rapidly evolving, understanding why some patients remain completely asymptomatic and why severe disease develops in others remains an active area of investigation. Approximately 41% of patients with COVID-19 remain completely asymptomatic. In a recent meta-analysis, authors found that 20% of people with COVID-19 remained symptom-free throughout the whole course of infection.<sup>27</sup> Severe disease will develop in approximately 13% to 20% of infected individuals and largely depends on the presence of risk factors such as age, race, ethnic background, or sex; existence of underlying health conditions such as diabetes, hypertension, malignancy, and asthma; and other factors such as viral dose, viral strain, intensity of exposure, immunization status, and socioeconomic factors.<sup>28,29</sup> Determining the full distribution and epidemiology of COVID-19 infection is challenging because the full spectrum of COVID-19 infection—from being completely asymptomatic to being paucisymptomatic (ie, subclinical), having mild to moderate and severe disease, fulminant pneumonia, and acute respiratory distress syndrome (ARDS), and nonpulmonary COVID-19 involvement—is difficult to ascertain, and an overlap between various subtypes is not uncommon.<sup>30</sup>

SARS-CoV-2 invasion of the epithelial cells of the upper airway and of type I and II alveolar cells in the lower respiratory passages is essential for establishing infection, and the localized effects on the airway parenchymal and vascular endothelial cells are responsible for the clinical manifestation of respiratory disease.<sup>7</sup> Patients with COVID-19 often present with varying degrees of respiratory involvement ranging from dyspnea, cough, sore throat,

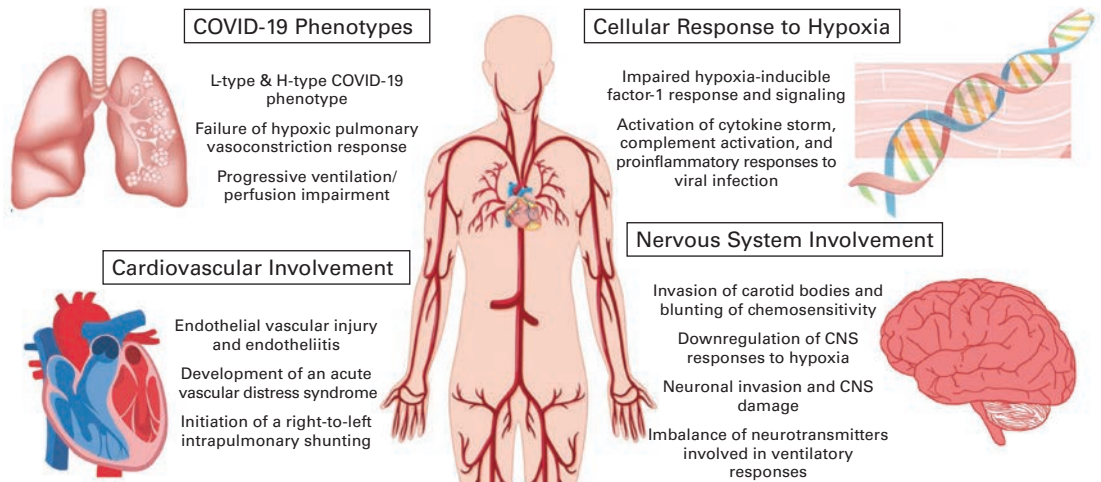
sputum production, pneumonia, ARDS, acute hypoxic respiratory failure, to sudden death due to severe hypoxia refractory to oxygen therapy.<sup>15</sup> Epidemiologic studies have shown that less than 50% of patients with COVID-19 present with dyspnea, suggesting that breathing difficulties are not pathognomonic or diagnostic of the disease.<sup>31</sup> It was reported, however, that the occurrence of dyspnea is more common among patients in whom acute respiratory distress and hypoxemia develop—the subset of patients with COVID-19 who are more likely to die.<sup>32</sup> In a recent meta-analysis, authors reported that dyspnea is associated with disease severity and, together with a low baseline oxygen saturation in the emergency department, is a marker of negative prognosis in COVID-19.<sup>33</sup>

Hypoxemia without dyspnea has been reported in early COVID-19 and remains a perplexing phenomenon under investigation.<sup>1-5</sup> Severe hypoxemia in the absence of dyspneic symptoms, however, is not uncommon and is seen in other pulmonary conditions, such as in patients with right to left intracardial shunt, atelectasis, interstitial lung disease, or intrapulmonary shunt (arterio-venous malformations),<sup>34</sup> the commonest of which is among patients with type B phenotype chronic obstructive pulmonary disease, who may exhibit profound arterial hypoxemia as a result of  $\dot{V}/\dot{Q}$  ratio mismatching.<sup>17</sup> Although both hypercapnia and hypoxemia are effective triggers that can lead to increases in afferent impulse stimulation of the respiratory center to stimulate an increase in minute ventilation, the sensitivity of the respiratory center is more profound to exquisitely small changes in blood partial pressure of carbon dioxide levels than blood  $P_{aO_2}$  levels, and hypoxemia remains a weaker stimulus for breathing.<sup>35</sup>

In the following sections, the putative mechanisms are discussed that explain how silent hypoxia can develop in COVID-19 (Figure).

### Phenotypes of COVID-19 Pneumonitis

The mechanisms underlying hypoxia in COVID-19 can be best explained with our current understanding of the pathophysiologic changes associated with a COVID-19 lung. Gattinoni et al<sup>7</sup> have proposed the existence of 2 major phenotypes of acute lung injury in COVID-19, namely, L-type and H-type phenotypes, each with its own unique



**Figure:** Putative pathophysiologic mechanisms involved in the development of silent hypoxia in patients with COVID-19. CNS indicates central nervous system.

pathophysiologic features and management implications.

L-type COVID-19 is characterized by low elastance, low  $\dot{V}/\dot{Q}$  ratio, low lung weight, and low lung recruitability, which is often the most common presentation of COVID-19 pneumonia and is usually the stage in which silent hypoxemia occurs. Patients presenting with L-type COVID-19 phenotype have preserved and acceptable pulmonary compliance, and this preserved compliance allows these patients to maintain acceptable minute volumes, which are sufficient to keep blood oxygenation levels adequate without triggering the stimulus for dyspnea or respiratory distress.<sup>8</sup>

The main pathophysiologic changes involved in L-type COVID-19 phenotype is the disproportionate endothelial damage which results in disrupted vasoregulation,  $\dot{V}/\dot{Q}$  mismatching, and accelerated thrombogenesis.<sup>7</sup> This derangement is driven by a failure in the normal hypoxic pulmonary vasoconstriction (ie, the compensatory vasoconstriction of small pulmonary arteries in response to alveolar hypoxia to redirect blood flow to areas of the lungs with better ventilation and oxygenation). The admixing of deoxygenated blood (shunting) leads to the development of hypoxemia in the absence of accompanying symptoms, and this derangement drives the initial hypoxemia in COVID-19 pneumonitis, well before the exudative and alveolar inflammatory processes develop.

Some patients may deteriorate as the inflammation worsens and progresses into interstitial edema and exudation, transitioning into the

second phenotype, the type H COVID-19. Type H is characterized by high elastance, high right to left shunt, increased lung weight, and high lung recruitability.<sup>7</sup> H-type COVID-19 resembles a typical, severe ARDS-like picture of hypoxemia, bilateral infiltrates, and increased lung weight: patients may feel severe shortness of breath and hypoxemic respiratory failure may develop as the lungs fill with fluids and become increasingly consolidated. By the time the sensation of dyspnea is felt, the pulmonary damage is usually already profound. The airway edema and inflammation lead to significant reduction and shrinking of the recruitable alveolar spaces (ie, “baby lung”), which, over time, can lead to the development of right ventricular afterload.<sup>8</sup>

#### Hypocapnia and Right to Left Intrapulmonary Shunting Due to an Acute Vascular Distress Syndrome

Endothelial injury and the resulting endotheliitis increasingly have been recognized as common pathologic features of COVID-19 infection and are a result of SARS-CoV-2's infection of endothelial cells, where it displays a particular tropism.<sup>36</sup> Angiotensin-converting enzyme-2 (ACE-2) receptors are abundant in the blood vessels lining the heart, lungs, kidneys, and intestines, and they offer a rich source of attachment site for SARS-CoV-2 binding and infection. Histopathologic studies have shown that SARS-CoV-2 can invade endothelial cells and can cause microvascular lymphocytic endotheliitis, leading to accelerated

apoptosis, pyroptosis, and cytopathy.<sup>37</sup> More importantly, it has been demonstrated that COVID-19 can induce intussusceptive and sprouting angiogenesis in pulmonary vessels as a response to tissue hypoxia, inflammation, and thrombosis.<sup>38</sup> Consistent with other studies, SARS-CoV-2 viral invasion in the endothelium and the accompanying apoptosis lead to disruption in the endothelial barrier, increased recruitment and infiltration of immune cells, accelerated widespread endothelial inflammation, and enhanced thrombogenesis and coagulation.<sup>37-39</sup>

Early pneumonia in patients with COVID-19 is characterized by an acute vascular distress syndrome, wherein hypoxemia occurs despite a preserved ventilation and an increased pulmonary vascular flow (ie, low  $\dot{V}/\dot{Q}$  ratio).<sup>40</sup> This impairment in gas exchange occurs as a result of the development of a significant amount of microthrombi in the pulmonary vasculature, severely altering gas exchange at the pulmonary capillary level.<sup>41</sup> In addition to causing the blunting of the hypoxic pulmonary vasoconstriction response, a pure intrapulmonary right to left shunting develops, and this leads to a mild hypoxemia.<sup>7</sup> At this early stage of hypoxemia, patients initially compensate by increasing minute ventilation, as manifested by tachypnea and a slight respiratory alkalosis. As the tachypnea and hyperventilation worsens, patients develop marked hypocapnia, which then leads to the blunting, loss, and inhibition of the ventilatory trigger to breathe. With this marked depression of the ventilator stimuli, dyspnea may not be felt and may be completely absent (because the carbon dioxide remains normal or low) despite the development of worsening hypoxemia.<sup>42</sup> The worsening of hypoxemia in the presence of normal or even low carbon dioxide levels triggers silent hypoxia up until the point of decompensation where signs of lung injury and end-organ damage become apparent.

### Angiotensin-Converting Enzyme-2 Receptor Invasion and Downregulation of Interoception

The functional integrity of the afferent pathways, higher processing structures, and efferent pathways is essential for keeping the body aware of the changes present in the internal and external environment and to

respond appropriately to these changes. These homeostatic functions and processes, called the interoceptive system, are responsible for sensing and conveying minute changes or shifts in the internal environment, relaying these impulses to the projections and nerve tracts in the spinal cord and the brain, and processing them to elicit a physiologic or compensatory response.<sup>43</sup> Any disruption in the structure or functioning of this system can lead to an altered awareness, integration, or response, which can severely affect normal physiology and homeostasis.

One of the ways by which COVID-19 alters the interoceptive responses is by disrupting the structure and function of body sensors, the most explored of which is the way SARS-CoV-2 affects the carotid bodies. The cells in the carotid body contain the primary chemoreceptors responsible for sensing hypoxemia (ie, low partial pressures of oxygen in arterial blood), and the resulting reflex involves activation of the cardiorespiratory centers, which triggers hyperventilation and sympathetic activation (hypoxic ventilatory response).<sup>44</sup> In COVID-19, it was proposed that the signal of arterial hypoxia, which reflects the physiologic stimulus of the need to breathe, is absent or at least impaired, particularly in patients with severe disease.<sup>45</sup>

Angiotensin-converting enzyme-2, the SARS-CoV-2 receptor, is highly enriched in the glomus cells of the carotid body, the primary cells involved in oxygen sensing and responsible for releasing a variety of neurotransmitters that trigger excitatory postsynaptic potentials to the respiratory center in response to hypoxia. Accumulated evidence has shown that the carotid body, with its surface enriched with ACE-2, may be a potential target for SARS-CoV-2 infection.<sup>43</sup> Histopathological autopsy specimens of patients with severe COVID-19 pneumonitis have demonstrated that SARS-CoV-2 can invade the carotid body and cause substantial functional and microvascular changes.<sup>46</sup> It is proposed that SARS-CoV-2 infection of the glomus cells can alter the normal chemosensitivity of the carotid body and disrupts its ability to detect the changes in oxygen levels, leading to a blunting of hypoxic response and a lack of sensorial awareness to hypoxemia.<sup>47</sup> SARS-CoV-2 infection impairs the hypoxic response through various mechanisms, including induction of biochemical changes in the mitochondrial oxygen

sensing mechanism, initiation of inflammation and glomus cell death, and downregulation of the chemoreceptors.<sup>48</sup>

SARS-CoV-2 invasion of the cells and tissues in the central nervous system has also been proposed to contribute to the respiratory failure associated with COVID-19. SARS-CoV-2 can infect the neurons of the central nervous system via different mechanisms, including direct infection of the vascular endothelium, retrograde invasion from the olfactory bulb cells through the neuroepithelium, or infection of leukocytes and crossing of the blood-brain barrier via diapedesis.<sup>49</sup> Autopsy samples of patients who had COVID-19 have shown that SARS-CoV-2 can induce direct neuronal damage to the cells of the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer (ie, the corticolimbic network), inducing subsequent cellular injury and leptomeningeal inflammation.<sup>2</sup> The neuroinvasiveness potential of SARS-CoV-2 has been implicated as a cause of respiratory failure in some patients, because SARS-CoV-2 has been reported to spread from the chemoreceptors involved in ventilation and invade the medullary cardiorespiratory center via the synapse-connected route.<sup>50</sup> Similarly, the cytokine storm elicited by COVID-19 infection has been reported to result in neuroinflammation and brain tissue injury, which can affect the neural structures involved in voluntary breathing and perception of breathlessness.<sup>2</sup> The resulting derangement in the balance of neurotransmitters and neuropeptides brought about by hypoxia, inflammation, and cell death has also been proposed to play a pivotal role in the perceptual effects of dyspnea and the subsequent development of respiratory failure.

### SARS-CoV-2 Downregulation of Transcription Factors Involved in Hypoxic Responses

Apart from the role that HIF plays in the regulatory responses of cells to low-oxygen conditions, our understanding has increased of the role HIF plays in the activation of immune response in humans and, in particular, to some infectious and inflammatory diseases.<sup>51</sup> Under normoxic conditions, HIF-1 $\alpha$  is rapidly targeted for polyubiquitination and undergoes rapid proteasomal degradation.<sup>52</sup> In hypoxic situations, HIF is rapidly expressed, which leads to the transcription of genes that encode for proteins crucial for increasing oxygen delivery

to cells, including those that are needed for cell survival in ischemic conditions.

HIF-1 $\alpha$  expression is modulated in viral infections in a context-specific and species-specific manner, and upregulation of HIF-1 $\alpha$  activity favors the pathogen's survival rather than the host's.<sup>51</sup> Several studies have demonstrated that hypoxic signaling regulates the ability of viral cells to replicate and infect host cells.<sup>52,53</sup> Hypoxia is a common pathophysiologic feature of SARS-CoV-2 infection, and reports have shown that HIF-1 $\alpha$  signaling in SARS-CoV-2-infected cells inhibits ACE2 expression and suppresses the activity of all enzymes controlling the entry of SARS-CoV-2 into the cells, namely ACE, ACE2, transmembrane protease serine 2, and ADAM17.<sup>53</sup> Furthermore, HIF-1 $\alpha$  also upregulates the ACE promoter directly and downregulates ACE-2 receptor expression, which limits the availability of receptors present for SARS-CoV attachment and binding.<sup>54</sup> Together, these findings suggest that HIF-1 $\alpha$  signaling can be host protective by decreasing the invasiveness of SARS-CoV-2 infection and reducing the risk of tissue and organ damage due to COVID-19 infection.

How HIF-1 $\alpha$  activation can lead to the development of silent hypoxia remains uninvestigated. The HIF-1 signaling pathway is involved in multiple areas of immune function, including differentiation of T cells, activation of monocytes and macrophages in response to inflammation, enhancement of phagocytic activity and intracellular killing of macrophages in response to bacterial infection, and modulation of cytokine activity and proinflammatory responses to viral infections.<sup>55</sup> HIF-1 $\alpha$  expression in COVID-19 can lead to the activation of cytokine storm, mediated by the recruitment of immune cells into the alveolar type II cells, production and release of proinflammatory mediators, increased vascular leakage and damage, and destruction of the alveolar-endothelial barrier.<sup>10</sup> HIF-1 $\alpha$  has also been postulated to induce and elicit complement activation, which drives the respiratory failure, intra-alveolar endothelial damage, microvascular thrombosis, and pneumonia in COVID-19 infection.<sup>56</sup> Together, these pathophysiologic changes can elicit an ARDS response characterized by acute lung injury, vascular dysfunction, and massive thrombosis, which drive hypoxemia in COVID-19.

## Nursing Management and Clinical Implications

An understanding of the mechanisms involved in the development of silent hypoxia in COVID-19 is essential in the identification of strategies that can be used to prevent complications associated with hypoxemia. More recently, reports have shown that early implementation of interventions with the potential to identify patients exhibiting subtle signs of hypoxia were often missed.<sup>57</sup> It has been highlighted that strategies aimed at early detection of silent hypoxia can be lifesaving and may improve outcomes in patients with COVID-19.<sup>58-59</sup> Finally, measures aimed at optimizing oxygen delivery have the potential to correct hypoxemia associated with COVID-19 and can be easily implemented in both acute and emergency settings.

### Monitoring

Monitoring oxygen saturation levels in primary care and home settings is a way to detect hypoxemia in patients with chronic lung disease, asthma, and pneumonia, to good effect.<sup>58</sup> Presently, home monitoring of oxygen saturation levels using portable pulse oximetry ( $\text{SpO}_2$ ) has been used as part of a package of care for the early detection of hypoxemia in individuals who have a higher risk of mortality and morbidity with COVID-19.<sup>59</sup> Pulse oximetry is used to determine the percentage of oxygen bound to hemoglobin in the blood; the device does this by measuring the difference in the quantity of light transmitted back into the photodetector from oxygenated and deoxygenated hemoglobin. Although the true difference between recorded  $\text{SpO}_2$  and  $\text{PaO}_2$  may be discordant and less accurate at low saturations, and  $\text{SpO}_2$  readings may have poorer reliability in critically ill patients, early detection of desaturation can be helpful in facilitating prompt and timely emergency department admissions before hypoxemia becomes profound and life-threatening.<sup>59</sup> For instance, health organizations such as the National Health Service England have advocated the use of remote monitoring of  $\text{SpO}_2$  readings in the community setting as a means to detect early desaturation among a specific subset of patients who are at highest risk for deterioration.<sup>57</sup> These include the elderly and people with diabetes, who may have profoundly impaired and blunted ventilatory responses to hypoxia—the patient groups who are most likely to suffer from silent hypoxemia.<sup>41</sup>

### Correction of Hypoxemia

Correction of hypoxemia in COVID-19 with supplemental oxygen is also a matter of ongoing investigation.<sup>60</sup> The aim of oxygen supplementation in COVID-19 is to correct hypoxemia and prevent tissue hypoxia, thereby avoiding end-organ hypoxic damage to vital organs. Current guidelines from the US National Institutes of Health suggest that a saturation target of 92% to 96% appears safe and is associated with fewer complications, based on studies in critically ill patients without COVID-19.<sup>61</sup> Furthermore, the recent Surviving Sepsis guidelines recommend commencing oxygen supplementation for  $\text{SpO}_2$  levels less than 90%, with an aim of achieving modest  $\text{SpO}_2$  levels between 92% and 96%.<sup>62</sup> Saturation targets should be individualized for patients. Some patients with underlying lung disease, such as chronic obstructive pulmonary disease or interstitial lung disease, may require lower target saturations, because a higher level may be unsafe or dangerous. Hyperoxygenation should be avoided because it is associated with adverse complications such as pulmonary, ocular, and central nervous system toxicities, and, in the light of the pandemic situation, is wasteful, costly, and not resource effective. Among patients with acute hypoxemic respiratory failure in the intensive care unit, aiming for a lower oxygenation target (ie, 60 mm Hg [8.0 kPa]) did not result in an increase in adverse events and mortality rate compared with higher oxygenation targets, suggesting that modest oxygenation targets should be considered in high-risk critically ill patients.<sup>63</sup> The use of high-flow oxygen therapy or noninvasive ventilation strategies such as continuous positive airway pressure masks can be considered for patients with worsening hypoxemia, signs of tissue hypoxia, and respiratory muscle fatigue; and invasive tracheal intubation can be instituted for patients with severe COVID-19 pneumonitis, acute hypoxic respiratory failure, refractory hypoxemia, and ARDS.

Improving oxygen delivery in COVID-19 should address the underlying pathology behind the hypoxia and hypoxemia. Because thrombotic derangement may be common in COVID-19 infections and can be associated with poor perfusion, particularly to pulmonary capillaries where gas exchange occurs, strategies to improve flow and perfusion should be considered in clinical situations



where hypoxemia is concerning. The mechanisms for vascular involvement is an interplay of vascular inflammation or endotheliitis, increased platelet aggregation, and deranged clotting leading to the formation of microthrombi, which block the vessels at the capillary level or cause local changes in the vessel microvasculature. These conditions lead to increased distance and decreased efficiency of gas exchange in the capillary-endothelial interface.<sup>40</sup> Widespread prophylactic use of anticoagulants for thromboprophylaxis in critically ill patients with COVID-19 has been implemented in clinical practice to prevent complications associated with thromboembolism, which is associated with increased mortality risk and poor prognosis, but authors of a recent Cochrane Review reported finding nonsuperiority to standard care.<sup>64</sup> Several studies are underway, and the effects of anticoagulant use on added respiratory support or occurrence of pulmonary embolisms are being investigated. Inhaled pulmonary vasodilators can be used as a rescue therapy for patients receiving mechanical ventilatory support who have severe hypoxemia refractory to other conventional therapies, but these medications should not be used long term, because of the harms associated with their use and a lack of mortality benefit.<sup>62</sup>

Patient positioning and postural changes have significant physiological effects on ventilatory function, respiratory mechanics, breathing effort, and gas exchange, which can have a protective effect against hypoxemia. Assuming an upright, sitting position (ie, with the thorax angled  $>30^{\circ}$ - $45^{\circ}$  from the horizontal plane) is associated with improved end-expiratory lung volumes, reduced airway resistance, improved lung compliance, decreased work of breathing, and better oxygenation.<sup>65</sup> Prone positioning improves oxygenation by reducing the dorsal-ventral transpulmonary pressure difference, making ventilation more homogeneous; reducing lung compression by the heart and the diaphragm, thereby decreasing the compression of posterior-caudal lung parenchyma; and improving the  $\dot{V}/\dot{Q}$  matching as blood flow is redistributed toward the ventral lung and making the  $\dot{V}/\dot{Q}$  ratio more closely locally matched.<sup>66</sup> Prone positioning in awake patients with COVID-19-associated ARDS has been shown in observational and case studies to improve oxygenation and slow respiratory deterioration in early phases of

COVID-19 pneumonitis. Therefore, prone positioning is advocated, given its acceptable safety profile and clinically tangible benefits.<sup>67</sup>

### Other Interventions

The clinical management of dyspnea in COVID-19 should consider the psychological and emotional factors associated with the sensation of breathlessness. Dyspnea is a very subjective condition and although objective manifestations (eg, tachypnea, hyperventilation, use of accessory respiratory muscles, distention of neck veins, cough, cyanosis, diaphoresis, tremors, added lung sounds) may be helpful to assess and quantify the degree of dyspnea, the patient's description, discrimination, and language of their own degree of respiratory distress remain the criterion standard in diagnosing dyspnea.<sup>10</sup> Although the perception and discrimination of dyspnea are mainly under cortical neural control, the cognitive awareness and the respiratory sensations felt by the individual incorporates an affective dimension, and the activation of limbic cortical structures also triggers emotional and attentional responses.<sup>68</sup> Both of these responses can be partially consciously modulated or controlled.

Nonpharmacologic approaches and interventions that modify the cognitive and affective experience of dyspnea can be helpful in alleviating the feelings of discomfort and distress associated with this symptom. Use of various breathing-control exercises (ie, diaphragmatic breathing, pursed-lip breathing, biofeedback, and breathing retraining) can improve breathing dynamics and pattern, increase vital capacity, and reduce anxiety associated with breathlessness. Use of distractive auditory stimuli (eg, music), relaxation techniques, acupuncture, handheld fans, and chest-wall vibration improve dyspnea in patients with chronic lung diseases.<sup>69</sup> Interventions such as cognitive-behavioral therapy, dyspnea self-management programs, and psychotherapy benefit patients experiencing chronic dyspnea and can be tried in some patients with COVID-19-associated dyspnea, because breathlessness is a common symptom in patients with long COVID-19.<sup>68,70</sup> A calm, reassuring, and coaching presence of a health care provider at the patient's bedside can be helpful in alleviating sensations of dyspnea and the accompanying anxiety, fear, and discomfort that can be associated with this distressing experience.

## Conclusion

Our understanding of the full spectrum of the pathobiology and symptomatology of COVID-19 is continuously evolving. As the pandemic unfolds, a wide range of novel signs and symptoms, which may have very important diagnostic significance, continues to emerge and affect populations on a global scale. SARS-CoV-2 primarily infects the lungs and brings about a wide gamut of respiratory manifestations that are associated with increased morbidity and mortality rates. More importantly, the discovery of silent hypoxia in COVID-19 has been perplexing clinicians because it continues to challenge long-term notions and principles of basic physiology.

The mechanisms underlying silent hypoxia in COVID-19, as we currently understand them, involve the different COVID-19 phenotypes as well as SARS-CoV-2's neuroinvasiveness potential and ability to cause vascular endotheliitis and damage, modulate transcription factors involved in hypoxia, and disrupt normal interoception and response, together with a variety of susceptibility and host factors. Early detection and prompt treatment of hypoxemia are important to prevent complications associated with respiratory deterioration and compromise and can be done through meticulous and preemptive monitoring, early access and admission to a medical facility, prudent and sensible use of oxygen therapy, and prompt institution of various respiratory modalities in a safe and controlled setting. As our understanding of the pathogenesis of COVID-19 improves, developing safe, effective, and timely interventions based on sound knowledge and clinical judgment is paramount if we are to promote positive outcomes in patients who continue to suffer from this devastating disease.

## REFERENCES

- Levitan R. The infection that's silently killing coronavirus patients. *New York Times*. April 20, 2020. Accessed April 10, 2021. <https://www.nytimes.com/2020/04/20/opinion/coronavirus-testing-pneumonia.html>
- Teo J. Early detection of silent hypoxia in COVID-19 pneumonia using smartphone pulse oximetry. *J Med Syst*. 2020;44(8):134.
- Nouri-Vaskeh M, Sharifi A, Khalili N, Zand R, Sharifi A. Dyspneic and non-dyspneic (silent) hypoxemia in COVID-19: possible neurological mechanism. *Clin Neurol Neurosurg*. 2020;198:106217.
- Ottestad W, Seim M, Mæhlen JO. COVID-19 with silent hypoxemia. *Tidsskr Nor Lægeforen*. 2020;140:1-3.
- Wilkerson RG, Adler JD, Shah NG, et al. Silent hypoxia: a harbinger of clinical deterioration in patients with COVID-19. *Am J Emerg Med*. 2020;38(10):2243.e5-2243.e6.
- Chandra A, Chakraborty U, Pal J, Karmakar P. Silent hypoxia: a frequently overlooked clinical entity in patients with COVID-19. *BMJ Case Rep*. 2020;13(9):e237207.
- Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46(6):1099-1102.
- Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330.
- Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc*. 2020;95(6):1138-1147.
- Rahman A, Tabassum T, Araf Y, Al Nahid A, Ullah MA, Hosen MJ. Silent hypoxia in COVID-19: pathomechanism and possible management strategy. *Mol Biol Rep*. 2021;48(4):3863-3869.
- Mahler DA, Selecky PA, Harrod CG. Management of dyspnea in patients with advanced lung or heart disease: practical guidance from the American College of Chest Physicians consensus statement. *Pol Arch Med Wewn*. 2010;120(5):160-166.
- Burki NK, Lee LY. Mechanisms of dyspnea. *Chest*. 2010;138(5):1196-1201.
- Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435-452.
- American Thoracic Society. Dyspnea. Mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med*. 1999;159(1):321-340.
- Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. *Front Med (Lausanne)*. 2020;7:526.
- Herigstad M, Hayen A, Wiech K, Pattinson KT. Dyspnoea and the brain. *Respir Med*. 2011;105(6):809-17.
- Sarkar M, Niranjana N, Banyal PK. Mechanisms of hypoxemia. *Lung India*. 2017;34(1):47-60.
- Samuel J, Franklin C. Hypoxemia and hypoxia. In: Myers JA, Millikan KW, Saclarides TJ, eds. *Common Surgical Diseases*. Springer; 2008.
- MacIntyre NR. Tissue hypoxia: implications for the respiratory clinician. *Respir Care*. 2014;59(10):1590-1596.
- Mythen M, Clutton-Brock T. The oxygen trail: measurement. *Br Med Bull*. 1999;55(1):109-124.
- Leach RM, Treacher DF. Oxygen transport-2. Tissue hypoxia. *BMJ*. 1998;317(7169):1370-1373.
- Leach RM, Treacher DF. The pulmonary physician in critical care-2. Oxygen delivery and consumption in the critically ill. *Thorax*. 2002;57(2):170-177.
- Wang GL, Jiang B-H, Rue EA, et al. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O<sub>2</sub> tension. *Proc Natl Acad Sci U S A*. 1992;92(2):5510-5514.
- Ziello JE, Jovin IS, Huang Y. Hypoxia-inducible factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. *Yale J Biol Med*. 2007;80(2):51-60.
- Cramer T, Yamanishi Y, Clausen BE, et al. HIF-1alpha is essential for myeloid cell-mediated inflammation. *Cell*. 2003;112(5):645-657.
- Rebar EJ. Development of pro-angiogenic engineered transcription factors for the treatment of cardiovascular disease. *Expert Opin Investig Drugs*. 2004;13(7):829-839.
- Byambasuren O, Cardona M, Bell K, Clark J, Mcclaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. *J. Assoc. Med Microbiol Infect Dis Can*. 2020;5(4):223-234.
- Rashedi J, Mahdavi Poor B, Asgharzadeh V, et al. Risk factors for COVID-19. *Infez Med*. 2020;28(4):469-474.
- Pijls BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. *BMJ Open*. 2021; 11(1):e044640.

30. Pollock AM, Lancaster J. Asymptomatic transmission of COVID-19. *BMJ*. 2020;371:m4851.
31. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
32. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
33. Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, et al; COVID-19 Research Group of CSAPG. Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One*. 2020;15(10):e0239571.
34. Dhont S, Derom E, Van Braeckel E, et al. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res*. 2020;21(1):1-9.
35. Ora J, Rogliani P, Dauri M, O'Donnell D. Happy hypoxemia, or blunted ventilation? *Respir Res*. 2021;22(1):4.
36. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417-1418.
37. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J*. 2020;41(32):3038-3044.
38. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383(2):120-128.
39. Azouz E, Yang S, Monnier-Cholley L, Arrivé L. Systemic arterial thrombosis and acute mesenteric ischemia in a patient with COVID-19. *Intensive Care Med*. 2020;46:1464-1465.
40. Mahjoub Y, Rodenstein D, Jounieaux V. Severe COVID-19 disease: rather AVDS than ARDS? *Crit Care*. 2020;24(1):327.
41. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Respir Crit Care Med*. 2020;202(3):356-360.
42. Jounieaux V, Basille D, Abou-Arab O, et al. Pure SARS-CoV-2 related AVDS (acute vascular distress syndrome). *BMC Infect Dis*. 2021;21(1):122.
43. González-Duarte A, Norcliffe-Kaufmann L. Is 'happy hypoxia' in COVID-19 a disorder of autonomic interoception? A hypothesis. *Clin Auton Res*. 2020;30(4):331-333.
44. López-Barneo J, Macías D, Platero-Luengo A, Ortega-Sáenz P, Pardal R. Carotid body oxygen sensing and adaptation to hypoxia. *PLoS Arch*. 2016;468(1):59-70.
45. Machado BH, Paton JFR. Relevance of carotid bodies in COVID-19: a hypothetical viewpoint. *Auton Neurosci*. 2021;233:102810.
46. Lambermont B, Davenne E, Maclot F, Delvenne P. SARS-CoV-2 in carotid body. *Intensive Care Med*. 2021;47(3):342-343.
47. Porzionato A, Emmi A, Stocco E, et al. The potential role of the carotid body in COVID-19. *Am J Physiol Lung Cell Mol Physiol*. 2020;319(4):L620-L626.
48. Villadiego J, Ramírez-Lorca R, Cala F, et al. Is carotid body infection responsible for silent hypoxemia in COVID-19 patients? *Function*. 2021;2(1):zqaa032.
49. Armocida D, Palmieri M, Frati A, Santoro A, Pesce A. How SARS-Cov-2 can involve the central nervous system. A systematic analysis of literature of the department of human neurosciences of Sapienza University, Italy. *J Clin Neurosci*. 2020;79:231-236.
50. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555.
51. Alves dos Santos S, Ramos de Andrade Jr, D. HIF-1-alpha and infectious diseases: a new frontier for the development of new therapies. *Rev Inst Med Trop Sao Paulo*. 2017;59:1-10.
52. Sutter CH, Laughner E, Semenza GL. Hypoxia-inducible factor 1alpha protein expression is controlled by oxygen-regulated ubiquitination that is disrupted by deletions and missense mutations. *Proc Natl Acad Sci U S A*. 2000;97(9):4748-4753.
53. Serebrovska ZO, Chong EY, Serebrovska TV, et al. Hypoxia, HIF-1 $\alpha$ , and COVID-19: from pathogenic factors to potential therapeutic targets. *Acta Pharmacol Sin*. 2020;41(12):1539-1546.
54. Zhang R, Wu Y, Zhao M, et al. Role of HIF-1 alpha in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol*. 2009;297(4):L631-640.
55. Palazon A, Goldrath AW, Nizet V, Johnson RS. HIF transcription factors, inflammation, and immunity. *Immunity*. 2014;41(4):518-528.
56. Holter JC, Pischke SE, de Boer E, et al. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. *Proc Natl Acad Sci U S A*. 2020;117(40):25018-25025.
57. NHS England. Pulse oximetry to detect early deterioration of patients with COVID-19 in primary and community care settings. Published January 12, 2021. Accessed May 10, 2021. <https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/06/C0445-remote-monitoring-in-primary-care-jan-2021-v1.1.pdf>
58. Plüddemann A, Thompson M, Heneghan C, Price C. Pulse oximetry in primary care: primary care diagnostic technology update. *Br J Gen Pract*. 2011;61(586):358-359.
59. Greenhalgh T, Knight M, Inada-Kim M, et al. Remote management of COVID-19 using home pulse oximetry and virtual ward support. *BMJ*. 2021;372:n677.
60. Cajanding R. Oxygen use and saturation targets in patients with COVID-19: are we giving too much or aiming too low? *Nurs Crit Care*. 2021;1-4.
61. National Institutes of Health. COVID-19 treatment guidelines: oxygenation and ventilation. Published December 17, 2020. Accessed May 10, 2021. <https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation>
62. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469.
63. Schjørring OL, Klitgaard TL, Perner A, et al; HOT-ICU Investigators. Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med*. 2021;384(14):1301-1311.
63. Flumignan RL, Tinôco JDS, Pascoal PI, et al. Prophylactic anticoagulants for people hospitalised with COVID-19. *Cochrane Database Syst Rev*. 2020;10(10):CD013739.
65. Mezidi M, Guérin C. Effects of patient positioning on respiratory mechanics in mechanically ventilated ICU patients. *Ann Transl Med*. 2018;6(19):384.
66. Johnson NJ, Luks AM, Glenny RW. Gas exchange in the prone posture. *Respir Care*. 2017;62(8):1097-1110.
67. Koeckerling D, Barker J, Mudalige NL, et al. Awake prone positioning in COVID-19. *Thorax*. 2020;75(10):833-834.
68. Laviolette L, Laveneziana P; ERS Research Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J*. 2014;43(6):1750-1762.
69. Marciniuk DD, Goodridge D, Hernandez P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2011;18(2):69-78.
70. Raman B, Cassar MP, Tunncliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*. 2021;31:100683.