Neurological Manifestations of Severe SARS-CoV-2 Infection: Potential Mechanisms and Implications of Individualized Mechanical Ventilation Settings

Denise Battaglini 1*, Iole Brunetti 1, Pasquale Anania 2, Pietro Fiaschi 2,3, Gianluigi Zona 2,3, Lorenzo Ball 1,4, Daniele Roberto Giacobbe 5, Antonio Vena 5, Matteo Bassetti 5, Nicolò Patroniti 1,4, Angelo Schenone 3,8, Paolo Pelosi 1,4, Patricia R. M. Rocco 7,8,9† and Chiara Robba 1†

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Edited by:
Jordi A. Matias-Guiu,
Servicio de Neurología, Hospital Clínico San Carlos, Spain

Reviewed by:
Patrick M. Chen,
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United States
Cristina Valencia-Sanchez,
Mayo Clinic Arizona, United States

*Correspondence:
Denise Battaglini
battaglini.denise@gmail.com

†These authors share senior authorship

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In December 2019, an outbreak of illness caused by a novel coronavirus (2019-nCoV, subsequently renamed SARS-CoV-2) was reported in Wuhan, China. Coronavirus disease 2019 (COVID-19) quickly spread worldwide to become a pandemic. Typical manifestations of COVID-19 include fever, dry cough, fatigue, and respiratory distress. In addition, both the central and peripheral nervous system can be affected by SARS-CoV-2 infection. These neurological changes may be caused by viral neurotropism, by a hyperinflammatory and hypercoagulative state, or even by mechanical ventilation-associated impairment. Hypoxia, endothelial cell damage, and the different impacts of different ventilatory strategies may all lead to increased stress and strain, potentially exacerbating the inflammatory response and leading to a complex interaction between the lungs and the brain. To date, no studies have taken into consideration the possible secondary effect of mechanical ventilation on brain recovery and outcomes.

The aim of our review is to provide an updated overview of the potential pathogenic mechanisms of neurological manifestations in COVID-19, discuss the physiological issues related to brain-lung interactions, and propose strategies for optimization of respiratory support in critically ill patients with SARS-CoV-2 pneumonia.

Keywords: COVID-19, SARS-CoV-2, coronavirus, neurological manifestations, neurotropism
INTRODUCTION

In December 2019, an outbreak of disease caused by a novel coronavirus (2019 novel coronavirus, 2019-nCoV) was reported in Wuhan, China (1). On February 11, 2020, the novel virus was renamed the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, and on the same day, the disease it causes was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (2). The rising number of daily confirmed cases globally led the WHO to characterize the outbreak as a pandemic on March 11, 2020 (3–8). The typical manifestations of COVID-19 include fever, dry cough, fatigue, and respiratory distress (9). Among patients with symptoms requiring hospitalization, 5–20% require invasive mechanical ventilation and admittance to an intensive care unit (10). COVID-19 is a complex, multisystem disease, perhaps best defined as a multiple organ dysfunction syndrome (MODS-CoV-2) (11) which includes neurologic manifestations (9). In a recent meta-analysis (12), headache was identified as one of the most common neurologic symptoms in the early stages of the disease (occurring in 3.5 to 34% of patients), followed by dizziness. More specific neurological manifestations were also observed, including impairment of smell, taste, or vision; limb weakness; acute cerebrovascular disease; and seizures. The causative mechanisms for neurological involvement in COVID-19 are still under-investigated because of a lack of prospective studies (12, 13). Furthermore, mechanical ventilation, commonly used in the management of COVID-19 patients, can itself induce an inflammatory response, causing distal organ failure. Thus, a complex cross-talk between the lungs and other organs, including the brain (14), may occur during severe COVID-19. Despite the paucity of evidence, there are three key hypotheses for the neurological manifestations of COVID-19 patients (Figure 1): (1) viral neurotropism; (2) a hyperinflammatory and hypercoagulable state; and (3) brain–lung crosstalk. While neuroinvasion may be restricted to most severe cases, other cases may be epiphenomena of systemic disease (11). The latter hypothesis is particularly interesting because it may be amenable to adjustment of ventilator settings to minimize lung and brain injury. Within this context, the aim of this manuscript is to provide an updated overview of the potential pathogenic mechanisms of neurological manifestations in COVID-19, discuss the physiological issues related to brain-lung interactions, and propose strategies for optimization of respiratory support in critically ill patients with SARS-CoV-2 pneumonia.

VIRAL NEUROTROPISM

Pathogenesis

The coronaviruses are large, enveloped, non-segmented, single-stranded, positive-sense ribonucleic acid (RNA) viruses. Seven coronaviruses in two genera have been identified as possibly infectious in humans, of which SARS-CoV-1, Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2 can cause life-threatening respiratory failure (15, 16). Genomic and structural analyses have shown that SARS-CoV-1 binds to angiotensin-converting enzyme-2 (ACE2) receptors and transmembrane serine protease-2 (TMPRSS2) (17). MERS-CoV instead binds to dipeptidyl dipeptidase-4 (DPP4) receptors, which are mainly present on the epithelium of the lower respiratory tract, small intestine, liver, kidneys, and immune cells (18). ACE2 receptors are widely distributed in the lung alveolar epithelial cells, nasopharyngeal and oral mucosa, endothelium and vascular smooth muscle cells in the brain, vascular endothelium and smooth muscle cells of the liver, vascular and red pulp sinus endothelium of the spleen, and cytoplasm of distal tubules and collecting ducts in the kidney (17). However, binding to ACE2 and DPP4 receptors alone is not enough to make host cells susceptible to infection. Some human epithelial cells which overexpress these receptors are not infected, whereas other cells with lower expression of these receptors, such as central nervous system (CNS) cells, have shown SARS-CoV-1 and MERS-CoV infection (19). As with the other coronaviruses, the classical route of SARS-CoV-2 infection is the passage of infected droplets through the upper airway and binding to ACE2 receptors. Ocular transmission has also been proposed as a possible alternative route for SARS-CoV-2 infection, since the aqueous humor contains ACE2 receptors (20). SARS-CoV-2 enters the host cell by endocytosis. After viral uncoating, the virion is released, followed by translation, replication, virion assembly, and new virion coating, a process which induces programmed cell death (21). A cascade of cerebral involvement in SARS-CoV-2 infection has been proposed by many authors (22–24). Coronaviruses may pass from the systemic to the cerebral circulation by several routes. Trans-synaptic passage through infected neurons via the olfactory bulb has been demonstrated with other coronaviruses, which are able to invade peripheral nerve terminals and spread in a retrograde fashion through synapses into the CNS; neuroimaging evidence from COVID-19 patients suggests SARS-CoV-2 can do so as well. SARS-CoV-2 can also spread across the blood–brain barrier (BBB) by two distinct mechanisms: (a) leukocyte migration across the BBB (named the Trojan horse mechanism); and (b) sluggish movement of blood within the microcirculation, crossing the BBB by binding to endothelial...
cells (17). Infected leukocytes can bind to ACE2 receptors and cross the BBB, migrating into the CNS (22–26). Expression of ACE2 receptors has been demonstrated in neurons, astrocytes, oligodendrocytes, the motor cortex, the cytoplasm of neurons, and sympathetic pathways (22). Binding to ACE2 produces vasodilatation and counteracts inflammation, while binding to the Mas receptor exerts neuroprotective and cardioprotective effects (27).

Experimental and Clinical Evidence

Trans-synaptic Spread

Literature from the previous SARS epidemic revealed that the virus primarily infects pneumocytes, but can also enter neuronal cells (28). Trans-synaptic spread has been demonstrated in experimental studies; in SARS-CoV-1 infected mice, extensive virus replication in brain cells was mediated by cerebral invasion through the olfactory epithelium (29). This has been also confirmed by another murine study with human coronavirus OC43 (30). In the clinical setting, SARS-CoV-1 genome sequences were detected in brain cells of infected patients by electron microscopy, real time-polymerase chain reaction (PCR), and light microscopy. Among brain areas, the thalami, cerebellum, white matter, and brainstem were primarily affected, with edema and scattered red degeneration of neurons (31). SARS-CoV-1 has been also detected in cerebrospinal fluid, probably reflecting spread through the BBB (29). Coronaviruses can also spread to the medullary cardiorespiratory center, which may at least partially account for the acute respiratory failure of SARS (32). Although previous literature on other coronaviruses clearly suggests neuronal involvement, data specific to SARS-CoV-2 are still limited; magnetic resonance imaging (MRI), autopsy findings, and brain biopsies should unravel the mystery. As with other coronaviruses, SARS-CoV-2 could potentially enter the nervous system through the olfactory bulb and spread to specific brain areas (33). This trans-synaptic spread theory is corroborated by multiple retrospective reports of anosmia and ageusia in COVID-19 patients (9, 29, 34). Most recently, anosmia and hyposmia were identified in 5.6% of 214 hospitalized patients (9), while 33.9% of 20 patients who completed a questionnaire experienced either olfactory or taste disorder and 18.6% experienced both (35). Smell and taste disorder were detected in 39.2% of 79 patients who were positive for COVID-19 PCR vs. 12.5% of 40 controls (adjusted odds ratio [OR] 21.4, confidence interval [CI] 95% 2.77–165.4, \( p = 0.003 \)). Of these, 25 (80.6%) reported smell disorders and 28 (90.3%) reported taste disorders (34). A single center study on 1,480 patients with influenza-like symptoms revealed that smell and taste loss occurred in the majority of patients who tested positive for SARS-CoV-2, was significantly associated with COVID-19 (\( p < 0.001 \)), and resolved after illness remission (36). A multicenter European study of 417 COVID-19 patients identified olfactory and gustatory dysfunctions as prevalent, early symptoms, which can indeed be used to identify SARS-CoV-2 infection (37). Finally, this hypothesis was
confirmed in vivo by MRI evidence of cortical hyperintensity in the right gyrus rectus and olfactory bulb, suggesting viral invasion of the brain—although not all the patients who develop olfactory dysfunction present with abnormal brain imaging (38)—and in post-mortem brain MRI studies, which found olfactory bulb and tract impairment without brainstem involvement (39). This provides very compelling evidence of SARS-CoV-2 entry via the olfactory tract and subsequent spread to specific brain areas, although limited to isolated cases (2).

Endothelial and Lymphocyte Invasion

Electron microscopy studies have recently demonstrated that SARS-CoV-2 can cross the BBB by binding to endothelial cells (40). SARS-CoV-2 neurotropism was further confirmed in autopsies of infected patients who died of cardiorespiratory failure (>65 years old) and massive intracranial hemorrhage (younger). In both groups, all patients showed lymphocytic panencephalitis and meningitis (41), confirming the neurotropic hypothesis, perhaps guided by leukocyte invasion.

Irrespective of mechanism, neurotropism is thus clearly demonstrated. When brain involvement does occur, the presence and persistence of human coronaviruses in the CNS, as occurs in mice, can determine long-term neurological sequelae. Mice surviving acute coronavirus encephalitis exhibited long-term sequelae associated with decreased activity in an open field test and a reduced hippocampus, with neuronal loss in the Ammon’s horn (CA)1 and CA3 areas (42). It has also been hypothesized that human coronaviruses may play a triggering role in long-term neurological conditions, such as multiple sclerosis. Although research has not led yet to a direct link to any specific virus, an association of coronaviruses with multiple sclerosis has been suggested (43, 44). A significantly higher prevalence of human CoV-OC43 was observed in the brains of multiple sclerosis patients than in controls (45). Moreover, during infection by human CoV-OC43 and CoV-229E, an autoreactive T-cell response directed to both viral and myelin antigens was discovered in multiple sclerosis patients, but not in controls (46, 47). This underlines the possibility that long-term infection of the CNS by human coronaviruses may play a role in the onset of multiple sclerosis-like demyelinating lesions, as reported during the COVID-19 pandemic (48). Evidence of CNS infection by SARS-CoV-2 has been associated with poor prognosis, worse clinical condition, and sudden death in COVID-19 patients (9). However, there is limited evidence to confirm this hypothesis, since the majority of observed cerebrospinal fluid (CSF) samples have been negative for SARS-CoV-2 infection (49, 50). This makes it difficult to confirm that neurotropism could be the main mechanism of neurological complications in COVID-19.

HYPER-INFLAMMATION AND HYPERCOAGULABILITY

Pathogenesis

SARS-CoV-2 may pass across the respiratory epithelium and spread from the alveolar-epithelial barrier to the systemic circulation, enhancing the local inflammatory response (51) and producing a systemic “cytokine storm,” affecting other organs such as the brain (52). Furthermore, inflammation is one of the main mechanisms that trigger the coagulation cascade and promote hypercoagulability. In severe SARS-CoV-2 infection, recent findings suggest a key role of endothelial cells (ECs) in vascular dysfunction, immunothrombosis, and inflammation (53). Histopathological studies have provided evidence of direct viral infection of ECs, diffuse endotheliitis, and micro- and macrovascular thrombosis, both in the venous and arterial circulations. The pro-inflammatory cytokine storm, with elevated levels of interleukin-6 (IL-6), IL-2 receptor, and tumor necrosis factor (TNF)-α, could also participate in endothelial dysfunction and leukocyte recruitment in the microvasculature. COVID-19-induced endotheliitis may explain the systemic impaired microcirculatory function in different organs observed in COVID-19 patients. Next, we will discuss the role of hyperinflammation and hypercoagulability as potential mechanisms for secondary brain involvement in COVID-19.

On the immune side, after antigen binding to the host receptor, monocytes are activated, with the release of pro-inflammatory cytokines (such as MMP9, which increases BBB permeability, and TNF-α, which increases expression of intracellular adhesion molecule [ICAM]-1 on endothelial cells). Infected and activated monocytes cross the damaged BBB, inducing the local release of pro-inflammatory cytokines and resulting in oligodendrocyte and neuronal damage. Coronavirus primarily infects monocyte-derived macrophages, which produce chemokines and then present CoV antigens to T-cells and other pro-inflammatory cells (51). Astrocytes may also release other chemokines that will recruit other leukocytes. This hyperactive neuroinflammatory response could induce immune-mediated neuropathology (2, 51). On the coagulation side, increased consumption and decreased production of platelets in the damaged lungs are all factors that can contribute to thrombocytopenia (54). As a consequence, it seems reasonable that infected patients are more prone to developing posttraumatic or spontaneous intracranial hemorrhage (55), as well as these alterations suggest a trend of SARS-CoV-2 infection to induce consumption coagulopathy, which, if unchecked, could lead to disseminated intravascular coagulation (DIC) and an unfavorable clinical course (56). In fact, viral infections may lead to sepsis, which represents the most common cause of DIC. DIC is determined by the release of injury-related cytokines, which activate monocytes and endothelial cells, leading to overexpression of tissue factors and secretion of von Willebrand factor. The presence of free thrombin in the circulation can activate platelets, stimulating fibrinolysis (57).

Experimental and Clinical Evidence

Inflammation

Inflammatory involvement was recently confirmed by an experimental murine model of murine coronavirus (MHV-A59), which can enter the brain via intranasal or intracerebral exposure and whose virulence is mediated by cytokine secretion.
In one experimental study, injection of mouse hepatitis virus (MHV), a member of the Coronaviridae family, into the murine CNS demonstrated that coronavirus infection elicits both innate and adaptive immune responses (58). The genomic RNA is then translated, replicated, assembled, and coated for future release and infection of other cells. As replication increases with the aid of macrophages, microglia, astrocytes, and oligodendrocytes, the virus can spread from the ependyma to the brain parenchyma. By this point, inflammation is established, and is followed by BBB damage and enhanced innate and adaptive immune responses (58). Immunofluorescence and immunohistochemistry revealed that microglia and astrocytes are involved in activation of the innate immune system of the brain, releasing cytokines that are involved in the pathogenesis of encephalitis (59). A study on human autopsy specimens showed that SARS-CoV-1 was able to infect brain tissue, with necrosis of neuronal cells and glial hyperplasia. These studies suggested that neuronal involvement in SARS was characterized by a massive inflammatory process, especially with enhancement of monokine expression in glialcytes induced by interferon (IFN)-γ (60). An experimental study on bronchoalveolar lavage fluid (BALF) of COVID-19 patients identified that SARS-CoV-2 infection of the airway leads to pro-inflammatory cytokine and chemokine release. This enhances the interaction with receptors expressed on thoracic sensory neurons of the lung, thus causing the release of neupeptides, followed by vasodilation, immune-cell recruitment, neurogenic inflammation, and potential pain. This mechanism could be theoretically involved in the hyperinflammatory state, which first involves the lung and then extends to the nervous system, with sensory neurons thus potentially acting as drivers of neurogenic pulmonary dysfunction (61). In a retrospective cohort cited above, severe patients were more likely to exhibit impaired consciousness and acute cerebrovascular disease than non-severe patients (p < 0.001 and p < 0.05, respectively). Severe patients also showed a more florid inflammatory response (higher white blood cell and neutrophil counts, lower lymphocyte counts, higher C-reactive protein levels) and higher D-dimer levels than non-severe patients, and developed more extensive multiple organ involvement (9). Acute necrotizing encephalopathy (ANE) has been related to a brain cytokine storm, which results in BBB disruption (62). ANE has been previously reported as a rare complication of viral infections such as influenza (62). Radiological findings from computed tomography (CT) scans and MRI in COVID-19 have been recently published (62). ANE was also identified in a patient with aplastic anemia (63). Non-contrast CT scan demonstrated bilateral symmetric hypattenuation in the medial thalami with negative CT angiogram and venogram findings, while MRI showed bilateral hemorrhagic rims in the thalami, sub-insular regions, and medial temporal lobes. ANE usually presents a bilateral distribution, with predominance of lesions in the thalami, brainstem, cerebral white matter and cerebellum, which is consistent with the cerebral insults observed in COVID-19 (62). Studies have concluded that men and women might show different responses to COVID-19. Women seem to be less susceptible to viral infections than men overall. The presence of two X chromosomes influences immune regulatory genes to blunt the inflammatory response and increase levels of antibodies and cluster of differentiation (CD)4+ T-cells, and consequently, promoting the expression of cytokines. Moreover, the X chromosome acts on other proteins and genes, including forkhead box (FOXP)-3, toll like receptor (TLR)-8, CD40L, and chemokine receptor (CXC)R3. Nevertheless, the increased susceptibility of women to autoimmune and auto-inflammatory disorders has to be taken into account (64). Coronavirus infection of the CNS has long provided a model for studying demyelinating diseases such as multiple sclerosis, vaccine design, and novel immunotherapeutic to limit virus spread (58). Hemophagocytic lymphohistiocytosis (HLH) is characterized by a severe dysregulation of T-lymphocytes, natural killer cells, and macrophages within the contest of cytokine storm and multiorgan failure, and represents a clear link between hyperinflammation and hypercoagulability (65). This condition has been described in patients with SARS-CoV-2 (1). HLH patients present with pancytopenia, coagulopathy, hepatic dysfunction, hypertriglyceridemia, and high ferritin levels (66).

Coagulopathy
Neurological damage in COVID-19 patients may also be associated with coagulopathy. In a recent meta-analysis, Lippi et al. showed that low platelet counts are associated with poor prognosis in COVID-19 (67). As reported by Yang et al. (54), hematological changes were common in patients with SARS, most notably including lymphopenia and thrombocytopenia, through different potential mechanisms. Preliminary data from COVID-19 cohorts described a major impairment of blood coagulation and derangement of hemostasis in a large number of patients. Han et al. (68) studied alterations in blood coagulation parameters of patients with SARS-CoV-2 infection, observing lower antithrombin values and higher D-dimer, fibrin/fibrinogen degradation products, and fibrinogen levels. Tang et al. (56) observed high levels of D-dimer and fibrin/fibrinogen degradation products in all non-survivors, confirming activation of coagulation cascade and secondary hyperfibrinolysis. Within this context, the neurological manifestations associated with SARS-CoV-2 may be determined by a hypercoagulable state with high D-dimer levels. The association between ischemic stroke and high D-dimer levels has been previously described in the literature (69, 70). D-dimer elevation reflects ongoing thrombus formation, although it is also an acute-phase reactant that enhances the inflammatory process itself by stimulating monocyte synthesis and release of proinflammatory cytokines (e.g., IL-6), thus contributing to stroke occurrence and progression (71). Coagulopathy and antiphospholipid antibodies were found in patients affected by COVID-19. These findings were associated with both arterial and venous thrombotic events, including cerebral infarcts and limb ischemia. Patients presented with prolonged activated partial thromboplastin and prothrombin times, while two of three patients showed thrombocytopenia (72). Fourteen cases of stroke have been reported out of 214 patients in China (9). Likewise, MRI and CT scans revealed a high prevalence of...
stroke in COVID-19 patients (49, 73–75), including in patients younger than 50 years (76). The association between stroke and COVID-19 could be explained also by the fact that both diseases share the same risk factors such as hypertension and diabetes (77, 78), and by the pathological hypercoagulability state that characterize COVID-19. An association between high levels of D-dimer and intracerebral hemorrhage (ICH) was described in a prospective study carried out by Di Castelnuovo et al. (79), although a previous meta-analysis did not show a causal relationship (80). A recent meta-analysis by Zhou et al. (81), which included 13 studies on 891 patients with ICH, concluded that high levels of D-dimer were associated with an elevated risk of ICH. In fact, high D-dimer levels stimulate fibrinolysis with subsequent plasmin generation and microvascular lesions, which might cause the inhibition of hemostasis and a hypo-coagulable state, thus triggering cerebral hemorrhage (79). Moreover, an association between elevated D-dimer levels and large hematoma volume, intraventricular and subarachnoid blood extension, and early mortality has been reported in ICH (82). In summary, although literature is inconclusive concerning the relationship between COVID-19-related hypercoagulability and neurological complications, a possible correlation should be taken into account. Possible mechanisms for activation of intrinsic and extrinsic coagulation pathways, followed by inflammation by SARS-CoV-2 infection are proposed in Figure 2.

**BRAIN–LUNG CROSSTALK IN COVID-19: AN UNDERESTIMATED MECHANISM**

**Pathogenesis**

Brain–lung crosstalk and its implications for ventilator management are illustrated in Figure 3. The respiratory management of COVID-19 shares some characteristics with that of the acute respiratory distress syndrome (ARDS) (83), but different hallmarks must be considered and discussed. COVID-19 pneumonia is as a typical "pulmonary" ARDS (84). In experimental settings (85), "pulmonary" as compared to "extrapulmonary" ARDS is distinguished by increased alveolar–epithelial damage, more neutrophil cell infiltration and fibroinuous exudate, increased collagen fibers in the alveoli and interstitium. In clinical studies, different radiological patterns have been identified, with different characteristics and responses to alveolar recruitment. In non-COVID patients, ARDS is characterized by interstitial and alveolar edema homogeneously distributed along the vertical gradient (86, 87), leading to collapse of the most dependent alveoli in the supine position. Regional perfusion follows a gravitational gradient (more perfusion in dependent lung regions), and severe hypoxemia is explained mainly by increased "true shunt" in atelectatic, dependent lung regions. Application of higher levels of positive end-expiratory pressure (PEEP) is associated with alveolar recruitment, improving respiratory mechanics and gas exchange. Thus, in classical ARDS patients, therapeutic maneuvers leading to improvement in gas exchange are associated with better lung aeration. Conversely, COVID-19 pneumonia is characterized by minimal interstitial and alveolar edema, alveolar cellular infiltration and necrosis, with alveolar consolidation and pneumolysis. Regional perfusion follows a non-gravitational gradient (more perfusion in non-dependent lung regions), with hyperperfusion of normally aerated and poorly aerated ("ground glass") tissue, leading to major changes in ventilation-perfusion ratio. Additionally, perfusion in consolidated, dependent lung regions contributes to "true" shunt. Application of higher levels of PEEP does not recruit alveoli; instead, it leads to deterioration of respiratory mechanics, gas exchange, and hemodynamics. Thus, in COVID-19 patients, therapeutic maneuvers leading to improvement in gas-exchange are not associated with improved lung aeration, but rather with redistribution of regional perfusion (88). Interestingly, areas of hyperperfusion may occur in poorly aerated ground-glass areas as well as in non-aerated lung regions. This suggests that some hyperperfusion might be protective against further deterioration of ventilation-perfusion ratio as well as "true" shunt.

Three distinct radiological phenotypes of COVID-19 pneumonia have been described (79). Phenotype 1 is characterized by multiple, focal, overperfused ground-glass opacities, normal or high lung compliance, and severe hypoxemia, probably caused by low ventilation/perfusion and regional shunting. In this case, PEEP should be set according to the lowest driving pressure and/or minimal oxygenation, and inhaled nitric oxide might be useful. Phenotype 2 is characterized by an inhomogeneous and/or asymmetrical distribution of atelectasis, partial alveolar derecruitment, and/or consolidation with peribronchial opacities. In these cases, lateral or prone positioning might be helpful. Finally, phenotype 3 is characterized by patchy, ARDS-like diffuse lung infiltration, with a mixed pattern of overperfused, normally aerated and ground-glass areas as well as hyperperfused, non-aerated lung regions with low compliance. In this setting, mechanical ventilation should follow standard protective ventilatory strategies used for ARDS, with minimal PEEP, prone positioning, and escalation to extracorporeal membrane oxygenation (ECMO) as needed. In all cases, possible microthrombosis and multiorgan failure must be considered.

A correlation between acute lung injury and brain hypoxia has been described by Oddo et al. (89). Reduced systemic oxygenation may affect brain tissue oxygenation, thus leading to secondary brain damage. Measurement of brain tissue oxygenation tension (PbtO$_2$) has confirmed that this parameter is strongly correlated with systemic oxygenation and markers of lung function, including partial pressure of carbon dioxide (PaCO$_2$) and mean arterial pressure. Accordingly, impaired partial pressure of oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) ratio has been associated with lower PbtO$_2$ (89). In another study, patients who underwent an oxygen challenge with 100% FiO$_2$ showed higher PbtO$_2$ (90). Hypoxic–ischemic damage is also associated with impaired outcome (91). We believe this phenomenon should be considered one of the main mechanisms implicated in neurological dysfunction following SARS-CoV-2 infection. In fact, given these respiratory characteristics, "silent" hypoxia with normal/hypercapnic respiratory failure can occur due to compromised alveolar gas
FIGURE 2 | SARS-CoV-2-induced hypercoagulability. Passage of the virus from the airway to the systemic circulation is facilitated by the sluggish movement of blood within the microcirculation and subsequent binding of ACE-2 receptors, expressed on the capillary endothelium, followed by endothelial damage, enhanced inflammation, and hypercoagulability. In this figure, we represent the activation of both intrinsic and extrinsic coagulation pathways as a possible mechanism for hypercoagulability and potential brain damage. Intrinsic pathway: activation of factor (F) XIIa, followed by activation of FXIa and VIII. Extrinsic pathway: activation of FVIIa and tissue factor. Both pathways converge in the common pathway with activation of FXa, FVa, prothrombin into thrombin, fibrinogen into fibrin, and fibrin degradation products (FDP) such as D-dimer.

FIGURE 3 | Bohr effect. The oxyhemoglobin dissociation curve is shifted to the left in response to respiratory alkalosis (lower PaCO2 and higher pH), with increased affinity of oxygen for the hemoglobin. Conversely, during respiratory acidoses (higher PaCO2 and lower pH), the alveolar oxygen tension and systemic saturation improve, thus reducing alveolar carbon dioxide tension, as explained by the Bohr effect: the higher the acidity, the more carbon dioxide is eliminated. Our knowledge concerning hypobaric hypoxia can be derived from aviation medicine. High altitude correlates with severe hypoxemia, which triggers the carotid chemoreceptors, activating the respiratory drive; hypocapnia ensues. The oxyhemoglobin dissociation curve shifts to the left in response to respiratory alkalosis and increased affinity of oxygen for hemoglobin, thereby increasing the alveolar oxygen tension and systemic saturation after reducing alveolar carbon dioxide tension, as explained by the Bohr effect—the greater the acidity, the more carbon dioxide is eliminated. PaO2 and oxygen delivery (DO2) can be optimized by modulating blood pH and PaCO2, hemoglobin concentration, cardiac output, and arterial content of oxygen. These factors mean close attention is warranted when implementing lung-protective strategies, particularly when using low oxygen targets (55–80 mmHg) and permissive hypercapnia. In phenotype 1, characterized by lower potential alveolar recruitability, raising hemoglobin and cardiac output should be considered as a strategy to improve DO2, as explained in Figure 4. One possible side effect of higher hemoglobin is increased blood viscosity, raising the risk of cerebrovascular events. In phenotype 3 (ARDS-like COVID), prone positioning, higher PEEP, and RMs should be attempted instead to increase PaO2 and control PaCO2 levels.
this point, it is crucial that brain–lung–hemodynamics crosstalk be addressed (Figures 5A–C) (96). Current knowledge on the cerebral effects of mechanical ventilation has shifted in favor of moderate-PEEP strategies instead of low- or zero-PEEP strategies, due to possible beneficial effects on brain tissue oxygenation (97–99). Nevertheless, higher PEEP levels may be considered in COVID-19 phenotype 3 to reach acceptable levels of oxygen saturation in the brain (100), thus improving cerebral blood flow and perfusion (101). In this phenotype (but not in phenotypes 1 or 2), lung recruitment maneuvers might also improve oxygenation by improving gas exchange, although their effects on intracranial pressure (ICP) could be detrimental due to impaired jugular venous outflow and venous return (102).

According to the “blast injury theory,” the sympathetic storm, cytokine storm, and hyperinflammatory state caused by infection can induce a transient increase in intravascular pressure, with endothelial damage, raised pulmonary vascular hydrostatic pressure, and increased capillary permeability, thus promoting lung derangement and a secondary brain insult (103). This could explain, at least in part, why patients with severe COVID-19 have worse neurological outcomes (104). Both oxygen and carbon dioxide have been considered important determinants of cerebral homeostasis, due to their effects on cerebral blood flow (105). Low cerebral blood flow due to low PaCO$_2$ is associated with cerebral ischemia, while high cerebral blood flow results in cerebral hyperemia and higher ICP (105). A rise in ICP may also be achieved by increasing PaCO$_2$ if intracranial compliance is reduced. In patients not amenable to alveolar recruitment maneuvers, such as those with COVID-19 phenotype 1, overdistension of alveolar areas contributes to a rise in PaCO$_2$ due to the increase in dead space, followed by cerebral vasodilatation. Conversely, in patients responsive to recruitment maneuvers (COVID-19 phenotype 3), shunt is reduced, oxygenation improves, and the PaCO$_2$ is decreased, with lower dead space and less changes in ICP and cerebral perfusion (83, 106). PaO$_2$, PaCO$_2$, pH, hemoglobin, and DO$_2$ might all be considered as clinical targets for bedside monitoring where available, to protect both the brain and the lung.

**Experimental and Clinical Evidence**

The first report of brain autopsies in COVID-19 patients was published on June 12, 2020. Impressively, the authors reported that, at histologic analysis, all 18 examined patients (100%) had evidence of acute hypoxic ischemic damage to the cerebrum and cerebellum. Neither encephalitis nor any evidence of specific viral invasion was identified (107). The neuroimaging features of 108 hospitalized COVID-19 patients demonstrated a non-specific pattern, with predominance of acute
ischemic infarcts and intracranial hemorrhage. MRI findings included the posterior reversible encephalopathy syndrome (PRES), hypoxic–ischemic encephalopathy, and exacerbation of preexisting demyelinating disease, corroborating the role of a hyperinflammatory/hypercoagulable state and brain–lung crosstalk as major mechanisms potentially underpinning neurological complications in COVID-19 (108). Further evidence of neurological involvement is the higher incidence of ICU delirium in COVID-19 patients when compared to non-COVID patients (26.8 vs. 7.7%, \( p = 0.003 \)) (109). This may be explained by the fact that profound hypoxia is known to predispose to long-term cognitive impairment and hypoxic delirium phenotypes, whether caused by BBB dysfunction, inflammation, hypoperfusion, hypoxemia, or a combination thereof (110–112).

In summary, encephalopathy and cerebrovascular disease are the main neurological features identified in severe COVID-19 (73, 113). Despite compelling evidence of viral neurotropism, we believe this is not the primary causative factor of neurological involvement. Instead, in most cases it is likely due to impairment of the delicate equilibrium between the brain and the lung and to the hyperinflammatory, pro-coagulative state that is characteristic of SARS-CoV-2 infection.

**CONCLUSIONS**

In COVID-19 patients, central and peripheral nervous system changes may be caused by viral neurotropism (such as impairment of olfaction and taste), by a hyperinflammatory and hypercoagulative state, or even by mechanical ventilation-associated impairment. Three distinct phenotypes of pulmonary injury have been identified in association with COVID-19 pneumonia, each requiring individualized respiratory support strategies to minimize lung injury and optimize oxygen delivery to different organs—including the brain. Data from prospective observational studies, randomized clinical trials, and autopsies are urgently needed to confirm the latest findings concerning the causal roles of hypoxic–ischemic brain damage, inflammation, and hypercoagulability in the neurological manifestations of COVID-19.
AUTHOR CONTRIBUTIONS

DB: design and conceptualization, drafting, and revising the manuscript for intellectual content. PA, PF, and PP: drafting and revising the manuscript for intellectual content. IB, GZ, LB, NP, DG, AV, MB, and AS: revising the manuscript for intellectual content. All authors: read and approved the final version of the manuscript.

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REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Naming the Coronavirus Disease (COVID-19) and the Virus that Causes It. Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)‐and‐the‐virus‐that‐causes‐it (accessed March 31, 2020).
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. NEJM. (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
4. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. (2020) 92:418–23. doi: 10.1002/jmv.25681
5. Choi WJ, Lee KN, Kang EL, Lee H. Middle east respiratory syndrome-coronavirus infection: a case report of serial computed tomographic findings in a young male patient. Korean J Radiol. (2016) 17:166–70. doi: 10.3348/kjr.2016.17.1.116
6. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. (2020) 25:2000045. doi: 10.2807/1560-7917.ES.2020.25.3.2000045
7. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. Adv Virus Res. (2020) 41:1–5. doi: 10.1016/s0072-173x(20)30441-0
8. The Lancet. Emerging understandings of 2019-nCoV. (2020) 395:e391. doi: 10.1016/s0140-6736(20)30318-7
9. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol. (2020) 77:1–9. doi: 10.2109/jnsn.2017.5.4840
10. McGrath BA, Brenner MJ, Warrilllow SJ, Pandian V, Arora A, Cameron TS, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. Lancet Respir Med. (2020) 8:717–25. doi: 10.1016/s2213-2600(20)30230-7
11. Robba C, Battaglini D, Pelosi P, Rocco RPM. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Exp Rev Respir Med. (2020) 14:21–4. doi: 10.1080/17476348.2020.1778470
12. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nusnjo PN. Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Front Neurol. (2020) 11:565. doi: 10.3389/fneur.2020.00565
13. Ferrarese C, Silani V, Pioriti A, Galimberti S, Agostoni E, Monaco S, et al. An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROC0VID). Neurol Sci. (2020) 41:1–5. doi: 10.1007/s10072-020-04450-1
14. Pelosi P, Rocco RPM. The lung and the brain: a dangerous cross-talk. Crit Care. (2011) 15:168. doi: 10.1186/cc10259
15. Cormain VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. Adv Virus Res. (2018) 100:163–88. doi: 10.1016/ba.avir.2018.01.001
16. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. J Pathol. (2015) 235:185–95. doi: 10.1002/path.4454
17. Hamming I, Timmens W, Bultuijs M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. (2004) 203:631–7. doi: 10.1002/path.1570
18. Mattern T, Scholtz W, Feller AC, Flad HD, Ulmer AJ. Expression of CD26 (Dipeptidyl Peptidase IV) on resting and activated human T-lymphocytes. Scand J Immunol. (1991) 33:737–48. doi: 10.1111/j.1365-3083.1991.tb02548.x
19. Chan PKS, To KF, Lo AW, Cheung JKL, Chu I, Au FWL, et al. Persistent infection of SARS coronavirus in colonic cells in vitro. J Med Virol. (2004) 74:1–7. doi: 10.1002/jmv.20138
20. Lu C-W, Liu X-F, Jia Z-F. 2019-nCoV transmission through the ocular surface must not be ignored. Lancet. (2020) 395:e39. doi: 10.1016/S0140-6736(20)30313-5
21. Koester V. Coronavirus entering and replicating in a host cell. ChemViews. (2020) 5:e1000428. doi: 10.1002/chemv.202000018
22. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuvurilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. (2020) 77:1–9. doi: 10.1016/j.jaut.2020.06.002
23. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
24. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, et al. Neurological manifestations of SARS-CoV-2: a review. Front Neurol. (2020) 11:518. doi: 10.3389/fneur.2020.00518
25. Trojanowicz B, Ulrich C, Kohler F, Bode V, Seibert E, Fiedler R, et al. Monocytic angiotensin-converting enzyme 2 relates to atherosclerosis in patients with chronic kidney disease. Nephrol Dial Transplantat. (2017) 32:287–98. doi: 10.1093 NDt/gfw206
26. Spiegel M, Schneider K, Weber F, Weidmann M, Hufert FT. Interaction of severe acute respiratory syndrome-associated coronavirus with dendritic cells. J Gen Virol. (2006) 87:1953–60. doi: 10.1099/vir.0.81624-0
27. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. Stroke. (2020) 11:322–5. doi: 10.1097/s1097-02-00818-9
28. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis virus transmission pathways. J Pathol. (2004) 203:622–30. doi: 10.1002/path.1560
29. McCray PB, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, et al. Interaction of Severe Acute Respiratory Syndrome Coronavirus OC43. J Virol. (2006) 80:10195–60. doi: 10.1128/Jvi.02012-06
30. Dube M, Le Coupencac A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol. (2018) 95:4004–18. doi: 10.1128/Jvi.04004-18
31. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med. (2005) 202:415–24. doi: 10.1084/jem.20050828
32. Li VC, 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) 92:552–5. doi: 10.1002/jmv.25728
33. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. (2008) 82:7264–75. doi: 10.1128/JVI.00737-08
34. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Conrado J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicenter PCR-based case-control study. Eur J Neurol. (2020) 2020:14273. doi: 10.1111/ejn.14273
35. Iqbal S, Muneer M, Qureshi A, Bello T, Pal M, Khan M, et al. Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. Virology. (2006) 349:335–46. doi: 10.1016/j.virol.2006.01.049
36. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV-2 and human coronavirus 229E cross-reactive T cells in multiple sclerosis patients. J Neurol Neurosurg Psychiatry. (2020) 101:1080–1084. doi: 10.1136/jnnp-2020-332522
37. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. (2020) 92:424–32. doi: 10.1002/jmv.25685
38. Heuer JF, Selke M, Crotzer TA, Pelosi P, Herrmann P, Perske C, et al. Effects of acute intracranial hypertension on extracerebral organs: a randomized experimental study in pigs. J Neurol Surg A Cent Eur Neurosurg. (2012) 73:289–95. doi: 10.1155/2012/1304813
39. Pons S, Fodil S, Azoulay E, Zafra F. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care. (2020) 24:353. doi: 10.1186/s13054-020-03062-7
40. Yang M, Ng MHL, Chi KL. Thrombocytopenia in patients with severe acute respiratory syndrome (review). Hematology. (2005) 10:101–5. doi: 10.1080/1024533040026170
41. Gonzalez-Duarte A, Garcia-Ramos GS, Valdes-Ferrer SI, Cantu-Brito C. Clinical description of intracranial hemorrhage associated with bleeding disorders. J Stroke Cerebrovas Dis. (2008) 17:204–210. doi: 10.1016/j.jstrokecerebrovasdis.2008.02.008
42. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thorac Haemost. (2020) 18:844–7. doi: 10.1111/jth.14768
43. Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). Hematol Am Soc Hematol Educ Progr. (2009) 2009:240–6. doi: 10.1182/asheducation-2009.1.240
44. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. Nat Rev Microbiol. (2006) 4:121–32. doi: 10.1038/nrmicro1343
45. Lavi E, Cong L. Type I astrocytes and microglia induce a cytokine response in an encephalitic murine coronavirus infection. Exp Mol Pathol. (2020) 115:104474. doi: 10.1016/j.yexmp.2020.104474
46. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin Inf Dis. (2005) 41:1089–96. doi: 10.1086/444461
47. Ray P, Wangzhou A, Ghinein N, Youssuf M, Paige C, Tavares-Ferreira D, et al. A Pharmacological interaction between COVID-19 patient samples and human sensory neurons reveals potential drivers of neurogenic pulmonary dysfunction. Brain Behav Immun. (2020). doi: 10.1016/j.bbi.2020.05.078. [Epub ahead of print].
48. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19—volume, page range.associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology. (2020) 2020:21187. doi: 10.1148/radiol.202021187.
49. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JF, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
50. Skinner J, Yankey B, Shelton BK. Hemophagocytic lymphohistiocytosis. AAGN Adv Crit Care. (2019) 30:151–64. doi: 10.4037/aacnc20 19463
51. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. (2020) 506:145–8. doi: 10.1016/j.cca.2020.03.022
52. Han H, Yang L, Liu R, Li F, Wu K-L, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. (2020) 58:1116–20. doi: 10.1515/cclm-2020-0188
53. Yao T, Tian BL, Li G, Cui Q, Wang CF, Zhang Q, et al. Elevated plasma D-dimer levels are associated with short-term poor outcome in patients with acute ischemic stroke: a prospective, observational study. BMC Neurol. (2020) 20:115. doi: 10.1186/s12883-019-1386-3
54. Koch HJ, Horn M, Bogdahn U, Ickenstein GW. The relationship between plasma D-dimer concentrations and acute ischemic stroke subtypes. J Stroke Cerebrovas Dis. (2005) 14:75–9. doi: 10.1016/j.jstrokecerebrovasdis.2004.12.002
71. Zi W-I, Shuai J. Plasma D-dimer levels are associated with stroke subtypes and infarction volume in patients with acute ischemic stroke. PLoS ONE. (2014) 9:e86465. doi: 10.1371/journal.pone.0086465
72. Goldberg MF, Goldberg MF, Cereijo R, Tayal AH. Cerebrovascular disease in COVID-19. AJNR Am J Neuroradiol. (2020) 41:1170–2. doi: 10.3174/ajnr.A6588
73. Scullen T, Keen J, Mathkour M, Dumont AS, Kahn L. COVID-19 associated encephalopathies and cerebrovascular disease: the New Orleans experience. World Neurosurg. (2020). doi:10.1016/j.wneu.2020.05.192. [Epub ahead of print].
74. Morassi M, Bagatto D, Cobelli M, D’Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol. (2020) 267:2185–92. doi:10.1007/s00415-020-09885-2
75. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild COVID-19 infection. J Thromb Haemost. (2020) 20:14938. doi:10.1111/jth.14938
76. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med. (2020) 382:e60. doi:10.1056/NEJMoa2009787
77. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. Clin Neurosurg. (2020) 194:105921. doi:10.1016/j.clineuro.2020.105921
78. Battaglini D, Robba C, Lopes da Silva A, dos Santos Samary C, Leme Silva P, Dal Pizzol F, et al. Brain–heart interaction after acute ischemic stroke. AJNR Am J Neuroradiol. (2020). doi:10.3174/ajnr.A6588
79. Dhurandhar S, Ananthakrishnan A, Tanneja D, Bhatia M, Majoee H, Gunther R, et al. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: a pilot study. J Crit Care. (2015) 30:1263–6. doi:10.1016/j.jcrc.2015.07.019
80. Pelosi P, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymondis K, et al. Management and outcome of mechanically ventilated neurologic patients. Crit Care Med. (2011) 39:1482–92. doi:10.1097/CCM.0b013e3182120998
81. Boone MD, Jindasa SP, Mueller A, Shaefi S, Kasper EM, Hanafy KA, et al. The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. Neurocrit Care. (2017) 26:174–81. doi:10.1007/s12028-016-0328-9
82. Alhazzani W, Hylander Moller A, Arabi YM, Loeb M, Ng Gong M, Fan E, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. (2020) 48:e440–69. doi:10.1097/CCM.0000000000004363
83. Huyynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH, et al. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. J Trauma. (2002) 53:488–93. doi:10.1097/01.TJR.000005373-20020900-000016
84. Pelosi P, Bonatti G, Battaglini D, Rocco PRM, Pelosi P. Mechanical ventilation in patients with acute ischaemic stroke: from pathophysiology to clinical practice. Crit Care. (2019) 23:388. doi:10.1186/s13054-019-2662-8
85. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. Neurocrit Care. (2009) 11:417–26. doi:10.1007/s12028-009-9242-8
86. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. (2020). doi:10.1056/NEJMc2009787. [Epub ahead of print].
87. Bouma GJ, Muizelaar JP. Cerebral blood flow in severe clinical head injury. Neurocrit Care. (2009) 11:417–26. doi:10.1007/s12028-009-00016
88. Mascia L, Grasso S, Fiore T, Bruno F, Bernardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med. (2005) 31:373–9. doi:10.1007/s00134-004-2491-2
89. Solomon IH, Normandin E, Bhattacharyya S, Mukerji S, Keller K, Ali AS, et al. Neuroophthalmological features of Covid-19. N Engl J Med. (2020) 382:1937–43. doi:10.1056/NEJMoa2009733. [Epub ahead of print].
90. Rosenthal G, Hemphill JC, Sorani M, Martin C, Morabito D, Meeker M, et al. The role of lung function in brain tissue oxygenation following traumatic brain injury. J Neurosurg. (2008) 108:39–65. doi:10.3171/NS/2008/108/01/0059
91. Van Sanbrink H, Vd Brink WA, Steyerberg EW, Suazo JAC, Avezaat CJJ, Maas AJB, et al. Brain tissue oxygen response in severe traumatic brain injury. Acta Neurochir. (2003) 145:429–38. doi:10.1007/s00701-003-0032-3
92. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis Dis. (2020). doi:10.1016/s1473-3099(20)30367-4. [Epub ahead of print].
93. Ottested W, Sovik S. COVID-19 patients with respiratory failure: what can we learn from aviation medicine? Br J Anaesth. (2020). doi:10.1016/j.bja.2020.04.012. [Epub ahead of print].
94. Tsuboi J, Scheren T. Understanding the Haldane effect. Intensive Care Med. (2017) 43:91–3. doi:10.1007/s00134-016-4261-3
95. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med. (2011) 17:796–808. doi:10.1038/nm.2399
96. Nemler SN, Caldeira JB, Santos RG, Guimarães BL, Garcia JM, Prado D, et al. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: a pilot study. J Crit Care. (2015) 30:1263–6. doi:10.1016/j.jcrc.2015.07.019
97. Zi W-J, Shuai J. Plasma D-dimer levels are associated with stroke in patients with mild Covid-19 infection. AJNR Am J Neuroradiol. (2020). doi:10.3174/ajnr.A6588
disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology.* (2020). doi: 10.1212/WNL.0000000000009848. [Epub ahead of print].

10. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med.* (2012) 185:1307–15. doi: 10.1164/rccm.201111-2025OC

11. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med.* (2018) 6:213–22. doi: 10.1016/S2213-2600(18)30062-6

12. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care.* (2019) 23:352. doi: 10.1186/s13054-019-2626-2

13. Deliwala S, Abdulhamid S, Abusalih MF, Al-Qasmi MM, Bachuwa G. Encephalopathy as the sentinel sign of a cortical stroke in a patient infected with coronavirus disease-19 (COVID-19). *Cureus.* (2020) 12:e8121. doi: 10.7759/cureus.8121

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