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UNDERSTANDING THE DISEASE

Lung–brain cross talk in the critically ill

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Severe acute brain injury predisposes to other organ dysfunctions, especially lung impairment. Neurological patients, despite being younger and having fewer comorbidities than other patients, develop intensive care unit (ICU)-acquired sepsis and respiratory failure more frequently [1]. Patients with traumatic brain injury and subarachnoid hemorrhage develop acute respiratory distress syndrome (ARDS) at rates similar to patients with sepsis, trauma, or aspiration [2]. Among several risk factors for ARDS in these patients including hypoxemia, acidosis, or vasopressor dependency, the single greatest risk factor for ARDS is high tidal volume, which is also an independent risk factor for mortality [2]. Using a lung-protective strategy in potential organ donors results in a higher number of eligible lung donors and harvested lungs compared with a conventional strategy, but had no effect on the number of harvested hearts, livers, and kidneys [3]. Brain injury increases pulmonary vascular hydrostatic pressure and endothelial permeability and triggers biological mechanisms that either directly render the lung more susceptible to mechanical injury (mechanical ventilation) or act to prime the lung so that additional non-mechanical insults could be relatively more deleterious [1].

On the other hand, lung injury can promote brain damage in patients with otherwise normal neurologic functions through complex network processes involving humoral, neural, and cellular pathways [4]. Mechanical and chemical stimuli can be sensed via mechanoreceptors located in lungs, airway or respiratory muscles or chemoreceptors, respectively, both through the autonomic nervous system [4, 5]. The lungs and brain share inflammatory mediators that when released into the bloodstream can spread to the brain, activating specific central nervous system receptors and influencing every aspect of brain function. The intact brain via an inflammatory reflex of the vagus nerve can balance excessive cytokine production, limiting tissue injury by means of the cholinergic anti-inflammatory pathway [6] (Fig. 1).

Recent reports highlight the remote effects of ventilator-induced lung injury (VILI) in the brain. Fries et al. [7] provided the first evidence for this pathway by comparing pigs with hypoxemia induced by a lavage model of acute lung injury versus pigs with the same degree of hypoxemia induced by a reduction in the fraction of inspired oxygen. Brain damage was greater in the lavage-induced hypoxemia group, suggesting that acute lung injury per se led to neuropathologic changes independent of hypoxemia. Moreover, ARDS has detrimental effects on the brain, acting synergistically with intracranial hypertension to cause hippocampal damage [8]. Since a theoretical biochemical response to excessive deformation of lung tissue might be an important component of VILI, Dos Santos et al. [9] postulated that stimulating the endogenous cholinergic anti-inflammatory pathway might attenuate inflammatory injury. In rats with VILI, inhibiting neural signaling by vagotomy exacerbated lung injury (pulmonary apoptosis), whereas stimulating neural signaling with the vagus mimetic drug semapimod attenuated lung injury, regardless of whether high or low volume ventilation strategies were used. These findings were confirmed in human bronchial epithelial cells, opening the door to electrical or pharmacological stimulation of the efferent vagus nerve to protect against and reduce lung tissue inflammation and apoptosis.

The role of afferent neural pathways in inducing and/or aggravating brain damage is poorly understood. To investigate a potential neuronal response to lung injury, Quilez et al. [10, 11] assessed neuronal activation by measuring the expression of c-fos protein, an early marker of neuronal activation in the brain, in rat models using injurious mechanical ventilation and lipopolysaccharide instillation. Compared with rats ventilated with

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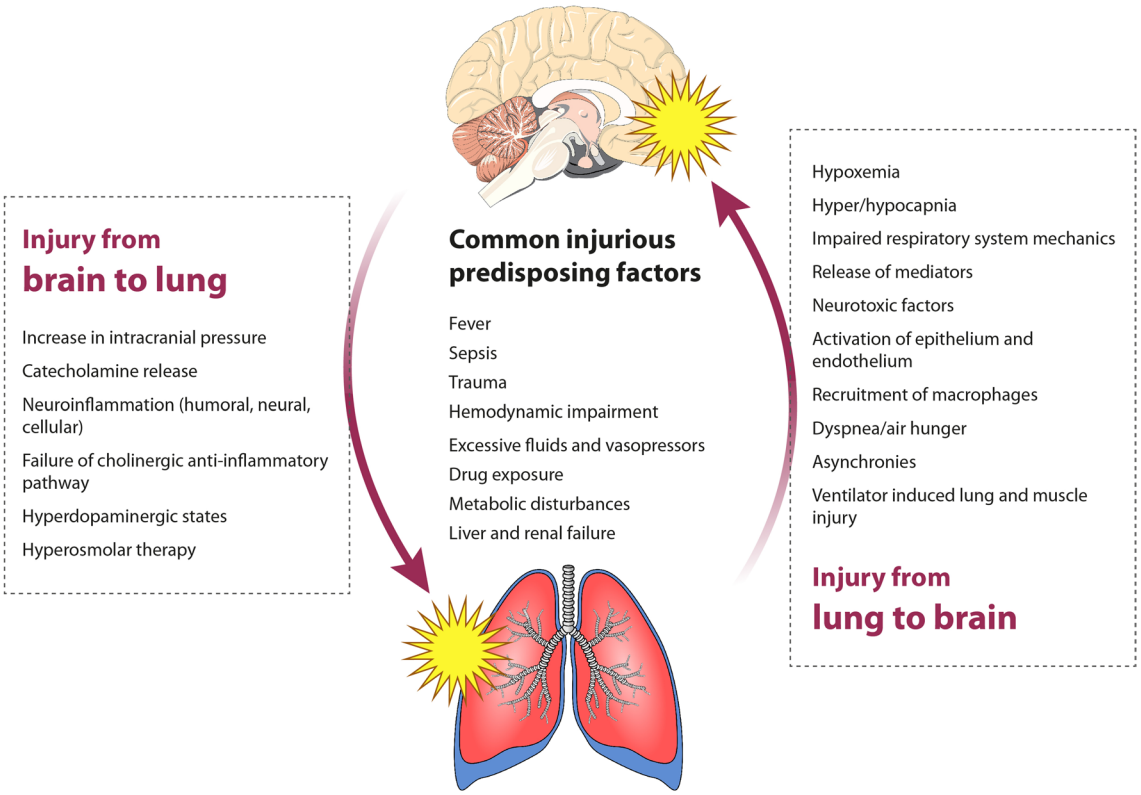

Fig. 1 Predisposing factors, main mechanisms, and tentative hypothesis of bidirectional brain–lung interaction in critically ill patients receiving mechanical ventilation (adapted from Refs. [4–6, 11, 12]). The authors thank Roger Sales for the design of the figure

low tidal volumes, those ventilated with high tidal volumes had increased c-fos expression in the central amygdala, retrosplenial cortex, and thalamus. Interestingly, c-fos expression also increased in the retrosplenial cortex and thalamus in rats under spontaneous ventilation. Of note, in lipopolysaccharide-challenged rats, applying moderate positive end-expiratory pressure (7 cmH_2O) at the same low tidal volume attenuated lung and systemic inflammation and increased c-fos expression in the same brain areas as in rats ventilated with high tidal volume. Whether lung overdistension accounts for this effect warrants further investigations. Since these brain regions are functionally connected to the hippocampus and affect adaptation to stress, memory, and emotions, characterizing the mechanisms that induce these brain alterations could help us develop strategies to prevent cognitive impairment in intensive care survivors. Lastly, González-López et al. [12] found that different degrees of lung stretch from positive-pressure ventilation induced a hyperdopaminergic state in the hippocampus in experimental models, causing apoptosis; this effect was attenuated by vagotomy, systemic haloperidol, or intracerebroventricular raclopride (a type 2 dopamine receptor blocker). Interestingly, they compared brain samples from ventilated and non-ventilated patients and found increased hippocampal dysbindin-1 (a protein that increases to mitigate the detrimental effects of hyperdopaminergia). These studies highlight several mechanisms, none of which are mutually exclusive, that may have implications in the development of innovative therapeutic strategies.

Finally, in patients undergoing mechanical ventilation, interaction with the ventilator induces continuous cross talk between respiratory muscles, lung, and brain when respiratory system-mediated sensations such as anxiety, discomfort, and dyspnea activate different brain structures [4, 13]. Akoumianaki et al. [14] found that the ventilator entrained neural efforts at different ratios in deeply sedated patients with ARDS; they coined the term "reverse-triggered breath" to describe this form of neuromechanical coupling with potentially important clinical consequences. This cross talk between ventilation, respiratory muscles, and brain could have originated as a pure muscular reflex or was produced by slowly adapting stretch receptors responsible for Hering–Breuer reflexes as well as by rapidly adapting receptors and vagal C-fibers, along with cortical and subcortical influences. Given that this type of asynchrony is probably underdiagnosed

and can occur in all modes of mechanical ventilation [15], further research is warranted.

In conclusion, lung–brain cross talk involves more than the simultaneous deterioration of individual organs during the course of disease. Cross talk involves specific pathways that can be triggered by different mechanisms (Fig. 1), even when none of the organs involved is apparently sick. Cross talk has short- and long-term consequences. Understanding cross talk between organs under different conditions can have a profound impact on how we treat critically ill patients.

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Compliance with ethical standards

Conflicts of interest
LB is inventor of a US patent owned by Corporació Sanitaria Parc Taulí: "Method and system for managing related patient parameters provided by a monitoring device," US Patent No. 12/538, 940. LB owns stock options in Better Care S. L., a research and development start-up of Corporació Sanitària Parc Taulí (Spain).

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