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EDITORIAL

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The brain–lung–brain axis

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Severe neurological dysfunction and injury are associated with a propensity to develop concurrent pulmonary edema and lung injury which can further worsen clinical outcomes [1]. This has been observed in a range of settings including traumatic brain injury [2], aneurysmal subarachnoid hemorrhage [3], status epilepticus [4], and in brain death [5]. More recently, studies have shown that critical pulmonary disorders such as acute lung injury and acute respiratory distress syndrome (ALI/ARDS) may be responsible for brain injury and poor neurocognitive outcomes [6, 7]. While the implications of these findings are considerable, the underlying biological mechanisms need clarification.

In this issue of *Intensive Care Medicine*, Heuer et al. [8] use a porcine model to evaluate the independent and combined effects of sustained acute intracranial hypertension (AICH) and experimental ARDS on measures of lung injury and brain damage. They noted that markers of lung injury were augmented with AICH and further rose with concurrent AICH/ARDS. Moreover, measures of cerebral damage were increased in ARDS and even more elevated in combined AICH/ARDS. The study is remarkable if only because of its comprehensive design and the generous array of methods used to assess organ function and tissue injury including physiological measures (intracranial pressure, brain tissue pO_2, heart rate variability, transpulmonary thermodilution), radiological assessments (quantitative brain and lung CT), biological markers (neuron-specific enolase, S100beta, cytokines), and histopathological analysis of lung and brain tissue. To our knowledge, it is one of the first studies to systematically address and quantify the independent and additive effects of neurological and lung injury. Limitations of this work must also be acknowledged. The balloon/AICH model is physiologically remote from traumatic brain injury in which the preponderance of damage is diffuse, not focal, and in which ICP elevations are generally paroxysmal in nature, not constant. Second, the animals were killed after only 4 h, resulting in a loss of valuable information on the natural history of AICH and/or ALI/ARDS in this model. Third, while increased edema was observed in both brain and lung, the available data do not address the underlying physiologic mechanism: was the pulmonary edema hydrostatic or due to increased capillary permeability? Was the brain edema vasogenic or cytotoxic in nature? It has been suggested that pulmonary edema following brain injury is in large part mediated via unbalanced catecholamine release resulting in pulmonary venous constriction and/or left ventricular failure [9, 10]; however, Heuer et al. do not clarify these aspects.

It is becoming increasingly apparent that lung and brain represent an integrated physiological ensemble such that insults involving one will compromise the other and

vice versa. These effects are mediated via a complex web of signaling involving neural, inflammatory, immunologic, and neuroendocrine pathways. The observations of Heuer et al. shed valuable light on this process and raise additional hypotheses which are testable in the experimental and clinical realm. Detailed physiological investigations are needed to explain how pulmonary edema develops following brain injury, specifically teasing out the respective contributions of left ventricle dysfunction, pulmonary venous constriction, and capillary leak or stress failure. Additional work is warranted to determine what are the respective—and potentially synergistic—roles of autonomic dysequilibrium and proinflammatory signaling in this process.

Can one envision interventions to limit pulmonary dysfunction in acute brain injury? Major randomized trials of lung protective mechanical ventilation in ALI/ARDS consistently excluded patients with concurrent neurologic injury on the argument that lung protective settings, such high PEEP and permissive hypercapnia, can compromise intracranial physiology [11, 12]. However, recent research suggests that lung protective ventilatory strategies may be safe and effective in managing concurrent ALI/ARDS and severe brain injury [3, 13, 14]. In an intriguing recent report on organ donors who had suffered catastrophic brain injury, the use of a lung protective strategy was associated with a higher proportion of eligible and harvested lungs compared with a conventional strategy [15]. Taken together, these results suggest there is sufficient equipoise to undertake a randomized clinical trial of lung protective ventilation in patients with severe brain injury provided that $PaCO_2$ is maintained within a normal range.

Research is also needed to elucidate the neurological consequences of ALI/ARDS. These effects seem mediated in part by a hypoxic mechanism but other processes may be at work [6, 7]. A large body of experimental and clinical evidence indicates that sepsis is injurious to the brain through a range of mechanisms [16–18], and results from a large prospective cohort indicated to an association between sepsis and cognitive decline [19]. Given the significant epidemiologic and mechanistic overlap between sepsis and ALI/ARDS, it seems plausible that some of the known effects of sepsis on the brain may be relevant to brain dysfunction encountered in ALI/ARDS. Studies are needed to demonstrate these links, and to determine what specific therapeutic strategies (e.g., enhancement of brain oxygen delivery or decreasing neuroinflammatory signaling) might improve neurologic and cognitive outcomes.

Conflict of interest None.

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