CRITICAL CARE

COMMENTARY

The lung and the brain: a dangerous cross-talk

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See related research by Quilez *et al.*, http://ccforum.com/content/15/3/R124

Abstract

Brain or lung injury or both are frequent causes of admission to intensive care units and are associated with high morbidity and mortality rates. Mechanical ventilation, which is commonly used in the management of these critically ill patients, can induce an inflammatory response, which may be involved in distal organ failure. Thus, there may be a complex cross-talk between the lungs and other organs, including the brain. Interestingly, survivors from acute lung injury/acute respiratory distress syndrome frequently have some cognitive deterioration at hospital discharge. Such neurologic dysfunction might be a secondary marker of injury and the neuroanatomical substrate for downstream impairment of other organs. Brain-lung interactions have received little attention in the literature, but recent evidence suggests that both the lungs and brain can promote inflammation through common mediators. The present commentary discusses the main physiological issues related to brain-lung interactions.

The study by Quilez and colleagues [1] in this issue of *Critical Care* reports morpho-functional and biochemical effects of mechanical ventilation with lower (8 mL/kg) and higher (30 mL/kg) tidal volume (V_T) on lung and brain in healthy rats. Mechanical ventilation may have a serious impact on lung structure and function, leading to ventilator-associated lung injury (VALI) as well as promoting damage of peripheral organs, including the brain. In this respect, mechanical ventilation and sedation in healthy and diseased lungs have been reported to be associated with neurologic impairment, memory, and cognitive dysfunction [2]. On the other hand, brain injury may enhance lung damage in experimental settings [3], probably by promoting a higher rate of pulmonary complications as well as by altering neurologic outcome [4]. Overall, the information in regard to the multiple-pathway cross-talk between the brain and lungs is quite limited [5].

In the study by Quilez and colleagues [1], different variables, including lung function, plasma, and lung levels of cytokines as well as *c-fos* gene, were measured. *c-fos* is a marker of neuronal activation and is correlated with an increase in functional and metabolic activity in the brain, involved in the phenomena of neuronal plasticity, expressed in response to a wide range of stimuli, and implicated in processes such as gene transcription, apoptosis, or proliferation [6]. The main results of the study by Quilez and colleagues can be summarized as follows: (a) independently of higher or lower V_T, mechanical ventilation 'per se' (compared with spontaneous breathing) induced neutrophil infiltration, increased lung damage, and was associated with a greater release of inflammatory markers in both the lung and plasma as well as *c-fos* activation in central amygdala, hippocampus, paraventricular hypothalamic nuclei, and supraoptic nucleus; and (b) higher V_T increased *c-fos* in the retrosplenial cortex and hypotalamus and increased tumor necrosis factor-alpha in the plasma. Therefore, mechanical ventilation promoted brain activation and the intensity of the response was increased with higher V_T, suggesting a cross-talk between the brain and lungs.

Different mechanisms may explain the possible negative effects of mechanical ventilation on the specific anatomical areas of the brain, even in the absence of previous lung disease [7]: (a) release of local pulmonary inflammatory mediators in the bloodstream with activation of brain response and (b) altered regional cerebral perfusion due to increased mean airway pressure, reduced lymphatic drainage, and activation of the autonomic system (Figure 1).

Brain injury-associated pulmonary dysfunction has long been attributed only to a greatly increased sympathetic activity with pulmonary venoconstriction and higher capillary permeability, but a recent study reported the role of systemic inflammatory response with pulmonary infiltration of neutrophils, cytokine release, and endothelial dysfunction triggered by an initial sympathetic

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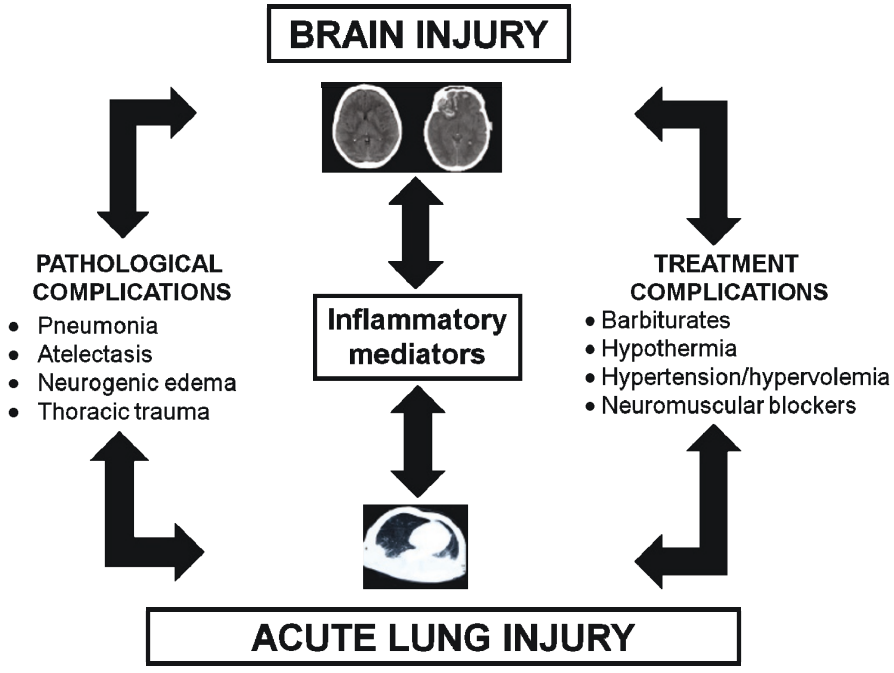

Figure 1. Factors affecting the cross-talk between the brain and the lung.

discharge [8]. A clinical study has shown that, after severe brain injury, higher V_T was associated with increased risk of acute lung injury (ALI) [9]. On the other hand, ALI itself induces a systemic inflammatory response with elevated cytokines and neutrophils as well as a dysfunction of other organs, including the brain [10]. Protective ventilation could be associated not only with less VALI but also with better cerebral oxygenation and perfusion [11]. Heuer and colleagues [3] found that acute intracranial hypertension increased extravascular lung water and increased the amount of poorly aerated tissue in previously healthy lungs without alterations in gas exchange. In experimental ALI, intracranial hypertension worsened pre-existing lung damage and further increased brain edema. Conversely, ALI alone increased the circulating concentrations of the neuronal damage markers (neuronal serum enolase and S100B), but the most severe hippocampal damage was seen in animals with combined ALI and intracranial hypertension. This is in agreement with clinical reports [11,12] and could indicate a reciprocal, synergistic effect of the two conditions.

The study by Quilez and colleagues, despite generating interesting data for the near future, has some limitations. First, small animals were used and thus similar results may not be obtained in larger animals with ALI. Second, rats were ventilated with very high V_T (30 mL/kg, which is equivalent to 2,100 mL in average-sized adult humans) [13]. Third, protective mechanical ventilation was not applied since no positive end-expiratory pressure (PEEP) was used. Therefore, the increase in brain damage and inflammation, even with lower V_T, could have been avoided by using moderate PEEP levels. Fourth, moderate hypercapnia and low pHa in the low V_T group may have affected the results. Also, the duration of the experiment was quite short (3 hours), so that different effects might be observed with longer periods of mechanical ventilation. Lastly, the type of sedation during spontaneous breathing and paralyzing agents during mechanical ventilation may affect lung inflammation [14,15].

In conclusion, recent data from experimental and clinical studies have shown (a) increased evidence of a cross-talk between the brain and lungs and (b) a reduction in VALI as well as brain injury when protective ventilation is adopted. Thus, early detection of VALI, through clinical signs and measurements of extravascular lung water and of brain injury by measuring specific markers, could help to optimize ventilatory settings and even the overall clinical management of critically ill patients.

Abbreviations

ALI, acute lung injury; PEEP, positive end-expiratory pressure; VALI, ventilator-associated lung injury; V_T, tidal volume.

Competing interests

The authors declare that they have no competing interests.

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