The Lung–Brain Axis in Ventilator-induced Brain Injury: Enter IL-6

Neurological dysfunction and delirium may affect up to 80% of patients in the ICU but are frequently underrecognized and underdiagnosed (1). Neurocognitive impairment and even brain structural alterations often persist after ICU release, rendering ICU-associated neurological deficits an important contributor to long-term morbidity and reduced quality of life in critically ill patients that imposes a significant burden on healthcare systems. In addition to psychological factors, including post-traumatic stress, depression, or adverse effects after prolonged sedation, mechanical ventilation has recently emerged as an important contributor to ICU-associated acute and long-term neurological impairment.

Epidemiological studies indicate that intubation and positive-pressure ventilation increase the incidence of delirium in patients in the ICU (2). A direct cause–effect relationship for this association was established in preclinical studies, which found altered neuronal activity in the hippocampus and increased hippocampal apoptosis in mechanically ventilated as compared with spontaneously breathing mice (3, 4). Mechanistically, these effects have been attributed to the activation of lung mechanosensors—namely transient receptor potential vanilloid 4 cation channels and purinergic receptors—triggering a local increase in hippocampal dopaminergic signaling that can be attenuated by vagotomy or type-2 dopamine receptor antagonists (3, 4). Yet, apart from vagal afferents, additional "lung–brain axes" acting via the blood route rather than the autonomic nervous system may independently or synergistically contribute to ventilator-induced brain injury. In particular, circulating inflammatory cytokines represent likely candidates for such interorgan communication.

In an article published in this issue of the *Journal*, Sparrow and colleagues (pp. 403–412) now report a critical role for IL-6 in the induction of neuronal injury by mechanical ventilation (5). In anesthetized mice, ventilation with supraclinical tidal volumes (V_T) of 35 mL/kg body weight induced neuronal apoptosis in frontal and hippocampal brain regions as evidenced by cleaved caspase 3 staining. In the frontal cortex, this was associated with enhanced immunostaining for three key inflammatory cytokines, namely, IL-6, IL-1β, and TNF, as compared with brain sections from spontaneously breathing mice. Importantly, inhibition of IL-6 signaling by intraperitoneal administration of antibodies against either IL-6 or IL-6R (IL-6 receptor) attenuated frontal and hippocampal apoptosis and reduced IL-6 and TNF immunostaining in the frontal cortex as compared with saline treated animals. In summary, these results identify inflammatory signaling via IL-6 as a novel and potentially targetable "lung–brain axis" in the induction of ventilator-induced neuronal injury.

The concept of an IL-6–mediated lung–brain cross-talk in mechanical ventilation is in keeping with a body of data highlighting the release of IL-6 from overventilated lungs and the association of IL-6 with neurological impairment. In their landmark paper that established the biotrauma concept of ventilator-induced lung injury, Tremblay and colleagues demonstrated the release of high levels of IL-6 (along with other cytokines, including IL-1β and TNF) that could be detected in the bronchoalveolar lavage of isolated rat lungs when subjected to injurious ventilation (6). In patients, circulating levels of IL-6 have been directly linked to mechanical ventilation strategies in the 2000 ARDS Network Trial, which demonstrated that lung protective ventilation with V_Ts of 6 mL/kg body weight as compared with conventional V_Ts of 12 mL/kg not only decreased 28 day mortality in acute respiratory distress syndrome patients from 39.8 to 31.0 percent, but also reduced circulating IL-6 levels (7). What is more, high preoperative IL-6 levels have been found to be associated with an increased risk for postoperative delirium in patients $>$ 65 years of age (8). Although IL-6 thus emerges as a likely mediator of ventilation-induced brain injury, several key questions remain.

First, in their study, Sparrow and colleagues observed increased BAL fluid levels of IL-6 and IL-6–mediated brain injury in mice ventilated at a V_T of 35 mL/kg, a finding that is in keeping with a recent study reporting IL-6 release from alveolar macrophages at V_Ts of 35–40 mL/kg (9). In the era of lung protective ventilation, however, clinically delivered V_Ts will rarely exceed 20 mL/kg even when considering that up to two thirds of total lung volume may not participate in mechanical ventilation in critically ill patients (10). Notably, the original biotrauma reported elevated IL-6 levels only in bronchoalveolar lavage fluid of rat lungs rigorously ventilated with excessive V_Ts of 40 mL/kg while IL-6 was virtually undetectable at moderate V_Ts of 15 mL/kg (6). Although data from the ARDS Network Trial cited above indicate that changes in circulating IL-6 levels may occur in patients at lower V_Ts (7), it remains to be shown whether IL-6 levels generated by clinically relevant V_Ts or even under lung protective ventilation will suffice to induce functional or structural neurological deficits.

Second, assuming that IL-6 is generated by activated macrophages, neutrophils, and potentially epithelial cells in overventilated alveoli and circulates to the brain via the blood, where it can be neutralized by systemically delivered anti–IL-6 antibodies, the question arises as to how IL-6 exerts its effect on frontal and hippocampal neurons. By immunohistochemical analyses, Sparrow and colleagues detected prominent IL-6 staining in cortical blood vessels, as well as in the brain parenchyma of overventilated mice. This finding suggests that IL-6 signaling crosses the blood-brain barrier, either by direct penetration of the cytokine or by induction of a local inflammatory response. Indeed, tracer studies of radioactively labeled IL-6 show uptake of blood-derived IL-6 into the brain parenchyma of healthy mice (11), yet whether this is the result of active IL-6 transcytosis or IL-6–mediated barrier failure remains unknown. Alternatively, IL-6 has been shown to induce the expression of adhesion molecules in microvessels of the central nervous system (12), thus

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potentially triggering neuroinflammation and release of *de novo* generated inflammatory cytokines from immune cells invading the brain parenchyma. As such, the exact mechanism of action of lung-derived IL-6 on the brain remains to be elucidated.

Finally, the obvious translational question arises as to whether we should treat or even prevent ventilator-induced brain injury by anti–IL-6 targeting strategies in critically ill patients. Notably, in the present study, Sparrow and colleagues initiated systemic treatment with anti–IL-6 or anti–IL-6R antibodies 2 hours prior to the onset of mechanical ventilation, a setup which—when applied to the clinical scenario—would translate into prophylactic treatment of all patients at risk for mechanical ventilation. Given the considerable side effect profile of anti–IL-6 strategies, including an increased risk for infection, hypertension, or hypersensitivity, such an approach is unlikely to yield a favorable risk/benefit ratio. More importantly, anti–IL-6 strategies may prove to be a double-edged sword given the ambivalent role of IL-6 in overventilation-induced pathologies and neuronal impairment. In that regard, at the brain level IL-6 has been reported to protect from depression, presumably via pleiotropic mechanisms (13), whereas IL-6 deficiency has been linked to increased oxidative stress and neurodegeneration (14). At the lung level, IL-6 neutralization by anti–IL-6 antibodies has been shown to aggravate protein leak in a murine model of ventilator-induced lung injury, a finding that could subsequently be attributed to a protective role of neutrophil-derived IL-6 on alveolar barrier function (15). In view of this Janus-faced character of IL-6 in both ventilator-induced lung and brain injury, extreme caution is warranted and more mechanistic data are needed before implementing IL-6–targeted strategies in critically ill patients. ■

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