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## **Reducing Ventilation Associated Brain Injury by Diaphragm Neurostimulation : Racking the Diaphragm to Protect the Brain?**

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Mechanical ventilation is of paramount importance in improving the survival of patients suffering from respiratory failure, as most recently confirmed by the SARS-CoV-2 pandemic. Notwithstanding, it is well established that mechanical ventilation has unfavorable effects, some of them being likely to worsen the prognosis of the primary disease, for which mechanical ventilation was indicated. Among the harmful effects associated with the use of mechanical ventilation, it has become evident that ventilation in critically-ill patients can augment or cause lung injury, leading to ventilator induced lung injury (1). Therefore, providing a lung protective ventilation – limiting stress and strain – is currently the basis of good clinical practice in critical care settings. However, this approach requires to put the respiratory muscles at rest, which may lead to ventilator-induced diaphragmatic dysfunction (2). Besides ventilator induced lung injury and ventilator-induced diaphragmatic dysfunction, studies have also reported a strong association between the use of mechanical ventilation and delirium in the intensive care unit (ICU) (3) and long term cognitive impairment in acute respiratory distress syndrome survivors, ventilated for prolonged periods (4, 5). The causal association between mechanical ventilation and neuro-cognitive dysfunction is extremely difficult to investigate and multifactorial, encompassing non-modifiable factors such as pre-ICU cognitive impairment, sepsis, acute illness severity and modifiable factors such as use of opiates, benzodiazepines and anticholinergic drugs. In addition, mechanical ventilation generates cyclic alveolar collapse and overstretching, causing local and systemic inflammation (6), potentially leading to neurological injury and ventilator associated brain injury ventilator associated brain injury. The concept of ventilator associated brain injury is supported by several findings confirming hippocampal neuronal cell apoptosis (7), but the long-term impact is still not fully elucidated, also considering the plasticity and regenerative capacity of specific hippocampal regions, such as the dentate gyrus (8). Whether ventilator associated brain injury is mediated through a systemic (hyper)inflammatory or a neural pathway is unclear and further investigations will have to address this point.

Here, Bassi et al. provided thought-provoking insights on ventilator associated brain injury and a novel preventive intervention (9). They used a porcine model to investigate a hybrid strategy of 50-

hour mechanical ventilation, including synchronized diaphragmatic neurostimulation. Neurostimulation of the diaphragm was provided through a catheter, advanced up to the diaphragm through the left subclavian, which stimulated the phrenic nerve to reduce ventilator pressure-time product by 15-20%. The intriguing hypothesis was that a “physiological” mechanical ventilation, generated by the contraction of the diaphragm and a preserved ventilation homogeneity would reduce inflammation and modulate the pulmonary afferent signal, leading to mitigation of cellular apoptosis in the hippocampus. Four interventions were investigated: lung-protective mechanical ventilation, diaphragm neurostimulation either every other breath or every breath in synchrony with lung-protective mechanical ventilation, or finally no ventilation. During the experimental protocol, the investigators applied consistent sedation protocols among all ventilated groups, and therapeutic regimens to control hemodynamics, temperature and gas exchanges. Interestingly, the heart rate variability was used as a surrogate of autonomic nervous system activity. Significant greater apoptotic indices, microglia percentages, and reactive astrocyte percentages were found in the mechanical ventilation group, in comparison to the other groups, suggesting a protective effect of diaphragm neurostimulation on hippocampal injury. In addition, blood biomarkers of brain injury were significantly lower in the group that had every breath in synchrony with lung-protective mechanical ventilation. Yet, systemic markers of inflammation and lung injury scores were similar between the groups, which may imply that hippocampal apoptosis rather than triggered by the inflammatory pathway, was possibly caused by a neuro-pathway of injury.

This study brings to light important new knowledge about pathophysiology of ventilator associated brain injury and a promising therapeutic advance. This study will certainly have further concrete dividends and the authors should be commended for such a complex investigation in animals mechanically ventilated up to 50 hours. Indeed, a main strength of the study was the accurate modelling of settings and interventions routinely applied in critically-ill patients, and the extensive panel of assessments to corroborate the authors’ hypothesis. The rather long use of diaphragmatic

neurostimulation is also reassuring, specifically considering that no major adverse events were recorded.

However, a few important factors should be considered to appropriately infer from these novel findings and extrapolate the evidence to clinical practice. First, the findings highlighted by Bassi et al. suggested association and not causality between mechanical ventilation and brain injury; thus, the mechanistic process of the brain lung interaction remains to be elucidated. Second, the authors reported evidence of hippocampal apoptosis associated with mechanical ventilation, which does not necessarily indicate that in clinical settings this would translate in relevant clinical symptoms, such as delirium or cognitive impairment after 50 hours of mechanical ventilation. Indeed, to distinguish between a permanent loss of cells and a reversible atrophy is pivotal, and it is still uncertain the association between ventilator associated brain injury and long-term neurological disabilities. Further investigations will have to feed the gap between histological data and clinical outcomes in critically ill patients, and in particular should address whether diaphragmatic neurostimulation could exert any benefit in patients on mechanical ventilation with neurological injury, i.e. traumatic brain injury. Although in the study by Bassi et al., insertion through the left subclavian vein ensured optimal bilateral phrenic nerves stimulation, theoretically access through the left jugular vein (a privileged vascular access for clinicians) might provide comparable results. Irrespective, in brain injury patients, potential risk of catheter-related venous thrombosis and intracranial hypertension should be also considered and explored in future investigations. Along the same line, the preliminary nature of these findings should be emphasized, because findings were obtained from a model of mechanical ventilation without lung injury, reservations remain on the benefits in the context of overwhelming lung inflammation. In addition, animals were kept supine horizontal, while mechanically ventilated patients are most commonly in the semi-recumbent position, possibly modifying risks of brain tissue (10). Third, the hemodynamic effect of diaphragm neurostimulation on cerebral perfusion warrant further investigation, specifically in light of some potential inter-species differences in cerebral blood flow auto-regulation that could have overexpressed deleterious effects of mechanical ventilation.

Finally, safety of the novel intervention was marginally appraised by the current investigation, and although no major adverse events were found, long-term stimulation of the phrenic nerve, beyond 50 hours, will be essential to ensure potential translatability into clinical settings.

In conclusion, the study by Bassi et al. undoubtedly provides a significant contribution to the field, introducing new applications of mechanical ventilation -synchronised phrenic nerve stimulation to hinder neurological dysfunction. While acknowledging possible limitations of preclinical tests in animal models of mechanical ventilation, these pioneering results – if confirmed in models of critical illnesses – could provide robust new evidence to be translated into clinical trials.

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