among hospitalized adults identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET). *Clin Infect Dis* 2021;72:e206–e214.
13. Brown RL, Clarke TB. The regulation of host defences to infection by the microbiota. *Immunology* 2017;150:1–6.
14. Wang J, Li F, Sun R, Gao X, Wei H, Li LJ, *et al.* Bacterial colonization dampens influenza-mediated acute lung injury via induction of M2 alveolar macrophages. *Nat Commun* 2013;4:2106.
15. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, *et al.* Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proc Natl Acad Sci USA* 2011;108:5354–5359.
16. Tsang TK, Lee KH, Foxman B, Balmaseda A, Gresh L, Sanchez N, *et al.* Association between the respiratory microbiome and susceptibility to influenza virus infection. *Clin Infect Dis* 2020;71:1195–1203.
17. Chu CY, Qiu X, McCall MN, Wang L, Corbett A, Holden-Wiltse J, *et al.* Airway gene expression correlates of respiratory syncytial virus disease severity and microbiome composition in infants. *J Infect Dis* 2021;223:1639–1649.

Reducing Ventilator-associated Brain Injury by Diaphragm Neurostimulation

Racking the Diaphragm to Protect the Brain?

Mechanical ventilation is of paramount importance in improving the survival of patients suffering from respiratory failure, as most recently confirmed by the severe acute respiratory syndrome coronavirus 2 (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 putting 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 ICU (3) and long-term cognitive impairment in acute respiratory distress syndrome survivors who are ventilated for prolonged periods (4, 5). The causal association between mechanical ventilation and neurocognitive dysfunction is extremely difficult to investigate and multifactorial, encompassing nonmodifiable factors such as pre-ICU cognitive impairment, sepsis, and 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. 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, considering the plasticity and regenerative capacity of specific hippocampal regions, such as the dentate gyrus (8). Whether ventilator-associated brain injury is mediated though a systemic (hyper)inflammatory or a neural pathway is unclear, and further investigations will have to address this point.

In this issue of the *Journal*, Bassi and colleagues (pp. 1391–1402) 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 superior vena cava 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 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. Significantly greater apoptotic indices, microglia percentages, and reactive astrocyte percentages were found in the mechanical ventilation group in comparison with 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 being triggered by the inflammatory pathway, was possibly caused by a neuropathway of injury.

This study brings to light important new knowledge about pathophysiology of ventilator-associated brain injury and a promising

Originally Published in Press as DOI: 10.1164/rccm.202110-2312ED on October 21, 2021

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 modeling 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 and colleagues 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 and colleagues, 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 patients with brain injury, 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 whereas mechanically ventilated patients are most commonly in the semirecumbent position, possibly modifying risks of brain injury (10). Third, the hemodynamic effect of diaphragm neurostimulation on cerebral perfusion warrants further investigation, specifically in light of some potential interspecies differences in cerebral blood flow autoregulation that could have overexpressed deleterious effects of mechanical ventilation. Finally, the 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 and colleagues undoubtedly provides a significant contribution to the field, introducing new applications of mechanical ventilation–synchronized phrenic nerve stimulation to hinder neurological dysfunction. Although 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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Martin Dres, M.D., Ph.D.
Sorbonne Université
UMRS_1158 Neurophysiologie Respiratoire Expérimentale et Clinique
Paris, France

and

Sorbonne Université
Hôpital Pitié-Salpètrière
Paris, France

Gianluigi Li Bassi, M.D., Ph.D.
Critical Care Research Group
The Prince Charles Hospital
Chermside, Queensland, Australia

The University of Queensland
Brisbane, Queensland, Australia

Intensive Care Unit
St Andrew's War Memorial Hospital
Spring Hill, Queensland, Australia

and

Intensive Care Unit
The Wesley Hospital
Auchenflower, Queensland, Australia

ORCID ID: 0000-0001-9191-6089 (M.D.).

References

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2014;370:980.
2. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med* 2004;169:336–341.
3. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, *et al.* Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291:1753–1762.
4. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160:50–56.
5. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, *et al.*; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–1304.
6. Chu EK, Whitehead T, Slutsky AS. Effects of cyclic opening and closing at low- and high-volume ventilation on bronchoalveolar lavage cytokines. *Crit Care Med* 2004;32:168–174.
7. González-López A, López-Alonso I, Aguirre A, Amado-Rodríguez L, Batalla-Solís E, Astudillo A, *et al.* Mechanical ventilation triggers hippocampal apoptosis by vagal and dopaminergic pathways. *Am J Respir Crit Care Med* 2013;188:693–702.
8. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. Functional neurogenesis in the adult hippocampus. *Nature* 2002;415: 1030–1034.
9. Bassi TG, Rohrs EC, Fernandez KC, Ornoswska M, Nicholas M, Gani M, *et al.* Transvenous diaphragm neurostimulation mitigates ventilation-associated brain injury. *Am J Respir Crit Care Med* 2021;204:1391–1402.
10. López-Aguilar J, Bassi GL, Quílez ME, Martí JD, Ranzani OT, Xiol EA, *et al.* Hippocampal damage during mechanical ventilation in trendelenburg position: a secondary analysis of an experimental study on the prevention of ventilator-associated pneumonia. *Shock* 2019;52:75–82.