Finally, as suggested by Jha, alternative mechanisms of injury remain to be investigated, including the role of increased blood flow to the right nonligated lung and possible inflammatory cross-talk between the two lungs. ■

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

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Stimulating Neural Pathways to Reduce Mechanical Ventilation–associated Neurocognitive Dysfunction

To the Editor:

We read the article by Bassi and colleagues with great interest, which provided insightful evidence to reduce ventilation-associated brain injury (VABI) by applying temporary transvenous diaphragm neurostimulation (1). Their innovative neurostimulation approach was based on the idea that diaphragm contraction by preserving lung homogeneity during mechanical ventilation (MV) activates pulmonary stretch receptors and pulmonary afferent signals, leading to the alleviation of VABI. In a porcine model, they demonstrated that diaphragm neurostimulation, synchronized with ventilator-delivered breaths, has neuroprotective effects against VABI. They suggested that VABI is mediated through a neural pathway independent of lung injury and systemic inflammation. Their study provides valuable knowledge about VABI pathophysiology and an innovative therapeutic approach to overcome this problem.

Notwithstanding, physiological breathing compensation could not be fully achieved by phrenic nerve stimulation and triggering diaphragmatic movements alone during MV. Another essential element of physiological ventilation is nasal breathing—the effects of which on the brain during MV need to receive more attention. In this way, another primary function of diaphragm contraction is rhythmically to draw air into the lungs during inspiration, mainly through nasal cavities. In nasal breathing, the airflow activates mechanosensitive olfactory sensory neurons (OSNs) of the nasal epithelium and entrains oscillatory neural activity in the olfactory bulb (OB) (2). Besides processing odorant information, OSNs also respond to mechanical stimulation of airflow passage (2). Rhythmic OB activation by nasal breathing generates respiration-coupled oscillations propagating throughout the cortical and subcortical regions implicated in cognitive functions such as learning and memory (3). Interestingly, nasal breathing diversion to the oral root as well as OB inhibition or OSN ablation abolishes these respiration-entrained brain rhythms, which are subsequently associated with cognitive impairments (3–5). Notably, intubation and tracheotomy obliterate hippocampal respiration-coupled rhythm, which can be restored by rhythmic air-puff delivery into nasal cavities (6). Furthermore, eliminated OB activity (e.g., by interrupting sensory inputs to OSNs or OB deafferentation) can impair the OB-related neurogenesis and induce oxidative and inflammatory conditions, particularly in the hippocampus (7, 8).

Altogether, we presumed that eliminated OB activity and respiratory-coupled oscillations might provoke cognitive dysfunctions observed in patients under prolonged MV. We recently applied rhythmic air-puffs into nasal cavities, synchronized with ventilator-delivered breaths, in endotracheal intubated animals under MV (9). This neurostimulation approach could restore respiration-coupled oscillations in the brain and, importantly, prevent memory impairments that are typically seen after recovery from MV (9). We proposed the rhythmic nasal air-puffs as a noninvasive stimulation approach to reduce or prevent MV-associated adverse neurological events.

Therefore, it seems that stimulating neural pathways of physiological breathing, such as diaphragm and OSNs, synchronized with ventilator-delivered breaths can improve neural homeostasis and notably reduce MV-associated neurocognitive dysfunction. However, manipulating other possible neural pathways needs to be addressed to mimic physiological breathing during MV. These preclinical

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experiments provide novel information for translational approaches in critical settings. Although further studies are required in human subjects, these findings can open a window for our knowledge to reduce neurological dysfunctions in critical patients, particularly those under long-term MV. ■

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Reply to Salimi *et al.*

From the Authors:

Our group greatly appreciated the comments from Salimi and colleagues in a recent letter on our article (1), proposing that the stimulation of neuropathways in conjunction with mechanical ventilation (MV) could result in better cognitive function after MV (1). Salimi and colleagues demonstrated that mice undergoing volume-control MV for 2 hours along with nasal puff synchronized to the breathing cycle had better working memory compared with mice undergoing volume-control MV alone (1). The authors reported that nasal puffs coupled with the respiratory cycle improved neural activity in many areas of the brain, especially the prefrontal cortex and ventral hippocampus (1). Furthermore, the authors stated that the resultant stimulation of the mechanoreceptors in the nasal cavity in synchrony with MV could promote neurogenesis and reduce neuroinflammation, and conversely, the inhibition of olfactory bulb activity has been associated with impaired neurogenesis and greater neuroinflammation (1). Although they concluded that the elimination of olfactory bulb activity might be associated with cognitive impairment after prolonged MV, the authors have not found statistical significance for the effect of nasal puffing on the protective theta and delta oscillations in the olfactory bulb and postulated that this was probably due to the inhibitory GABAergic circuits presented in this area (1). While the effects of nasal puffing on the theta and delta oscillations did not achieve statistical significance, the authors showed that nasal puffing considerably enhanced oscillatory activity in the prefrontal cortex and ventral hippocampus (1). The reported results supported the hypothesis that neural pathways might play an important role in ventilation-associated brain injury (VABI); moreover, VABI might be associated with cognitive impairment.

In addition to investigating a hybrid ventilatory strategy (temporary transvenous diaphragm neurostimulation [TTDN], synchronized to mechanical ventilation) to mitigate VABI, our group evaluated neurogenesis percentage (doublecortin-positive cells divided by doublecortin-positive cells plus doublecortin-negative cells) in the dentate gyrus in four groups, three of which were orally intubated: MV alone, TTDN every other breath plus MV (TTDN50% + MV), TTDN every breath plus MV (TTDN100% + MV), and never ventilated (NV, which were never intubated) (Figure 1). We found that the neurogenesis percentage was not statistically significantly different between the MV, TTDN100% + MV, and NV groups. The TTDN50% + MV group showed a statistically significant difference when compared with the NV group. However, the number of subjects analyzed was only four in the TTDN50% + MV group since we stored four of the eight brains from this group

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