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.

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

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Supported by Lungpacer Medical Inc., Mitacs, and TB Vets. Originally Published in Press as DOI: 10.1164/rcrn.202111-2512LE on January 3, 2022.

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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 neuropeathways 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), 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.
Our data support this hypothesis, showing a statistically significant difference between the TTDN100% + MV and NV groups. As we believe that a different pathway has affected hippocampal neurogenesis in our experiments, it is impossible to show whether nasal puffs would provide further neural protection beyond TTDN because these two therapies might act via two distinct pathways.

Our studies differ in a variety of variables, including, but not limited to, animal model, animal age, duration of experiment, medications used, mock ICU environment, and ventilation strategy. However, it is intriguing to consider that nasal puffs could be added as a supplementary strategy to TTDN for preventing VABI. This would require a larger study size to evaluate, as TTDN in synchrony with lung-protective MV for 50 hours also resulted in improved lung homogeneity, reduced atelectasis formation, and attenuated diaphragm atrophy in addition to the mitigation of VABI (3–7). Nevertheless, the noninvasive nature of providing nasal puffs synchronized to MV makes it an appealing intervention to study.

Although there is increasingly persuasive evidence that VABI exists, there is a need for more translational and functional studies to confirm the clinical impact of this injury. Mechanisms for mitigation of VABI, such as the one we report herein and the one Salimi and colleagues reported, are vitally important to evaluate new avenues to help patients (1, 3). For instance, studies aiming to investigate VABI mitigation in an injured-lung model should be conducted, increasing the generalizability of the findings. While they may be challenging to conduct, new studies could reveal new therapeutic modalities for mechanically ventilated patients since many complications secondary
to MV have been identified in recent years (3–7). Among these complications are ventilation-induced lung injury and ventilation-induced diaphragm dysfunction, and more recently, VABI (3–5, 8, 9). Thus, any new therapy intended to protect patients would also ideally mitigate ventilation-induced lung injury and ventilation-induced diaphragm dysfunction while mitigating VABI. Nevertheless, it is exciting to conceive of a future where ventilation strategies could be not only lung protective but also diaphragm and brain protective.

Despite the many questions that remain to be answered, the investigation of VABI and its mitigation should always be encouraged and congratulated, improving the knowledge in this emerging field.

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

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