189 dyne/s/cm^{-5}). A higher trend in PVR was maintained through 48 hours compared with the ligation group alone. However, the rise in mean arterial pressure after double insults of hypercarbia and PA ligation appears clinically insignificant. This finding is indeed clinically promising for anesthesiologists and critical care physicians managing various cardiac surgeries, noncardiac surgeries, and acute respiratory distress syndrome. Considering the extent of the rise in PA pressure after ligation and hypercarbia in the 5% CO_2 group in this study, a ventilator strategy involving permissive hypercapnia and hypercarbia to avoid volutrauma in acute respiratory distress syndrome appears safe. Furthermore, 5% CO_2 may offer protection from lung damage during PA ligation (pneumonectomy or lobectomy), PA banding, and PA occlusion to facilitate Blalock-Taussig shunt and cavopulmonary anastomosis.

PA ligation is akin to acute thromboembolism, which may lead to a rapid rise in right ventricular load, right ventricular dilatation, and reduction in cardiac output (5). Interestingly, cardiac output rose (4.4 L/min to 5.1 L/min) in the 5% CO_2 group, and therefore ligation and hypercarbia did not seem to produce right ventricular dysfunction until the end of the study. Thus, assessing change in systolic or diastolic right ventricular function compared with baseline after pulmonary artery ligation or hypercarbia could have further provided mechanistic insight.

Finally, the authors have stressed that the diversion of minute ventilation instead of blood flow is responsible for pulmonary edema in the nonligated lung (right lung). Nevertheless, hypercarbia in the 5% CO_2 group produced pulmonary vasoconstriction (PVR = 360 and 352 dyne/s/cm^{-5} at 12 and 24 hours) during the initial phases, which could have prevented the development of pulmonary edema in the right lung. Moreover, in addition to excessive ventilation in producing lung injury, the role of toxic or inflammatory mediators from the ligated hypoxic, anoxic, or infarcted lung in inflicting lung damage to the nonligated lung needs to be investigated. ■

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Ajay Kumar Jha, M.D., D.M.*
Jawaharlal Institute of Postgraduate Medical Education and Research Pondicherry, India

*Corresponding author (e-mail: drajaykjha@rediffmail.com).

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Reply to Jha

From the Authors:

We thank Jha for the insightful comments on our recent experimental study (1). Indeed, the experiment offers food for thought as we are at the very beginning of understanding pathophysiological changes induced by unilateral pulmonary artery ligation (UPAL) and mechanisms of lung protection by inhaled 5% CO_2.

After UPAL, Pa_{CO_2} did not increase, as if the additional experimental dead space did not affect the efficiency of gas exchange. Several pivotal studies on animals (2) and humans (3, 4) already showed that Pa_{CO_2} does not change after unilateral pulmonary artery occlusion, despite little or no increase in minute ventilation. Our and previous findings suggest that a compensatory mechanism, consisting of redistribution of ventilation toward perfused lung regions, maintains the effectiveness of CO_2 clearance, avoiding the increase in wasted ventilation. This might help with understanding the lack of increase in Pa_{CO_2} after UPAL in our experiment. Moreover, decreased total CO_2 production might also have occurred along the course of the experiment and affected the level of Pa_{CO_2} at stable minute ventilation independently from changes in dead space. As inhalation of 5% CO_2 counteracted the compensatory redistribution of ventilation after UPAL, wasted ventilation could have been higher in the ligation + FI_{CO_2} (fractional inspired CO_2) animals and might have contributed to the higher Pa_{CO_2} in this group.

With respect to the comments on the Pa_{CO_2}–end-tidal CO_2 (ET_{CO_2}) gradient, we would like to underline that the latter might have reflected regional alveolar CO_2 rather than the global average level. Indeed, unilateral bronchoconstriction and/or pneumoconstriction might have caused delayed or even incomplete exhalation from the ligated lung, which might have altered ET_{CO_2} values (4, 5), potentially hindering the reliability of the Pa_{CO_2}–ET_{CO_2} gradient to estimate wasted ventilation.

We appreciate the thoughtful comments on changes in pulmonary vascular resistance (PVR). As suggested by Jha, the combination of ligation and hypercapnia induced a relevant increase in PVR in the ligation + FI_{CO_2} group. Nevertheless, this effect tended to be dampened over time, possibly due to renal buffering of respiratory acidosis (6), while the increase in PVR seemed to progress in the ligation group, and we only foresee the development of injury as an underlying mechanism. The effects of inhaled CO_2 on PVR and right heart function in the presence of increased dead space definitely need further assessment before envisioning clinical applications (7).

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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. ■

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Elena Spinelli, M.D.
Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy

Tommaso Mauri, M.D.*
Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy
and
University of Milan
Milan, Italy

*Corresponding author (e-mail: tommaso.mauri@unimi.it).

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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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