when severely depleted neurons continue to activate central mechanisms (5). Although central sensitization has been reported in functional imaging studies in chronic cough in other contexts (1, 6), centrally acting neuromodulator medications were minimally effective in CANVAS-CC in our study. Cough is a vagally mediated phenomenon, and CANVAS is frequently associated with dysautonomia (2), with reports of neuronal loss in vagal nuclei (7). Airway hyperinnervation, reported in chronic cough (8), is unlikely in CANVAS given the known pathophysiology (2). GERD, or late features of CANVAS such as aspiration due to dysphagia, could contribute to cough. However, CANVAS cough usually precedes the onset of dysphagia by decades, and although GERD is common in CANVAS, response to treatment has been poor (9, 10).

Reflecting the rare nature of CANVAS, the sample size was small, with potential selection bias in favor of more severe cough. There was a higher proportion of men in the CANVAS group compared with the RCC and healthy control groups, albeit not statistically significant (Table 1 and Figure 1). Male sex is associated with lower capsaicin CRS compared with female sex (3), so it is unlikely that sex differences were responsible for the heightened CRS in patients with CANVAS-CC. The historical healthy control group used for comparison of capsaicin data was younger than participants with CANVAS-CC and RCC. The association between age and capsaicin CRS was very weak; therefore, this is unlikely to have influenced the interpretation of our findings (3) (Figure 1). Participants with CANVAS had less severe cough compared with those with RCC; the reason for this is unclear. It is possible that some of the differences may have been due to a higher female proportion in the RCC group. Patients with CANVAS without cough were not studied, and *RFC1* genetic testing was not performed in the RCC cohort, potentially overlooking small numbers of undiagnosed CANVAS-spectrum disease (10). However, these limitations should not distort our key findings.

CANVAS-CC is refractory, affects the quality of life, and has features of cough reflex hypersensitivity that are consistent with a neurally mediated etiology of cough. Further studies are needed to elucidate the mechanisms behind CANVAS-CC, which in this genetically determined condition may serve as a useful model to improve the understanding of chronic cough more generally. ■

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Negative Pressure Ventilation Can Prevent Ventilator-associated Brain Injury

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To the Editor:

With interest we have read the papers of Bassi and colleagues, converging in their viewpoint "Ventilator-associated Brain Injury: A New Priority for Research in Mechanical Ventilation," in which they emphasize that ventilator-associated brain injury (VABI) needs urgent attention (1). Therefore, we would like to draw attention to a neglected mechanical ventilation method that will not induce VABI: negative pressure ventilation (NPV) (2). In contrast to

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positive pressure ventilation (PPV), in which supraatmospheric driving pressure is applied to the airway, in NPV, subatmospheric driving pressure is applied around the torso, assisting natural breathing.

Bassi and colleagues (1) defined VABI as *de novo* brain injury directly resulting from PPV. They hypothesized that PPV causes VABI through injurious neurosignaling, activated by mechanical lung stress, and they suggested approaches to mitigate this. We contend in addition that NPV will not cause any lung stress. Also, various secondary injurious factors associated with PPV will not occur with NPV. We therefore anticipate that NPV will mitigate or even prevent VABI.

Neurosignaling

Bassi and colleagues (1) mention that using a high V_T during PPV promotes brain activation, presumably by the overactivation of mechanoreceptors in the lung that communicate directly to the brain stem (3). This causes injury in parts of the forebrain with which it is connected, such as the hippocampus. We suppose that these mechanoreceptor signals are not elicited by the V_T quantity (4) but by increased shear stress in areas of the lung lining the visceral pleura. During natural inspiration, the pleurae are pulled apart: the lung pulls the visceral pleura inward, while the chest wall pulls the parietal pleura outward, thus minimizing friction between the lung and the thoracic wall, letting the lungs expand smoothly. During PPV, the pleurae are pressed together by the supraatmospheric pressure applied in the lung, increasing friction and shear stress in the alveoli lining the visceral pleura. In contrast, NPV helps the thorax pull the pleurae apart, reducing friction between them. Therefore, NPV will not elicit VABI-causing pathological neurosignals.

Neuroinflammation

Preclinical studies with PPV showed elevated inflammatory markers in the lungs, plasma (3), and brain (5). In the brain, these markers might come from direct noxious neurosignaling (4) or via the circulation from systemic inflammatory processes (6). Many aspects of PPV risk peripheral inflammation: pneumonia from intubation and problematic oral and sanitary hygiene. Moreover, PPV often necessitates sedation, risking delirium, which harms the brain. NPV does not entail these risks: intubation is avoided, so consciousness and (limited) mobility are maintained, and activities such as eating, oral hygiene, and toileting remain possible.

Hemodynamics

Hemodynamic effects of PPV might add to VABI. Bassi and colleagues observed that oxygenation was at risk after lengthy PPV (5). Raising the intrathoracic pressure increases the pressure on the heart and blood vessels, hampering cardiac output and venous return to the heart. This also impedes perfusion of the brain, which might add to the injury observed in the brain. In contrast, NPV supports cardiac output and the venous return to the heart and so supports brain perfusion (2).

NPV: A Revived Frontier in Acute Respiratory Failure?

Polio survivors, having used NPV for decades, did not report lung damage or cognitive decline. Therefore, we would like to paraphrase the conclusion of Bassi and colleagues (1), incorporating NPV: NPV might be that brain-protective ventilation strategy that could be a new frontier for alleviating long-term disability and improving the quality of life in patients in need of mechanical ventilation. NPV deserves investigation, not only preclinically and clinically but also in the technical development of torso-only, lightweight, practicable devices (7). ■

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