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Does Lung Protective Ventilation Work in Acute Brain Injury?

The use of lower tidal volume (VT) and titration of positive end expiratory pressure (PEEP) are cornerstones of a lung-protective ventilation strategy, which is consistently linked to better outcomes in a range of patients receiving mechanical ventilation (1, 2). However, evidence is limited regarding the treatment effects in patients with acute brain injuries (ABIs), in whom the expected benefits of protective ventilation must be weighed against concerns of adverse impact on intracranial physiology (3, 4).

The PROLABI (Protect Lung in Acute Brain Injury) trial by Mascia and coworkers (pp. 1123–1131) in this issue of the *Journal* is an attempt to bring much-needed evidence to this issue (5). Between September 2014 and December 2018, patients with ABI enrolled in eight centers in Italy were randomized to lung-protective ventilation (targeting a V_T of 6 ml/kg predicted body weight [PBW] and PEEP of 8 cm H_2O) or conventional ventilation ($V_T \geq 8$ ml/kg PBW and PEEP 4 cm H_2O). The primary outcome was a composite of mortality, ventilator dependence, or acute respiratory distress syndrome (ARDS) at 28 days following randomization. Contrary to the study's primary hypothesis, patients in the protective ventilation group did significantly worse: they incurred a higher incidence of the primary outcome compared with patients in the conventional ventilation group (61.5% vs. 45.3%, respectively; relative risk, 1.35; 95% CI, 1.03–1.79; $P = 0.025$). Mortality and ventilator dependence were higher in the protective ventilation group, whereas the incidence of ARDS was similar. Outcomes at 6 months were also worse in patients who received protective ventilation (relative risk of dying or being in a persistent vegetative state, 1.55; 95% CI, 1.00–2.42; $P = 0.044$). The incidence of most secondary outcomes was not different between groups.

Mascia and coworkers are to be congratulated for completing the first multisite randomized controlled trial of lung-protective ventilation in the ABI population. The study was initiated more than 10 years ago, and the culmination of that effort in the face of slow recruitment and funding challenges is itself a remarkable accomplishment. Strengths of PROLABI include high levels of adherence to the assigned treatment strategy, use of V_T and PEEP in the treatment and control arms that represented the standards of care when the trial was designed (6), control of Pa_{CO_2} and Pa_{O_2} that were largely within guideline-recommended targets (7), and availability of primary outcome data for all randomized patients. Long-term neurologic function was included as a key patient-centered secondary outcome and was assessed blinded to treatment strategy.

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Nevertheless, several important caveats merit discussion. Disappointingly, the study lacks statistical power to detect a true difference between groups. Intended accrual was 524 patients based on a sample size calculated to identify a 40% difference in the incidence of the primary outcome, but the trial was halted at 190 subjects (36% of the target) as a result of the cessation of funding. The risk of type II error with underpowered trials is well understood and acknowledged by the authors. However, underpowered trials are also subject to type I error, whereby the detection of an effect might be due to random variability in the data. Because "significant" effects arising from smaller samples have a tendency to regress toward the mean as more patients are enrolled (8), it is possible that further accrual of participants would have shown no difference between ventilation strategies. In this context, the authors are appropriately cautious in inferring that lung-protective ventilation did not reduce the primary endpoint, rather than concluding that lung protective ventilation was "worse" than the control strategy, which would be misleading.

Another caveat is the robustness of results. The fragility index in this trial is 2, meaning that, if the outcomes of two participants in the treatment or control arm had been switched, the results of the trial would lose statistical significance (9). This is relevant considering that one of the components of the composite primary outcome was development of ARDS, for which the chance-corrected coefficient of agreement between two assessors to detect bilateral infiltrates was only 0.64, with a lower 95% CI limit of 0.36. In other words, misclassification of a small number of patients with ARDS could be sufficient to explain the study's findings independent of any effect of the treatment strategy.

Moreover, the reported clinical differences between groups seem at odds with the wide discrepancy in clinical outcomes. For instance, the mean daily Pa_{CO_2} was approximately 2 mm Hg higher in the protective ventilation group and the average daily PEEP was only 2–3 cm H_2O higher. The investigators postulate that these differences, albeit small, could have had clinically relevant intracranial effects in the treatment group. If this were true, we might expect a significant difference in intracranial pressure (ICP), but the mean daily ICP was $<$2 mm Hg higher in the lung-protective ventilation arm. In addition, the between-group mean difference in V_T was $<$2 ml/kg PBW, and the driving pressure and plateau pressure in both arms were within conventional lung-protective targets (10). It is argued that these once-daily recordings might not have been representative of the true daily data trends, but it seems implausible that more densely sampled data would reveal differences sufficient to explain the outcome disparities. For example, in a recent single-center clinical trial conducted in patients with ABI, the Pa_{CO_2} difference between lung-protective and control groups as derived using highly granular time-series data was $<$2 mm Hg (similar to the study of Mascia and coworkers), with minimal effect on ICP in the majority of patients (11).

Can we explain these counterintuitive results by the existence of unmeasured or undetected imbalances in baseline, acute illness–specific, or even treatment characteristics between the two groups? For example, there is no reported data on sedation practices and neuromuscular blocker use, which could have been imbalanced between groups (e.g., higher in the intervention group because of the greater need to attenuate respiratory drive and mitigate asynchrony in patients with ABI receiving lower V_T) (12, 13). There is also no description of prehospital insults (e.g., hypoxia or hypotension), which have important implications for clinical outcomes in this population (14). Moreover, mechanical ventilation and other key data elements were not reported beyond Day 6, yet the mean duration of ventilation was 18 and 19 days in the protective and control groups, respectively, and survival curves appear to separate at Day 8, during an apparently critical period during which no data are available.

Although the insights gained from PROLABI are valuable, high-level evidence to guide the delivery and optimization of ventilation in patients with ABI remains frustratingly elusive (3). An international expert panel recently proposed a detailed scientific agenda to resolve this issue (7), yet there are likely to be challenges in successfully completing large-scale randomized controlled trials with "conventional" ventilation arms, as available research suggests that protective ventilation is safe in this population (4) and may already be widely implemented (6, 15). At a higher level, research on mechanical ventilation in neurological patients may benefit from a mechanistic exploration of the so-called lung–brain axis, in particular an emerging body of investigation suggesting a biologic sequence connecting nonprotective ventilation, ventilator-induced lung injury, afferent neural signaling, systemic proinflammatory signaling, neuroinflammation, and neuronal cell death, a pathway referred to as "ventilator-induced brain injury" or "ventilator-associated brain injury" (16, 17). If such findings are generalizable, the use of the appropriate ventilation strategy might in fact be both lung- and brain-protective (17). To explore this, focused trials could be envisioned using biomarker-driven adaptive design strategies. ■

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Imaging the Intersection of Parenchymal Abnormalities and Pulmonary Vascular Pathways

In patients with pulmonary hypertension (PH), mild elevations in pulmonary arterial pressure and resistance have been shown to significantly associate with increased mortality (1). In the setting of chronic lung disease, PH is a common complication that significantly associates with mortality but to varying degrees, depending on the underlying lung disease, including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and interstitial lung disease (2). The pulmonary vascular bed is normally a highly compliant system that requires at least 50% of the pulmonary vasculature to be obstructed to appreciate an increase in pulmonary arterial pressure (3). So, although there is a growing appreciation for pulmonary vasculopathy beginning early in lung diseases, there need to be significant vascular abnormalities for pulmonary pressure to reach current hemodynamic thresholds for PH (4). Patients with early signs of interstitial abnormalities already exhibit a decrease in exercise capacity and an increase in shortness of breath (5). Noninvasive computed tomography (CT) provides an opportunity to quantitatively assess the parenchymal and pulmonary vascular structures at the same time.

The group at Brigham and Women's Hospital have pioneered the computational and analytical methods to quantitatively assess interstitial lung abnormalities, pulmonary arterial vasculature, and the right and left ventricular volumes from thin-slice chest CT (6–8). In their chest imaging platform, they developed and trained an automated method to detect radiographic features in CT images that associate with interstitial subtypes (reticulations, honeycombing, centrilobular nodules, linear scar, nodular changes, subpleural line, and ground glass) or emphysema subtypes (centrilobular, paraseptal) (Figure 1A). The proportion of interstitial features is termed the "quantitative interstitial abnormalities" (QIA). Using the same images, they can reconstruct the pulmonary vasculature to quantify clinically meaningful cardiopulmonary features, including blood volume in the preacinar arteries (aBV5-20/TBV), smaller distal vessels (aBV5/TBV), and ventricular volumes (Figure 1A). Comparisons of the blood volumes in smaller arteries with cross-sectional areas <5 mm^2 to intermediate-sized vessels >10 mm^2 is becoming more protocolized to characterize clinical vascular remodeling from CT imaging (9).

In this issue of the *Journal*, Harder and colleagues (pp. 1132–1142) used causal mediation analysis to determine that 6-minute-walk distance (6MWD) and the modified Medical Research Council dyspnea scale score are partially mediated by dilation in the preacinar arteries in ever-smokers from the Genetic Epidemiology of COPD (COPDGene) study cohort ($n = 8{,}200$) (10). To do this, they used radiographic features of QIA and three CT-based vascular measures and right heart metrics, including the ratio of the right/left ventricular volumes (RV/LV ratio), the pulmonary artery to aorta ratio (PA/Ao ratio), and the preacinar arterial blood volume (aBV5-20/TBV, PA volume 5–20 mm^2/total arterial volume cross-sectional area) (Figure 1B). The cohort had a median QIA burden of 4.67 (2.99–7.48%) with a median 6MWD of 425 [343–496] meters. They found that the QIA percentage correlated with decreased exercise capacity where a 1% increase in QIA was associated with a

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