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Perspective

How much tidal volume is sufficiently low to be called “protective lung ventilation”

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Since the success of ARMA study in 2000, small tidal volume (Vt, 4–8 mL/ predicted body weight [PBW]) is recommended in acute respiratory distress syndrome (ARDS) guidelines.[1,2] The ultra-protective strategy, further reducing Vt to 3–4 mL/PBW with/without extracorporeal carbon dioxide removal ($ECCO_2R$) with the aim to reduce the excess tidal lung strain and stress, is an appealing alternative for severe ARDS patients. In the last issue of *Lancet Respir Med*, Richard et al.[3] reported the results of Vt 4 mL/ PBW for coronavirus disease 2019 (COVID-19) pneumonia (VT4COVID) study, which demonstrated that in moderate-to-severe COVID-19-related ARDS patients, ultra-low Vt (ULT, 4 mL/PBW) without $ECCO_2R$ did not improve mortality and ventilator-free days at day 60 compared with the standard low Vt (LTV, 6 mL/PBW). Even in the per-protocol analysis including 63% and 86% patients successfully completing the ULT and LTV strategy respectively, ULT did not show superiority over LTV on mortality and ventilator-free days.

There are several factors to be considered before drawing a definite conclusion about the ULT strategy in severe ARDS. First, despite the significant low partial pressure of oxygen (PaO_2) /fraction of inspired oxygen (FiO_2) ratio at baseline in VT4COVID study (median 99 mmHg and 106 mmHg in ULT and LTV groups, respectively), median plateau pressure and driving pressure at baseline were 22 cmH_2O and 11 cmH_2O respectively, below the dangerous threshold (28–30 cmH_2O and 15 cmH_2O) and not as much high as the corresponding data in clinical research about extracorporeal life support for ARDS including REST[4], Xtravent,[5] and EOLIA study.[6] The dissociation between relatively preserved lung mechanics and the severity of hypoxemia is possibly due to high ventilation/perfusion mismatch and loss of hypoxic pulmonary vasoconstriction, which exists in the early phase of COVID-19-related ARDS [7,8] and non-COVID-19 ARDS.[9] Furthermore, despite the PaO_2/FiO_2 ratio is the most common variable to classify ARDS severity as shown in ARDS Berlin definition, PaO_2/FiO_2 ratio is influenced by many factors, for example, FiO_2, positive end-expiratory pressure (PEEP), cardiac output, etc.[10] The accuracy of PaO_2/FiO_2 ratio for reflecting ARDS severity would improve greatly if determined at standard mechanical ventilator parameters (PEEP and FiO_2) or combined with measured airway pressures (mean airway pressure). The reduced compliance of respiratory system at baseline in VT4COVID study was partly attributed to high body mass index (median value 29–30 kg/m^2). Second, the benefit effects of ULT on plateau pressure and driving pressure were marginal in VT4COVID study (the mean difference between the two groups were only 0.8 cmH_2O and 1.7 cmH_2O, respectively). In a secondary analysis from five randomized trials of comparing higher vs. lower Vt ventilation in ARDS patients, the possibility of mortality benefit from lower Vt ventilation was low when driving pressure was <15 cmH_2O (on the contrary maybe harmful).[11] Hence, because of preserved lung mechanics, the included patients in VT4COVID study were not all the candidates who may benefit from ULT strategy. Third, although mechanical power was significantly reduced after implementing ULT strategy in VT4COVID study, the magnitude was not large enough to translate into mortality benefit possibly due to the obvious respiratory rate increase aiming to keep partial pressure of arterial carbon dioxide ($PaCO_2$) and acid-base state at an acceptable level. From the view of ventilator induced lung injury energetics, driving pressure and respiratory rates are the two most important ventilator variables associated with mortality in patients with ARDS.[12] 4DPRR index (driving pressure multiplied by four plus respiratory rate), a simple model of mechanical power, demonstrates the complex seesaw relationship between driving pressure and respiratory rates to maintain $PaCO_2$ stability.[12] In VT4COVID study, the compen-

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satory increase of the respiratory rate might blunt the protective effect of ULT strategy in moderate-to-severe COVID-19-related ARDS patients.

In conclusion, the results of VT4COVID study provided the important insights of ULT strategy without $ECCOR_2$ in moderate-to-severe COVID-19-related ARDS patients. In ARDS patients with preserved lung mechanics demonstrating low plateau pressure and driving pressure, ULT strategy without $ECCOR_2$ may not be a "Less is More" method in mechanical ventilation.

Author Contributions

Rui Tang: Writing – review & editing, Writing – original draft, Validation, Writing – review & editing, Writing – original draft, Visualization, Validation. **Min Zhou:** Validation, Supervision, Validation, Supervision.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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