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EDITORIAL

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From protective ventilation to super-protective ventilation for acute respiratory distress syndrome

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For a long time, critical care physicians understood that positive pressure mechanical ventilation was a life-saving strategy in patients with acute respiratory failure, especially in patients with acute respiratory distress syndrome, originally described in 1967 [1]. However, the harmful effects of the traditional use of higher tidal volumes and higher airway pressures were not recognized until more than 30 years later when the beneficial effects of ventilation with a lower tidal volume (6 ml/kg predicted body weight, PBW) and a plateau airway pressure <30 cmH_2O were established in the landmark NHLBI ARDS Network trial in 2000 [2]. Some clinicians and investigators were slow to accept these findings, but subsequent trials and a meta-analysis convincingly confirmed the reduction in mortality by using lung-protective ventilator settings in patients with ARDS [3]. Currently, lung protective ventilation is considered standard of care for ARDS [4–6].

Is use of tidal volumes of 6 ml/kg PBW the only way to protect the lungs of ventilated patients? The answer is no. First, an important approach to protect the lungs of ventilated patients from the hazardous effects of ventilation is to reduce the total duration of positive pressure ventilation. Individualized sedation management using sedation assessment tools [7], weaning protocols [8], as well as restrictive fluid strategies [9] all can shorten duration of ventilation, and as such must be considered lung-protective as well. Second, if hyperinflation plays a role in the pathogenesis of ventilator-associated lung injury [10], then one may wonder whether lower tidal volumes of 6 ml/kg PBW is low enough. An experimental study of lung injury in rats reported that 3 ml/kg tidal volume was superior to 6 ml/kg in reducing alveolar epithelial injury and the degree of pulmonary edema as well as enhancing the rate of alveolar edema fluid clearance [11]. Clinically, Terragni and colleagues [12] found that tidal hyperinflation still occurs in one-third of patients with ARDS who are ventilated with tidal volumes of 6 ml/kg PBW. Thus, very low tidal volumes may be superior to the standard lower tidal volumes. With very low tidal volumes the plateau airway pressure will be lower, and lower plateau airway pressures are associated with a further reduction in ventilator associated lung injury [13].

Use of very low tidal volumes may be difficult since such low tidal volumes could result in potentially dangerously elevated $PaCO_2$ levels and a markedly decreased pH. One possible solution is the use of extracorporal, pumpless arterio-venous CO_2-removal, a technique that has become increasingly available and safer over the last decade. In this issue of *Intensive Care Medicine*, Bein et al. [14] report on the first randomized controlled trial with the use of ECCO2R, in which 79 patients with ARDS were randomized to a very low tidal volume

ventilation strategy (~3 ml/kg PBW) combined with ECCO2R, or to lower tidal volume ventilation (~6 ml/kg PBW) without the extracorporeal device. They report that ventilation with very low tidal volumes was feasible, safe and easy to implement with ECCO2R. Nevertheless, the number of ventilator-free days at day 60 (33 ± 20 vs. 29 ± 21 days) and mortality rates (18 vs. 15 %) were not significantly different between the two study groups. However, in a post hoc analysis, a lower number of ventilator-free days at 60 days was found in patients with severe hypoxemia (40 ± 13 vs. 28 ± 16 days, $P = 0.033$).

The results of the trial by Bein et al. are in line with findings from a small non-randomized trial of patients with ARDS [15]. In that trial, ECCO2R normalized $PaCO_2$ and pH, and made it possible to use a tidal volume less than 6 ml/kg PBW. More importantly, use of ECCO2R was associated with decreased levels of biological markers of lung injury. The results of this trial follow up on previous findings in observational studies in ARDS patients, in which use of ECCO2R facilitated the use of a lower minute volume ventilation to maintain adequate gas exchange [16, 17].

Unfortunately, the trial by Bein et al. was underpowered, at least in part because the DSMB decided to stop the trial after 3 years. Indeed, as the authors themselves state that the power calculation indicated that 106 patients would be needed to test the hypothesis that a very low tidal volume strategy with use of ECCO2R would increase the number of ventilator-free days. Alternatively, the investigators may have been too optimistic about the potential effects of very low tidal volume ventilation in the patient group studied. The post hoc analysis, however, importantly aids in determining the optimal indications for the use of ECCO2R and for the design of future trials. The suggestion that more severely hypoxemic ARDS patients may benefit from ECCO2R should stimulate a new trial in patients with more severe ARDS. Certainly, it could be that interventions have a better risk–benefit profile in more severely ill patients, such as suggested in a meta-analysis of studies on proning [18]. However, due to the limited blood flow, arterio-venous ECCO2R as used in the study by Bein et al. has a limited ability to correct arterial hypoxemia. A pumped veno-venous system may be more suitable to answering the research question whether super-protective ventilation can improve outcome in severe ARDS.

An important strength of this study is that it was performed in ten centers and the incidence of adverse events was low, suggesting that use of ECCO2R may be initiated without the need of specialized centers. This finding is promising for the design of new multicenter trials, with larger numbers of patients. Because ECCO2R is an expensive intervention, future trials should include an economic assessment of health care costs as well as clinical outcomes.

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