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SCIENTIFIC LETTER

Digital twins to analyse lung injury indices produced by a new protocol for transitioning to airway pressure release ventilation

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Dear Editor,
Airway pressure release ventilation (APRV) is a mechanical ventilation strategy that applies continuous positive airway pressure for increased inspiration periods followed by time-cycled pressure releases to achieve carbon dioxide clearance [1]. Although it is available on most mechanical ventilators, the clinical utility of APRV is still the subject of debate. Benefits attributed to APRV include improved alveolar recruitment and oxygenation, but the lack of standardized guidelines for its implementation may be contributing to the uncertainty around its use [2]. Nieman et al. [3] recently proposed a new protocol for transitioning from standard ventilator modes to APRV based on consensus expert recommendations informed by clinical experience and scientific evidence. The authors proposed that the protocol may have the potential to stabilize and homogenize the lung by reducing repetitive alveolar collapse and expansion (RACE)-induced atelectrauma.

Here, we aimed to investigate the potential impact of the proposed protocol on a range of ventilator-induced lung injury (VILI) indicators compared with current common practice, using digital twins matched to data from a cohort of 98 patients with acute respiratory distress syndrome receiving PCV under full sedation with no spontaneous respiratory efforts [4]. Comparisons of the digital twin outputs with patient measurements are shown in Figure S4.1 in the SM. The mean absolute percentage errors over the cohort between patient data and digital twin outputs were 0.26% for PaO_2, 0.75% for $PaCO_2$ and 1.68% for tidal volume (V_T). In the digital twins, the maximum and minimum lung pressures were used as surrogates for plateau pressure (P_{plat}) and end-expiratory lung pressure (EELP), respectively, to ensure an accurate representation of lung pressure during APRV (see SM for details).

The protocol proposed in [3] for transitioning from pressure control ventilation (PCV) to APRV was implemented in each digital twin as follows. The upper airway pressure (P_{high}) was initially set equal to the PCV peak inspiratory pressure (PIP), lower airway pressure (P_{low}) was set to 0, and inspiratory time (T_{high}) was set to match the respiratory rate from PCV. Expiratory time (T_{low}) was set to terminate when expiratory flow is 75% of the peak, and then T_{high} was re-adjusted to match the PCV minute ventilation. If V_T was less than 4 ml/kg, P_{high} was increased in steps of 2 cmH_2O until V_T exceeded 5 ml/kg, and if respiratory acidosis was present (pH $<$ 7.35), T_{high} was reduced in steps of 0.1 s (down to a minimum of 1.5 s)—see the flow chart in Figure S5.1 of the SM. For the purposes of comparison, the most popular settings for APRV reported in a recent survey of clinical practice [2] were also tested (referred to below as "common APRV"). This consists of setting P_{high} equal to 25 cmH_2O, P_{low} to 0, T_{high} to 5 s and T_{low} to terminate when expiratory flow is 75% of the peak.

Results of the simulations (Fig. 1) show that the proposed protocol reduced the mean percentage of alveolar units undergoing tidal de-recruitment by 41.6% compared to baseline PCV (from 7.3 to 4.3%), whereas the common APRV settings produced a 34.1% decrease (to 4.8%). In the protocol, T_{high} is readjusted to match PCV minute ventilation, and additional adjustments

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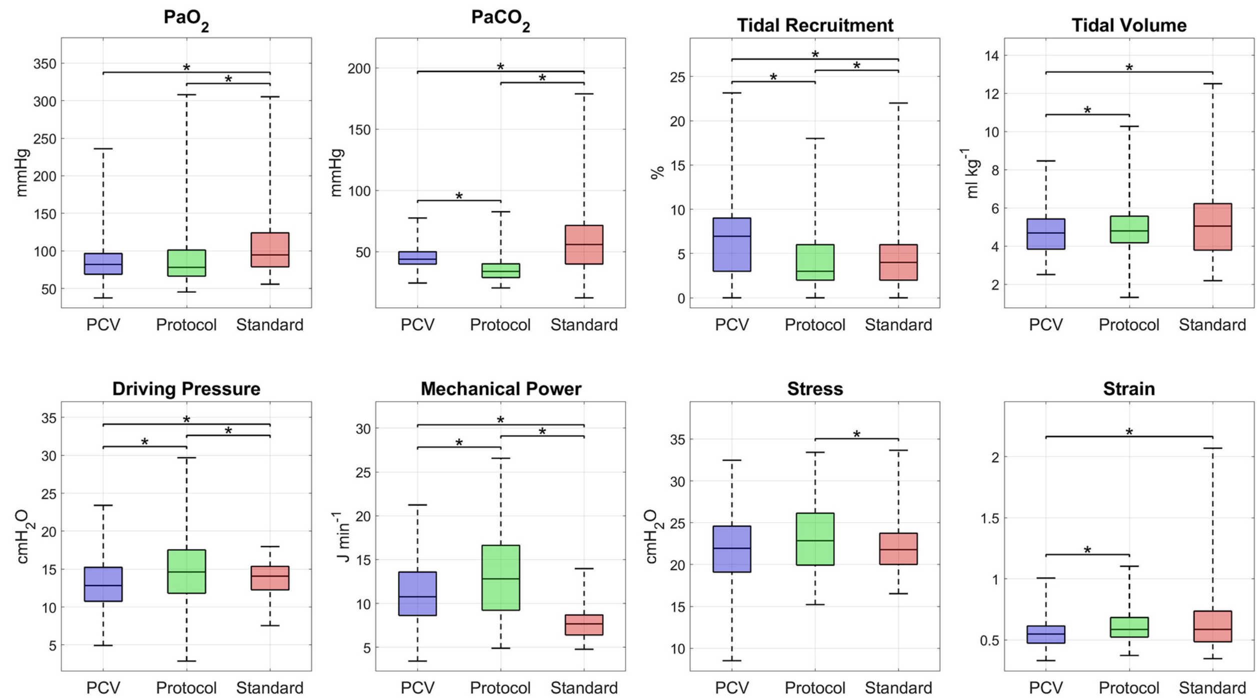

Fig. 1 Box-whisker plots (median, interquartile range and range) of the effects of PCV (blue), the proposed APRV protocol (green) and the "common" APRV settings from [2] (red) on gas-exchange, lung mechanics and VILI indicators. The statistical significance of the difference between strategies was tested using the Wilcoxon signed-rank test, with * indicating statistical significance ($p < 0.05$)

are applied as pH falls below 7.35 (down to Thigh 1.5 s). This allowed mean $PaCO_2$ to be decreased by 21.6% in the protocol group compared to baseline PCV, from 45.6 to 35.8 mmHg, whereas the common APRV settings increased $PaCO_2$ by 28.3–58.5 mmHg. Mean driving pressure increased by 10.5% from baseline in the protocol group (13.2–14.6 cmH_2O) compared to a 4.4% increase with the common APRV settings (to 13.8 cmH_2O). Mean mechanical power increased by 17.9% from PCV in the protocol group (11.4–13.4 J min^{-1}) compared to a 31.4% decrease in the common APRV group (to 7.8 J min^{-1}). Mean dynamic strain increased by 7.1% from PCV in the protocol group (0.28–0.3) compared to a 10.7% increase in the common APRV group (0.31). Full results including other VILI indices are presented in Table S5.2 of the SM.

In a recent study, Gaver et al. [5] produced evidence suggesting that RACE, while accounting for only a small fraction of total energy dissipation during mechanical ventilation, is (a) especially damaging due to the large effect on a small area of the lung, and (b) the only energy dissipation component of mechanical ventilation correlated with recovery. Our results suggest that the protocol for transitioning to APRV proposed in [3] reduces RACE compared to both common PCV and APRV settings, helping to stabilize and homogenize the lung. Once this "transition phase" has been successfully completed, adjustment of P_{high} and T_{high} in an "optimisation phase" needs to be performed to reduce driving pressure and mechanical power and avoid the risk of overdistension and/or hemodynamic compromise. Further research is needed on how best this can be achieved, on the effects of APRV on patients' hemodynamic status and cardiac output, and on the effects of APRV on patient effort synchronisation.

Several variations to the protocol were tested in the digital twins to investigate its optimality (see Sect. 5 of the SM). Maintaining P_{high} by accepting $V_T < 4$ ml/kg further reduced mean tidal de-recruitment, lung stress and strain compared to the protocol, but at the cost of lower total recruitment and oxygenation. Full results are presented in Table S5.2 of the SM.

Our results suggest that a recently proposed protocol for transitioning to APRV reduces RACE compared to common PCV and APRV settings, potentially leading to more protective mechanical ventilation, and motivating prospective clinical trials of this new ventilation strategy.

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Declarations

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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