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Original Research Article

ORIGINAL RESEARCH ARTICLE

Variable positive end-expiratory pressure in an experimental model of acute respiratory distress syndrome: an advanced ventilation modality

Roberta Südy[1], John Diaper[1], Davide Bizzotto[2], Rafaelle Dellàca[2], Ferenc Petak[3], Walid Habre[1] and Andre Dos Santos Rocha[1,4,*]

[1]Unit for Anaesthesiological Investigations, Department of Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, University of Geneva, Geneva, Switzerland, [2]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy, [3]Department of Medical Physics and Informatics, University of Szeged, Szeged, Hungary and [4]Department of Anaesthesia, North Lisbon University Hospital Centre, Lisbon, Portugal

*Corresponding author. Unit for Anaesthesiological Investigations, Department of Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, University of Geneva, Geneva, Switzerland. E-mail: andrerocha@medicina.ulisboa.pt

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Abstract

Background: Introducing variability in tidal volume, ventilatory frequency, or both is beneficial during mechanical ventilation in acute respiratory distress syndrome (ARDS). We investigated whether applying cycle-by-cycle variability in the positive end-expiratory pressure (PEEP) exerts beneficial effect on lung function in a model of ARDS.

Methods: Rabbits with lung injury were randomly allocated to receive mechanical ventilation for 6 h by applying a pressure-controlled mode with constant PEEP of 7 cm H_2O (PC group: n=6) or variable PEEP (VEEP) with a coefficient of variation of 21.4%, range 4–10 cm H_2O (PC-VEEP group; n=6). Lung oxygenation index (Pa_{O_2}/FiO_2) after 6 h of ventilation (H6) was the primary outcome and respiratory mechanics, lung volume, intrapulmonary shunt, and lung inflammatory markers were secondary outcomes.

Results: After lung injury, both groups presented moderate-to-severe ARDS (Pa_{O_2}/FiO_2 <27 kPa). The Pa_{O_2}/FiO_2 was significantly higher in the PC-VEEP group than in the PC group at H6 (12.3 [SD 3.5] *vs* 19.2 [7.2] kPa, P=0.013) and a lower arterial partial pressure of CO_2 at 1–3 h (P<0.02). The ventilation-induced increases in airway resistance and tissue elastance were prevented by PC-VEEP. There was no evidence for a difference in minute volume, driving pressure, end-tidal CO_2, lung volumes, intrapulmonary shunt fraction, and cytokines between the ventilation modes.

Conclusions: Prolonged mechanical ventilation with cycle-by-cycle VEEP prevents deterioration in gas exchange and respiratory mechanics in a model of ARDS, suggesting the benefit of this novel ventilation strategy to optimise gas exchange without increasing driving pressure and lung overdistension.

Keywords: gas exchange; lung function; lung oxygenation index; variable ventilation; ventilator-induced lung injury

The physiological benefits of variable ventilation (VV), a mode that applies breath-by-breath variability to reproduce the natural variation of spontaneous breathing, have been demonstrated in healthy and injured lungs.[1–12] The deterioration of lung structure and function that is observed during conventional ventilation (pressure- or volume-controlled) was prevented by the application of VV in animal models with healthy lungs[1,10,12] and diseased lungs with

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acute respiratory distress syndrome (ARDS),[2,4,9] asthma,[7] chronic obstructive pulmonary disease,[6] and pulmonary fibrosis.[5] These experimental findings were corroborated by two clinical trials using VV in humans with healthy lungs and ARDS, demonstrating improved oxygenation, respiratory compliance, and lower ventilation deadspace.[3,8] The advantages of VV stem from the fact that breath-by-breath variations in tidal volume (V_T), ventilatory frequency (VF), or both improve gas exchange, respiratory mechanics, and alveolar recruitment while reducing shear stress and inflammation[1–12] as a result of the non-linear properties of the respiratory system.[13] Furthermore, VV is also beneficial for the ventilation–perfusion matching and surfactant production.[14]

Previous studies of VV were based on variations of only V_T, VF, or both while maintaining the positive end-expiratory pressure (PEEP) constant. However, it has been well established that PEEP is of paramount to optimise gas exchange in protective ventilation strategies, particularly in the presence of ARDS.[15,16] Therefore, we hypothesised that an advanced ventilation strategy characterised by cycle-by-cycle variability in PEEP can offer advantages in gas exchange and respiratory function compared with conventional, constant PEEP. To test this hypothesis, we compared the effects of variable PEEP (PC-VEEP) with those of constant PEEP (PC) over a 6-h period of conventional pressure-controlled ventilation in a rabbit model of ARDS.

Methods

Ethical statement

The study was approved by the Animal Welfare Committee of the Canton of Geneva and the Experimental Ethics Committee of the University of Geneva, Switzerland (no. GE 144/20, approved 12/08/2020). All procedures were performed according to the current animal protection laws of Switzerland (LPA, RS455). The current work follows the ARRIVE guidelines for reporting animal studies.

Experimental animals

Twenty adult New Zealand White rabbits (male n=9, female n=11, aged 20 weeks, weighing 2.7 kg on average, with a range of 2.3–3.35 kg) were involved in the current study. Animals were purchased from the farm of University of Geneva (Arare, Geneva, Switzerland) and were delivered 1 week before the experiments to allow acclimatisation. Food and water were provided *ad libitum* before the experiments.

Study design and protocol

The scheme of the prospective randomised study protocol is depicted in Figure 1. After completing surgical preparation, a 15- to 30-min period was allowed for the stabilisation of the haemodynamic and respiratory conditions. A recruitment manoeuvre was performed to standardise lung volume history, followed by recording the baseline (BL) measurements that included ventilation (V_T, VF, and inspiratory pressure [P_{peak}]) and blood gas parameters, respiratory system mechanics using oscillometry, and the multiple breath washout technique to characterise lung volume. Lung injury was then induced using a triple-hit injury, as described below. After this intervention, another recruitment manoeuvre was performed and the ventilation parameters were set: PEEP set to 7 cm H_2O, P_{peak} set to achieve V_T of 7 ml kg^{-1}, and VF set to achieve normocapnia. After a period of stabilisation, these measurements were performed again to establish the respiratory outcomes before beginning mechanical ventilation (H0). Animals were randomised to receive 6 h of conventional PC with constant PEEP or variable PEEP (PC-VEEP). Ventilation parameters, blood gas, and respiratory mechanics were characterised hourly during the 6-h ventilation period. After 6 h (H6), the final set of measurements was performed, which was the

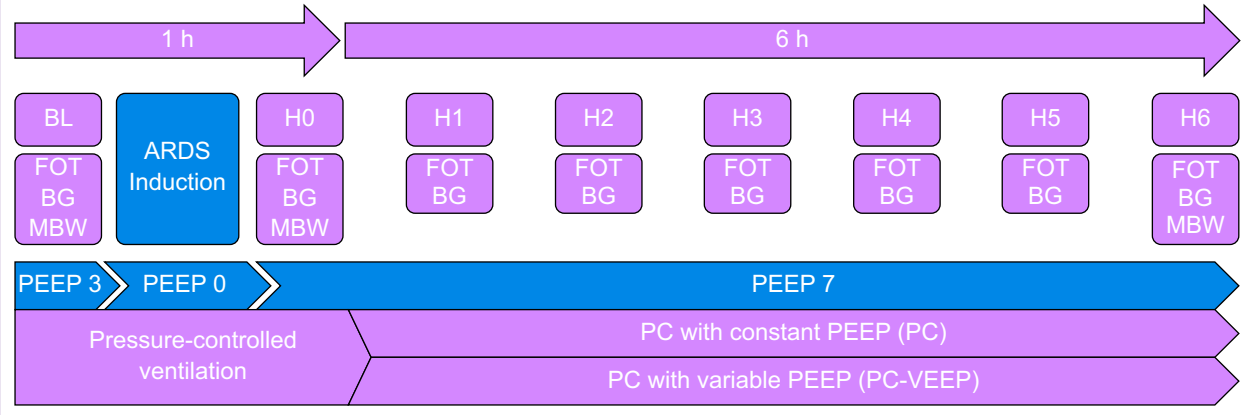

Fig. 1. Study protocol. Acute respiratory distress syndrome (ARDS) induction was achieved with injurious ventilation with positive end-expiratory pressure (PEEP) 0 and 100% fraction of inspired oxygen, total lung lavage, and i.v. endotoxin. BG, blood gas; BL, baseline; FOT, forced oscillometry; H0 to H6, hourly measurements from hour 0 to hour 6; MBW, multiple breath washout; PC, pressure-controlled ventilation; VEEP, variable PEEP.

same as the initial measurements at H0 but also included lung volume and intrapulmonary shunt fraction (Qs/Qt) assessments.

Primary and secondary outcomes

The primary outcome of the present study was the oxygenation index (partial pressure of oxygen in arterial blood divided by fraction of inspired oxygen [Pa_{O_2}/FiO_2]) after 6 h of mechanical ventilation. Secondary outcomes included airway pressure (P_{aw}), V_T, VF, airway resistance (R_{aw}), respiratory tissue elastance (H) and damping (G), Qs/Qt, end-expiratory lung volume (EELV), lung clearance index (LCI), and lung inflammatory markers.

Experimental procedures

Anaesthesia and surgical preparation

Animals in all groups were anaesthetised with an i.m. injection of ketamine 25 mg kg^{-1} and xylazine 3 mg kg^{-1}. After infiltration of the anterior cervical region with lidocaine 1%, a surgical tracheostomy with a 3.5-mm uncuffed tube was performed. The ear vein was cannulated with a 24-G catheter for the administration of i.v. anaesthesia and analgesia (propofol 10 mg kg^{-1} h^{-1}, fentanyl 5 μg kg^{-1} h^{-1}). After confirming adequate depth of anaesthesia by the absence of movement in response to stimuli and haemodynamic monitoring (stable heart rate and arterial blood pressure), neuromuscular block was performed with atracurium 0.6 mg kg^{-1} h^{-1}. Body temperature was maintained at 38 (SD 1) °C with a heating pad (Harvard Apparatus, South Natick, MA, USA). I.V. fluid replacement was administered with Ringer's acetate 2 ml kg^{-1} h^{-1}. Then, the femoral artery and internal jugular vein were cannulated for arterial and venous blood sampling and invasive pressure monitoring. At the end of the study protocol, still under general anaesthesia, the animals were euthanised by injecting a single i.v. dose of pentobarbital (50 mg kg^{-1}).

ARDS model

Lung injury was induced using a triple-hit injury involving surfactant depletion with lung lavage, i.v. lipopolysaccharide, and injurious ventilation with PEEP 0 cm H_2O, V_T 10 ml kg^{-1} and FiO_2 100% for 20–30 min, as described previously.[17]

Mechanical ventilation modalities

Mechanical ventilation was applied by a computer-controlled, custom-made, blower-based ventilator with software that continuously recorded tracheal airflow (V′), P_{aw}, and V_T, as described previously.[6] For BL measurements, all ventilation parameters were set identically between groups: P_{peak} to deliver an average V_T of 7 ml kg^{-1}, PEEP of 3 cm H_2O, FiO_2 of 40%, and inspiratory-to-expiratory ratio (I:E) of 1:2.

After induction of lung injury (H0), the P_{peak} was set to deliver V_T of 7 ml kg^{-1}, PEEP was set to 7 cm H_2O and FiO_2 was titrated between 60% and 90% to achieve oxygen peripheral saturation above 92%. At this time point, animals were randomised to receive either PC with the aforementioned parameters or PC-VEEP. The PC-VEEP group received the same average PEEP (7 cm H_2O) with a cycle-by-cycle variability following a Gaussian distribution and a coefficient of variation of 21.4% (PEEP range 4–10 cm H_2O). A representative period of PC-VEEP application is presented in Figure 2.

The P_{peak} and driving pressure were kept constant throughout the 6 h of ventilation (H0–H6), and VF was adapted

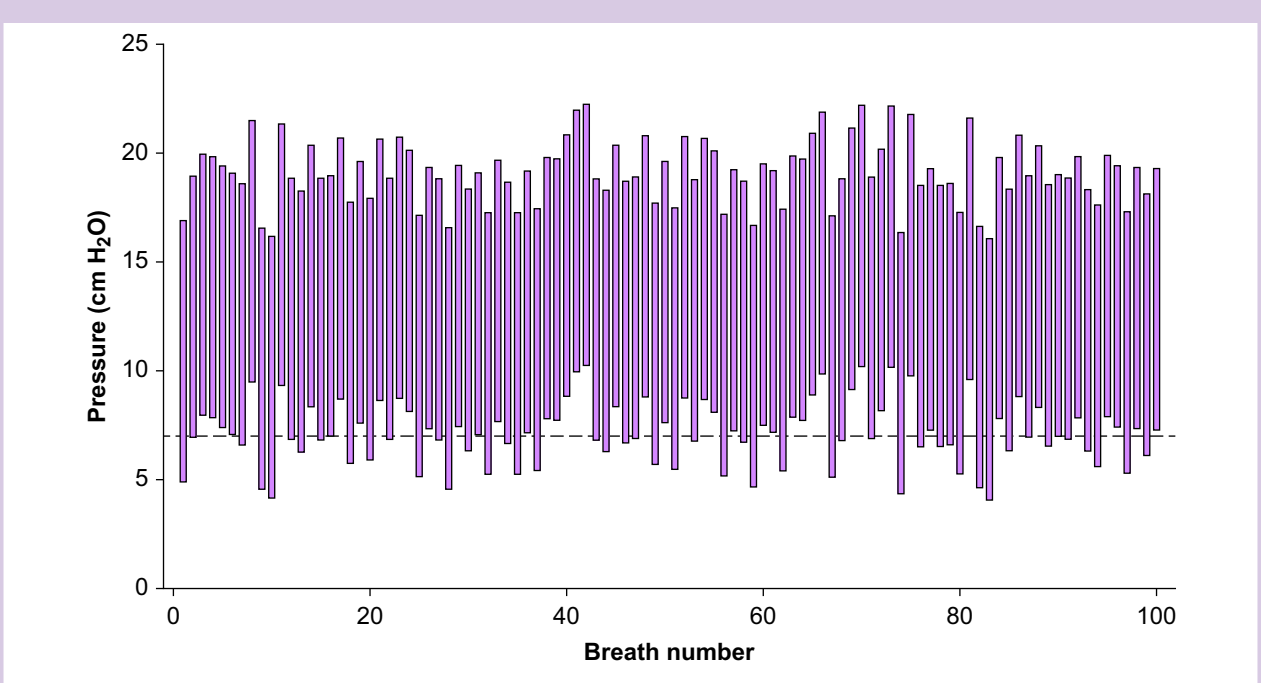

Fig. 2. Representative tracing of the airway pressure from one animal during the application of pressure-controlled ventilation with variable positive end-expiratory pressure (PC-VEEP). The mean PEEP was set to 7 cm H_2O, and the driving pressure was 12 cm H_2O.

to achieve constant minute volume and normocapnia (end-tidal CO_2 of 5.5–6%).

Measurements

Blood pressure, electrocardiogram, and P_{aw} were continuously recorded using PowerLab model 8/35 and LabChart 7 (ADInstruments, Dunedin, New Zealand). Peripheral oxygen saturation was continuously measured with LifeVet P Pulse Oximeter (Eickemeyer Veterinary Equipment, Appenzell, Switzerland). Ventilation parameters were continuously recorded by the ventilator and averaged over periods of 60 min to measure mean V_T, mean VF, and mean P_{peak}. Blood analyses were performed from arterial and central venous samples using a point-of-care blood gas analyser (i-Stat; Abbott Laboratories, Chicago, IL, USA) to measure the partial pressure of oxygen, carbon dioxide, and lactate concentrations in the arterial and venous blood. The Qs/Qt was calculated using the Berggren equation.[18]

The oscillatory impedance spectra of the respiratory system (Z_{rs}) were analysed using a method described previously.[19] Briefly, 2 cm H_2O peak-to-peak amplitude pseudorandom oscillations were applied for 10 s during end-expiratory pauses (15 non-integer multiples between 0.5 and 21 Hz) by the computer-controlled ventilator turbine. The flow (V') was measured using a pneumotachograph (PNT 3700 Hans Rudolph Inc., Shawnee, KS, USA) connected to a differential pressure transducer (Honeywell model 24PCEFA6D, Charlotte, NC, USA). The P_{aw} was measured by a second pressure transducer connected to a side port of the tracheal cannula. Z_{rs} ($Z_{rs}=P_{aw}/V'$) was calculated using Fast Fourier Transformation from the 10-s-long recordings with 4-s time windows and 95% overlap. The measured impedance was fitted to a model to obtain R_{aw} and tissue damping and elastance. The R_{aw} represents the flow resistance of the airways, whereas the tissue viscoelastic parameters reflect the energy loss (damping) and the energy storage capacity (elastance) of the respiratory tissues.

An ultrasonic flowmeter (Spiroson Scientific; ECO Medics AG, Dürnten, Switzerland) using helium as tracer gas was used to apply a multiple breath washout technique described in previous studies.[5,20] The washout curve was analysed to obtain the EELV and LCI before and after 6 h of ventilation. The LCI, an index which reflects the inhomogeneity of alveolar ventilation, was determined as the number of turnovers required to decrease the end-tidal helium concentration to 1/40th of the initial value before washout, as described previously.[21]

After euthanasia, the bronchoalveolar lavage fluid (BALF) and the frozen lung tissue homogenate were analysed with enzyme-linked immunosorbent assay (ELISA) to quantify interleukin (IL)-6 and IL-8 and tumour necrosis factor (TNF-α), as described in Supplementary material.

Sample size

Based on previous work using an animal model of ARDS[2] demonstrating that VV improved oxygenation after 5 h of mechanical ventilation (Pa_{O_2} 23.1 [4.0] *vs* 15.9 [3.1] kPa for VV and conventional ventilation, respectively), we hypothesised that VEEP increases oxygenation to a similar extent in comparison with constant PEEP. Accordingly, and assuming an alpha level of 0.05 and a power of 80%, the sample size estimation resulted in six rabbits per group. However, our previous experiments revealed a large intersubject variability (25%) and premature animal death (10–20%) when inducing lung injury, and thus, we added four supplementary animals per group to account for this.

Statistical methods

The statistical analysis plan and the outcome variables were approved by the authors before analyses began. Data are presented as mean (SD). Two-way repeated measure analysis of variance (ANOVA) with Holm–Šídák *post hoc* tests were used to assess differences between ventilation modes (PC *vs* PC-VEEP) and time points (BL and H0 to H6). Relative changes between H0 and H6 were compared using an unpaired Student's *t*-test or a Mann–Whitney test for data with normal and non-normal distribution, respectively. The statistical analysis was performed using SigmaPlot (Version 14.5; Systat Software, Inc., Chicago, IL, USA). Results were considered statistically significant if $P<0.05$, and all *P*-values are two-sided.

Results

Twenty rabbits were involved in the present study. Four animals did not survive the 6-h experimental protocol as a result of severe ARDS, pneumothorax, and technical problems (two randomised to PC and two to PC-VEEP). Four other animals were excluded from the final analysis for not meeting ARDS criteria (Pa_{O_2}/FiO_2 >40 kPa, two randomised to PC and two to PC-VEEP). Accordingly, six rabbits were included in the final analysis in both PC and PC-VEEP groups.

Changes in arterial blood gas parameters

After inducing lung injury, marked and significant decreases in Pa_{O_2}/FiO_2 and increases in Pa_{CO_2} were observed (BL *vs* H0, $P<0.001$ for both; Fig 3), demonstrating the presence of moderate-to-severe ARDS according to the Berlin criteria.[22] The significant interactions between the ventilation mode and time for Pa_{O_2}/FiO_2 and Pa_{CO_2} ($P<0.05$ for both) obtained by ANOVA indicate that the ventilation mode significantly affected the temporal changes in both blood gas parameters. The Pa_{O_2}/FiO_2 values after PC-VEEP ventilation became significantly higher when compared with PC after 5-h ventilation ($P=0.027$ and $P=0.013$ at H5 and H6, respectively). This finding was associated with lower Pa_{CO_2} in the ventilation period of 1–3 h ($P=0.002$, 0.01, and 0.014 for H1, H2, and H3, respectively). Application of PC-VEEP prevented the deterioration in Pa_{O_2} during the 6-h ventilation period, as demonstrated by significant differences in the percentage change of Pa_{O_2}/FiO_2 between H0 and H6 ($P=0.046$; Fig 3, top right panel).

Ventilation parameters

The ventilation parameters are summarised in Figure 4. The induction of ARDS resulted in a significant increase in VF ($P=0.02$) and P_{peak} ($P<0.001$) irrespective of the ventilation mode. As the P_{peak} was set to achieve a V_T of 7 ml kg^{-1} at H0, V_T remained stable between BL and H0 in both groups. There was a significant increase in VF in group PC from H3 ($P<0.05$) and a significant decrease in V_T from H2 of mechanical ventilation ($P<0.05$), whereas VF and V_T did not differ from H0 to H6 in the PC-VEEP group ($P=0.531$ and 0.112, respectively). Accordingly, the relative change in VF in the PC group during the 6-h ventilation protocol was higher than in the PC-VEEP group

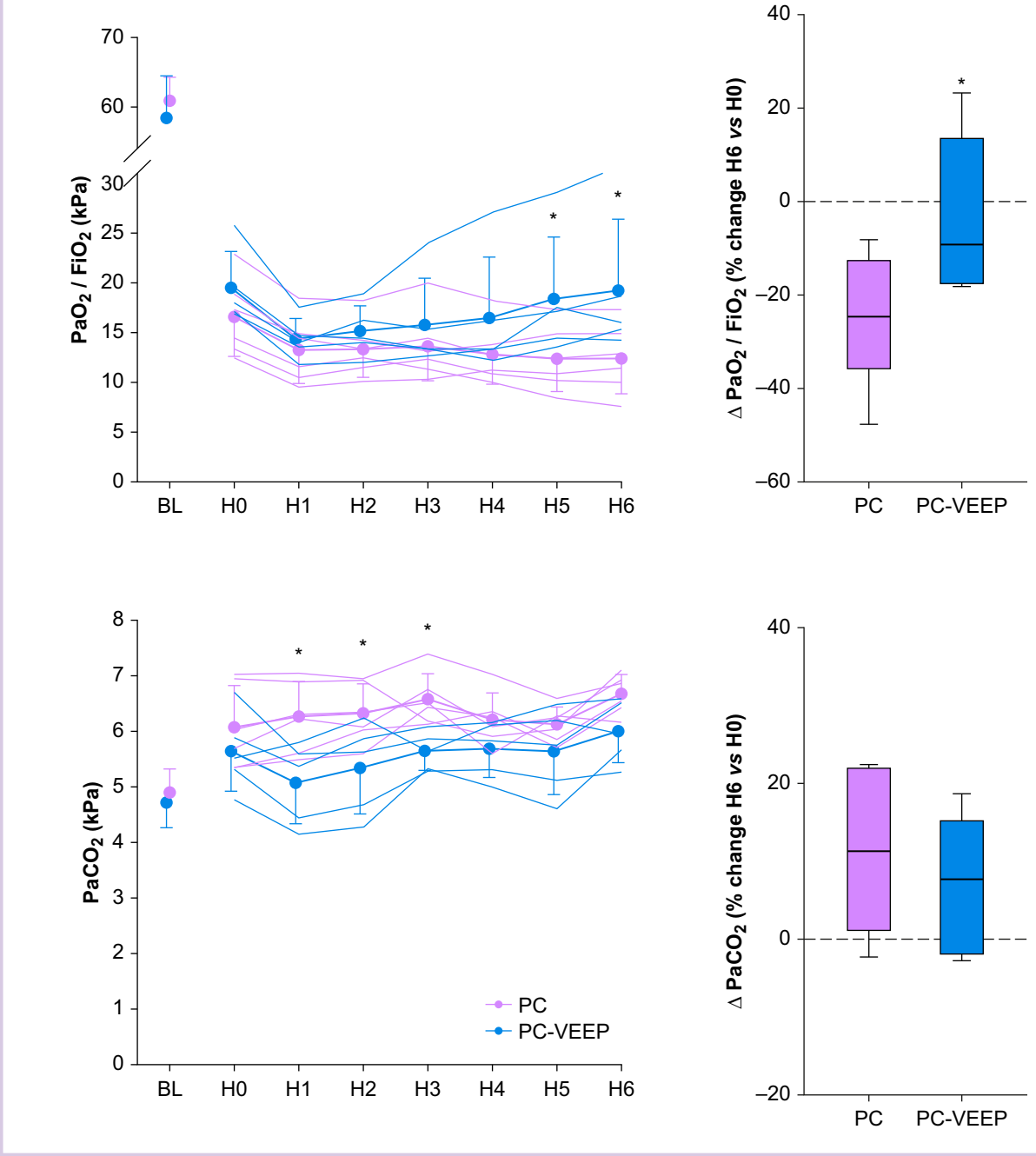

Fig. 3. Arterial blood gas parameters. Shown are the ratio of partial pressure of oxygen (Pa_{O_2}, kPa) to the fraction of inspired oxygen (FiO_2) and the partial pressure of carbon dioxide (Pa_{CO_2}) before (BL) and after (H0) the induction of lung injury and during the 6 h of ventilation (H1–H6) with pressure-controlled ventilation and constant PEEP (PC, black) or variable PEEP (PC-VEEP, red). The relative change in percentage (Δ) between H0 and H6 is represented on the right for Pa_{O_2}/FiO_2 and Pa_{CO_2} for groups PC and PC-VEEP. Values are mean (standard deviation) or median (inter-quartile range). *P<0.05 for PC *vs* PC-VEEP. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(P=0.002; Fig 4, top right panel). No significant difference was observed between the protocol groups in P_{peak} or its relative change (P=0.262 for ANOVA groups, and P=0.110 for relative change). For the PC and PC-VEEP groups, there was no evidence for significant differences regarding minute volume (688 [99] *vs* 735 [147] ml min^{-1}, respectively, at H6; P=0.546) and end-tidal CO_2 (6.7 [0.8] *vs* 6.7 [0.9]%, respectively, at H6; P=0.962) during the 6 h of mechanical ventilation.

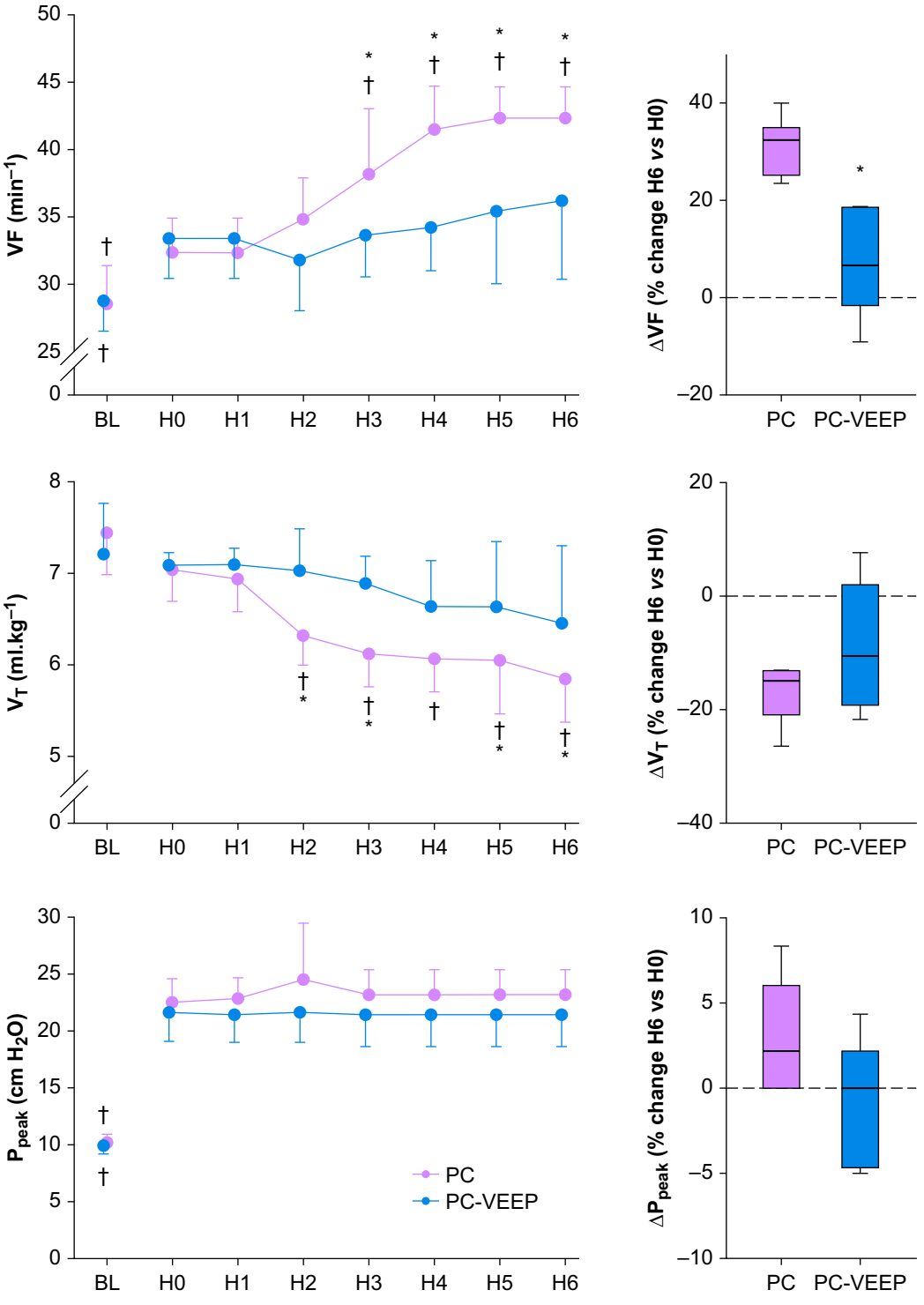

Fig. 4. Changes in ventilatory frequency (VF, min^{-1}), tidal volume (V_T, ml kg^{-1}), and airway inspiratory pressure (P_{peak}, cm H_2O) before (BL) and after (H0) the induction of lung injury, and during the 6 h of ventilation (H1–H6) with pressure-controlled ventilation and constant PEEP (PC, black) or variable PEEP (PC-VEEP, red). The relative change in percentage (Δ) between H0 and H6 is represented on the right panels for groups PC (grey) and PC-VEEP (red). Values are mean (standard deviation) or median (inter-quartile range). *P<0.05 for PC *vs* PC-VEEP. †P<0.05 *vs* H0. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Respiratory function

There was no evidence for a statistical difference between the protocol groups in the mechanical parameters of the respiratory system under BL condition: R_{aw} (12.6 [1.8] *vs* 11.5 [2.6] cm H_2O s L^{-1}, $P>0.05$), damping (96.7 [14.9] *vs* 87.4 [9.4] cm H_2O L^{-1}, $P>0.05$), and elastance (348 [16] *vs* 337 [43] cm H_2O L^{-1}, $P=0.978$). Figure 5 shows the relative changes of these outcomes during the 6-h ventilation period. After 6 h of ventilation, R_{aw} and elastance elevated significantly in group PC ($P=0.017$ and $P<0.001$, respectively), whereas these elevations were prevented by group PC-VEEP ($P>0.05$ and $P=0.618$, respectively).

The ventilation mode had no significant effect in the relative change in EELV after 6 h of ventilation (−13.3 [10.6]% *vs* +3.0 [30.3]% for the PC and PC-VEEP groups, respectively, $P=0.312$), and in LCI (16.5 [18.3] *vs* 3.7 [49.0], $P=0.638$).

The induction of lung injury resulted in significant increases in Qs/Qt (7.36 [1.2] *vs* 40.6 [13.7]% BL and 8.7 [0.3]% *vs* 32.1 [8.5]% H0 for the PC and PC-VEEP groups, respectively, $P<0.001$ for both) without affecting the lactate concentration. No difference in Qs/Qt between the protocol groups was detectable after 6 h of mechanical ventilation (52.5 [3.4]% *vs* 46.5 [14.1]% for the PC and PC-VEEP groups, respectively, $P=0.146$). Conversely, lactate concentrations elevated significantly after 6 h ventilation in both groups (1.8 [0.7] *vs* 5.7 [1.8] mM and 1.9 [1.5] *vs* 3.7 [1.3] mM at H0 and H6 in the PC and PC-VEEP groups, respectively, $P<0.001$ for both) despite stable haemodynamic conditions (data not shown).

Inflammatory markers

The total protein in the BALF and in the lung frozen tissue homogenates, and the inflammatory cytokines, TNF-α, IL-1β, and IL-8 did not differ between the groups after 6 h mechanical ventilation (see Supplementary material).

Discussion

In the present study, we evaluated the benefits of an advanced ventilation strategy by introducing cycle-by-cycle variability to PEEP and compared gas exchange and respiratory function parameters with those obtained during 6 h of conventional ventilation in a rabbit model of moderate-to-severe ARDS. We demonstrated that the long-term deterioration in blood gas parameters observed during conventional ventilation was mitigated by the application of VEEP. This improvement in lung oxygenation was associated with the protective potential of VEEP against ventilation-induced deteriorations in R_{aw} and respiratory tissue elastance. VEEP allowed the maintenance of minute volume and driving pressure without the need for adjustments in V_T and VF. The inflammatory profile of the lungs was not affected by the advanced ventilation modality.

The injury model used in this work was the previously described triple-hit model of ARDS,[17] which combines surfactant depletion, i.v. lipopolysaccharide, and injurious ventilation. The rationale for this experimental injury is to mimic the pathophysiological aspects of ARDS in humans, including tissue inflammation, alveolar and interstitial oedema, capillary leak, lung stiffness, and ventilation–perfusion mismatch. Previous imaging and histological analysis of this triple-hit ARDS model used with rabbits demonstrated considerable inflammation, lung condensation, neutrophilic infiltration, alveolar septal thickening, hyaline membranes, and increased protein and cell count in the bronchial lavage fluid.[4,17]

The application of pressure-controlled ventilation for 6 h with constant or variable PEEP demonstrated that VEEP provided a significant benefit on the primary outcome variables—lung oxygenation ratio and CO_2 clearance. This finding is in line with previous data obtained after introducing variability in V_T under constant PEEP in healthy lungs and in models of lung diseases.[2,5–7,23–25] Interestingly, the magnitude of the benefit for gas exchange observed previously using VV waveforms is in concordance with the present results demonstrating Pa_{O_2} improvements after 5–6 h of ventilation.

To our knowledge, this is the first study to systematically characterise the potential benefit of varying PEEP levels over the conventional, monotonous ventilation. The benefits of VV have been attributed to the non-linear properties of the respiratory system.[13,14] Although the principle of applying VEEP

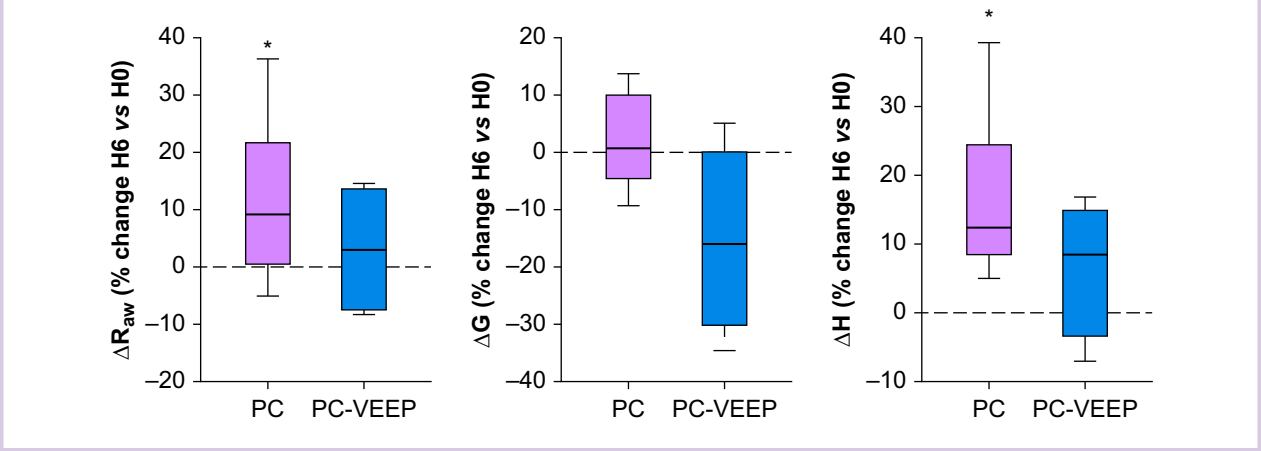

Fig. 5. Relative changes in percentage (Δ) between H0 and H6 for the respiratory mechanical parameters. Airway resistance (R_{aw}), tissue damping (G), and tissue elastance (H) in the group with pressure-controlled ventilation and constant PEEP (PC, grey) or variable PEEP (PC-VEEP, red). *$P<0.05$ for PC *vs* PC-VEEP. Values are median (inter-quartile range). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

may also be related to this phenomenon, the rationale may be somewhat different: by varying the PEEP in a cycle-by-cycle manner (keeping a constant driving pressure for each cycle), the non-linear nature of the pressure–volume curve will likely generate improved V_T delivery for the same level of average P_{peak}. This hypothesis is supported by our data demonstrating that despite a constant level of driving pressure during the 6 h of ventilation, V_T significantly decreased and VF was increased to maintain the minute volume with the conventional ventilation using constant PEEP, whereas V_T and VF did not significantly differ during the 6 h under PC-VEEP. A progressive decrease in V_T also indicates that derecruitment was more important with constant PEEP than with VEEP, although the same average PEEP level of 7 cm H_2O was maintained in both groups.

The level of PEEP was chosen considering the respiratory system properties of this species and for this disease model based on previous research, indicating a synergistic effect of VV and PEEP between 6 and 9 cm H_2O.[17] Although recruitment manoeuvres (sighs) could have equally prevented derecruitment, previous research with this model has indicated that lung function deterioration was better prevented by VV than a pressure-controlled mode with regular sighs.[17]

As the respiratory mechanical properties are non-linear, it seems reasonable to assume that under the same average driving pressure, the 'gain' during higher-than-average PEEP cycles exceeds the 'loss' during lower-than-average PEEP cycles. Thus, varying PEEP levels seems to prevent alveolar derecruitment. It is difficult to determine whether this beneficial effect resulted solely from the higher PEEP breaths or from the variability of PEEP itself, as the varying levels in consecutive breaths could benefit from different time constants and optime regional ventilation. This mechanism is reflected in the ability of PC-VEEP to protect ventilation-induced deleterious changes in the R_{aw} and respiratory tissue elastance (Fig 5), whereas both elastance and resistance significantly increased with PC. In addition, redistribution of pulmonary blood flow might have also played a role in the gas exchange benefit of VEEP, as introducing variability in V_T or pressure support was shown to redistribute pulmonary blood flow to the well-ventilated alveolar compartments.[26,27]

In addition to the benefits in ventilation parameters and gas exchange, VV has been shown to prevent derecruitment and improve ventilation–perfusion matching, respiratory mechanics, and inflammation.[2,4–7,9,23–27] In the present work, no difference could be evidenced in EELV, LCI and Qs/Qt, and inflammatory markers. In line with our findings, several studies on VV did not reveal differences in the cytokine quantification despite significant improvements in gas exchange and respiratory mechanics.[17,28–32] Considering that our study was not powered to detect a difference in these secondary outcomes with large variance, it is likely that improvements in these parameters would require more targeted investigations, in particular using lung functional imaging,[4] as previously reported.

PEEP titration and the determination of the 'optimal PEEP' are subjects of extensive research and clinical interest, especially in the fields of ARDS and intensive care medicine.[33] Maintaining an optimal PEEP balances the deleterious lung overdistension contributing to haemodynamic impairment and ventilator-induced lung injury, and underventilation causing derecruitment and atelectrauma. Another approach could have been the individualisation of PEEP for each animal. Although this approach might have identified the optimal PEEP, individualising and titrating PEEP would have introduced confounding effects into this experimental setting, which was designed to isolate a sole study variable: the coefficient of variation in PEEP. This approach represents both a limitation and a strength of the study design, as all animals in both groups received the same average PEEP. Using an advanced ventilation modality incorporating cycle-by-cycle variation in PEEP has the potential advantage of utilising the non-linear properties of lung tissue, thereby preventing derecruitment during mechanical ventilation, avoiding the need for recruitment manoeuvres and increased driving pressure.

The study has certain methodological considerations warranting discussion. In the present experiments, the mean PEEP level was set to 7 cm H_2O for both groups. Applying a high PEEP level (9 cm H_2O) was shown to abrogate most of the benefits of VV in a rabbit model of ARDS[17] that can be attributed to an extreme right-shift in the lung pressure–volume curve. Thus, it can be anticipated that even greater benefits are incurred by using a lower mean PEEP level during the application of VEEP. Another limitation of the study design is the ventilation time (6 h), which precludes drawing conclusions about the long-term effects of VEEP. Accordingly, whether the observed benefits in gas exchange and respiratory mechanics would extend over the course of days or weeks in ventilated ARDS subjects is a subject of further investigations.

In conclusion, the cycle-by-cycle variability in PEEP during pressure-controlled ventilation has beneficial effect on gas exchange and prevents ventilation-induced respiratory mechanical impairment in an experimental model of ARDS. Introducing variability in PEEP has the promise to offer a different modality to improve mechanical ventilation in the presence of lung injury without the need to increase the driving pressure to the potentially deleterious range. Further studies on larger cohorts are warranted for a more detailed investigation of the effects of VEEP and its optimisation under various lung conditions.

Authors' contributions

Conceived the study protocol: RS, WH, ADSR.
Data collection: RS, JD, ADSR.
Performed animal experiments: RS, JD, ADSR.
Created software and hardware for the experiments: DB, RD.
Data analysis: FP, HW, RS, ADSR.
Drafted the manuscript: FP, HW, RS, ADSR.
All authors read and approved the final manuscript.

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Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2024.100302.

References

1. Arold SP, Suki B, Alencar AM, Lutchen KR, Ingenito EP. Variable ventilation induces endogenous surfactant release in normal Guinea pigs. *Am J Physiol Lung Cell Mol Physiol* 2003; **285**: L370–5
2. Boker A, Graham MR, Walley KR, et al. Improved arterial oxygenation with biologically variable or fractal ventilation using low tidal volumes in a porcine model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; **165**: 456–62
3. Boker A, Haberman CJ, Girling L, et al. Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. *Anesthesiology* 2004; **100**: 608–16
4. Dos Santos Rocha A, Fodor GH, Kassai M, et al. Physiologically variable ventilation reduces regional lung inflammation in a pediatric model of acute respiratory distress syndrome. *Respir Res* 2020; **21**: 288
5. Dos Santos Rocha A, Peták F, Carvalho T, Habre W, Balogh AL. Physiologically variable ventilation prevents lung function deterioration in a model of pulmonary fibrosis. J Appl Physiol (1985) 2022; 132: 915–924
6. Dos Santos Rocha A, Südy R, Bizzotto D, et al. Benefit of physiologically variable over pressure-controlled ventilation in a model of chronic obstructive pulmonary disease: a randomized study. *Front Physiol* 2020; **11**, 625777
7. Dos Santos Rocha A, Sudy R, Petak F, Habre W. Physiologically variable ventilation in a rabbit model of asthma exacerbation. *Br J Anaesth* 2020; **125**: 1107–16
8. Kowalski S, McMullen MC, Girling LG, McCarthy BG. Biologically variable ventilation in patients with acute lung injury: a pilot study. *Can J Anaesth* 2013; **60**: 502–3
9. Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WA. Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlled mechanical ventilator. *Am J Respir Crit Care Med* 1996; **154**: 1567–72
10. Mutch WA, Eschun GM, Kowalski SE, Graham MR, Girling LG, Lefevre GR. Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia. *Br J Anaesth* 2000; **84**: 197–203
11. Samary CS, Moraes L, Santos CL, et al. Lung functional and biologic responses to variable ventilation in experimental pulmonary and extrapulmonary acute respiratory distress syndrome. *Crit Care Med* 2016; **44**: e553–62
12. Walesa M, Bayat S, Albu G, Baudat A, Petak F, Habre W. Comparison between neurally-assisted, controlled, and physiologically variable ventilation in healthy rabbits. *Br J Anaesth* 2018; **121**: 918–27
13. Suki B, Alencar AM, Sujeer MK, et al. Life-support system benefits from noise. *Nature* 1998; **393**: 127–8
14. Huhle R, Pelosi P, de Abreu MG. Variable ventilation from bench to bedside. *Crit Care* 2016; **20**: 62
15. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301–8
16. Santa Cruz R, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2013; **2013**: Cd009098
17. Fodor GH, Bayat S, Albu G, et al. Variable ventilation is equally effective as conventional pressure control ventilation for optimizing lung function in a rabbit model of ARDS. *Front Physiol* 2019; **10**: 803
18. Berggren SM. The oxygen deficit of arterial blood caused by non-ventilating parts of the lung. *Acta Physiol Scand* 1942; **II**: 1–92
19. Hantos Z, Daroczy B, Suki B, Nagy S, Fredberg JJ. Input impedance and peripheral inhomogeneity of dog lungs. J Appl Physiol (1985) 1992; 72: 168–178
20. Albu G, Wallin M, Hallbäck M, et al. Comparison of static end-expiratory and effective lung volumes for gas exchange in healthy and surfactant-depleted lungs. *Anesthesiology* 2013; **119**: 101–10
21. Becklake MR. A new index of the intrapulmonary mixture of inspired air. *Thorax* 1952; **7**: 111–6
22. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**: 2526–33
23. McMullen MC, Girling LG, Graham MR, Mutch WA. Biologically variable ventilation improves oxygenation and respiratory mechanics during one-lung ventilation. *Anesthesiology* 2006; **105**: 91–7
24. Mutch WA, Buchman TG, Girling LG, Walker EK, McManus BM, Graham MR. Biologically variable ventilation improves gas exchange and respiratory mechanics in a model of severe bronchospasm. *Crit Care Med* 2007; **35**: 1749–55
25. Mutch WA, Harms S, Lefevre GR, Graham MR, Girling LG, Kowalski SE. Biologically variable ventilation increases arterial oxygenation over that seen with positive end-expiratory pressure alone in a porcine model of acute respiratory distress syndrome. *Crit Care Med* 2000; **28**: 2457–64
26. Carvalho AR, Spieth PM, Guldner A, et al. Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury. *J Appl Physiol (1985)* 2011; **110**: 1083–92
27. Spieth PM, Carvalho AR, Pelosi P, et al. Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. *Am J Respir Crit Care Med* 2009; **179**: 684–93
28. Froehlich KF, Graham MR, Buchman TG, et al. Physiological noise versus white noise to drive a variable ventilator in a porcine model of lung injury. *Can J Anaesth* 2008; **55**: 577–86
29. Funk DJ, Graham MR, Girling LG, et al. A comparison of biologically variable ventilation to recruitment

manoeuvres in a porcine model of acute lung injury. *Respir Res* 2004; **5**: 22
30. Kiss T, Silva PL, Huhle R, et al. Comparison of different degrees of variability in tidal volume to prevent deterioration of respiratory system elastance in experimental acute lung inflammation. *Br J Anaesth* 2016; **116**: 708–15
31. Spieth PM, Carvalho AR, Guldner A, et al. Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. *Crit Care Med* 2011; **39**: 746–55
32. Spieth PM, Guldner A, Beda A, et al. Comparative effects of proportional assist and variable pressure support ventilation on lung function and damage in experimental lung injury. *Crit Care Med* 2012; **40**: 2654–61
33. Millington SJ, Cardinal P, Brochard L. Setting and titrating positive end-expiratory pressure. *Chest* 2022; **161**: 1566–75

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