Higher versus lower positive end-expiratory pressure in acute lung injury and acute respiratory distress syndrome: systematic review and individual patient data meta-analysis

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**P180**

**Evaluating the fibroproliferative response to ventilator-induced lung injury**

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**Introduction**

Acute lung injury (ALI), and its more severe subset acute respiratory distress syndrome (ARDS), are a major cause of mortality in the ICU [1]. Mechanical ventilation, a supportive therapy necessary to sustain life in many cases, may contribute to and worsen ALI, termed ventilator-induced lung injury (VILI). Fibroproliferation is an early response to lung injury [2]. Indeed, dysregulated repair resulting in pulmonary fibrosis may be at the heart of ventilator dependence in ARDS. Characterising the role of excessive lung stretch in contributing to aberrant repair mechanisms would assist in developing strategies to hasten recovery from ARDS.

**Methods**

Male Sprague–Dawley rats were anaesthetized, orotracheally intubated and subjected to injurious ventilation until a defined worsening of compliance was noted. The rats were then recovered and extubated. The level of ongoing injury/repair was characterised at time periods of 6, 24 and 48 hours and at 4, 7 and 14 days. Systemic oxygenation, lung compliance, wet/dry ratio, BAL total protein, cytokines and cell count and histological analysis was carried out at each time point.

**Results**

The results demonstrated a time-course-dependent improvement in compliance and oxygenation, together with clearance of neutrophil infiltration at 96 hours. TNFα and IL-1β decreased, IL-6 and IL-10 were significantly elevated in BAL fluid early post injury. Although total lung collagen remained similar at all time points, evidence of an early fibroproliferative response was present in the form of transforming growth factor-β activation and pro-collagen I and III peptide mRNA levels. Matrix metalloproteinase 3 and 9 zymography demonstrated increased levels of these matrikines. Histological assessment of injury revealed increased alveolar tissue fraction up to and including 96 hours post injury. Myofibroblasts were present in a smooth muscle actin stained sections in significantly increased numbers post injury.

**Conclusions**

This rat model of repair of VILI demonstrates some of the mechanisms by which excessive lung stretch can contribute to fibroproliferation in ARDS and will serve to improve our knowledge of aberrant lung tissue remodelling as well as provide a useful paradigm for testing strategies to hasten recovery in ALI.

**References**


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**P181**

**Effects of severe hemorrhage on pulmonary mechanics in ventilated pigs with ARDS**

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**Introduction**

The effects of hemorrhagic shock on respiratory system mechanics have rarely been investigated and published data are controversial. Pulmonary compliance depends in part on intrapulmonary blood and interstitial fluid volume. When compliance is severely reduced, small changes in these components may have important effects. The present analysis explored the effect of hemorrhagic shock on respiratory system mechanics and oxygenation parameters in a model of pigs with ARDS.

**Methods**

We evaluated the dynamic respiratory system compliance (Crs = VT / (inspiratory airways pressure – PEEP)) at set tidal volume ventilation of 10 ml/kg, respiratory rate at 15 bpm; PEEP at 0 cmH2O. Animals were separated into a control group (n = 9) and an ARDS group (n = 5). ARDS was induced by lung lavage with NaCl 0.9%. During hemorrhage 40% of the total blood volume was removed. The blood was then infused during the re-transfusion phase.

**Results**

In the control group, Crs (ml/cmH2O) did not change during hemorrhage or re-transfusion (Figure 1). In the ARDS group, Crs decreased with lung lavage (31.2 ± 5.7 (baseline) to 16.4 ± 3.6, **P <0.01**). After hemorrhage Crs increased (21.5 ± 2.9; **P <0.01** compared with lavage) and then decreased again after re-transfusion (18.7 ± 2.7; ***P <0.05***). In the same group PaO2/FiO2 (mmHg) decreased after ARDS (469 ± 50 (baseline) to 105 ± 38; **P <0.001**), increased during hemorrhage (218 ± 105; P <0.05) and did not change after re-transfusion (207 ± 125; P = 0.82). The shunt fraction (%) decreased during hemorrhage in the ARDS group (26.2 ± 14.9 (lavage) to 6.4 ± 6.6; P <0.05) but did not change significantly after re-transfusion (13.9 ± 17.0; P = 0.3).

**Conclusions**

Acute reduction of blood volume is associated with an increase in respiratory system compliance and oxygenation parameters. Reduction of intrapulmonary blood and interstitial fluid volume or thoracic cage compliance could be responsible for this effect.

**Figure 1 (abstract P181).** Respiratory system compliance. Tidal volume, 10 ml/kg.
were analyzed using uniform outcome definitions. We tested prespecified effect modifiers using multivariable hierarchical regression, adjusting for important prognostic factors and clustering effects.

**Results** Overall, there were 374 hospital deaths (52.9%) in the higher PEEP group and 409 (35.2%) in the lower PEEP group (adjusted relative risk, 0.86; 95% confidence interval, 0.86 to 1.04; \( P = 0.25 \)). Treatment effects varied with the presence or absence of ARDS, defined by a ratio of partial pressure of oxygen to fractional inspired oxygen concentration equal to or less than 200 mmHg (interaction \( P = 0.02 \)). The relative risks of hospital mortality for patients with and without ARDS were 0.90 (95% CI, 0.81 to 1.00; \( P = 0.049 \)) and 1.37 (95% CI, 0.98 to 1.92; \( P = 0.065 \)), respectively. Patients with ARDS were more likely to achieve unassisted breathing earlier (hazard ratio, 1.16 (95% CI, 1.03 to 1.30; \( P = 0.01 \)); whereas the hazard ratio for time to unassisted breathing was 0.79 (95% CI, 0.62 to 0.99; \( P = 0.04 \)) in patients without ARDS at baseline. Rates of pneumothorax and the use of neuromuscular blockers, vasopressors and corticosteroids were similar.

**Conclusions** Higher levels of PEEP are likely to improve survival for patients with ARDS, but not for patients with less severe acute lung injury.

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**Effect of different recruitment maneuvers on bacterial translocation**

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**Introduction** Experimental and clinical studies have shown beneficial effects of recruitment maneuvers (RMs) (sustained inflation (SI) or SIGH) on ventilatory and gas exchange parameters. In this study we investigated the effect of different RMs on bacterial translocation from lung to blood.

**Methods** Thirty-two rats were anesthetized, after tracheotomy was performed, a baseline blood culture was taken. Subsequently 0.5 ml of 10⁵ cfu/ml Pseudomonas aeruginosa was inoculated through the tracheotomy tube and PEEP was increased to 3 cmH₂O and ventilated for 30 minutes before randomization. After cannulation of the carotid artery was performed, a baseline blood gas sample was taken. Subsequently 0.5 ml of 10⁵ cfu/ml Pseudomonas aeruginosa was inoculated through the tracheotomy tube and PEEP was increased to 3 cmH₂O and ventilated for 30 minutes before randomization. Then rats were randomized into four groups: G1; SI was performed as 15-minute intervals), G2; SI was performed as 20 cmH₂O PEEP and 0 Paw for 40 seconds, four times in an hour (15-minute intervals), G3; SIGH was performed four times in an hour (15-minute intervals), G4; control group that was ventilated with \( P_{aw} \) 10 cmH₂O, PEEP 3cmH₂O during the study period. Multiplication of pressure and pressure performing time for each study group were equal. Blood cultures were taken at baseline, 15 minutes after randomization, which is after each RM for the first hour, and last blood culture was taken after 60 minutes from the fourth RM. Then rats were sacrificed with intra-arterial sodium thiopental, and the lungs were extirpated; the left lung was taken for measurement of the wet weight/dry weight ratio (WW/DW).

**Results** There were no differences in baseline pH, PAO₂, PCO₂, MAP, HR among groups. But PAO₂ were decreased in groups G1, G2, and G3, but only in G3 was statistically significant to compared baseline values. The WW/DW ratio was found higher in G3 when compared with G1 and G2, but this difference was not significant. The amount of positive blood culture was higher in G3 at early study periods.

**Conclusions** SIGH as a recruitment maneuver causes a high probability of bacterial translocation from the lung to the bloodstream.

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**Nonlinear recruitment model with viscoelastic component fit respiratory mechanics in ARDS**

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**Introduction** Alveolar recruitment/de-recruitment (R/D) seems to play an important role in the development of VILI [1]. Many clinicians base their determination of PEEP settings during mechanical ventilation of ARDS/ALI patients on an estimate of alveolar recruitability [2]. This project aims to establish an online tool that provides estimates of R/D in patients at the bedside.

**Methods** In volume-controlled ventilated piglets as ARDS models, the airway pressure \( P_{aw} \) (SI-Special Instruments, Nördlingen, Germany) and the flow rate Q (F + G GmbH, Hechingen Germany) were continuously recorded at 200 Hz. The pressure curve shows high nonlinearity being a suspect for recruitment effects during inspiration and a relaxation process during the end inspiratory pause. Based on the obtained data, the parameters of the linear viscoelastic model [3] are calculated by a LSE fitting process. As the parameter \( C_s \) represents a static constant compliance of the lung, this model is not capable of reproducing the nonlinear effects during inspiration. To improve on this, the constant compliance \( C_s \) is replaced by a nonlinear pressure-dependent compliance describing recruitment and dilatation as proposed by Hickling [1].

**Results** Since the nonlinear model has far more variable parameters to be optimized in the fitting process than the linear model, an approach via fitting the linear model first is helpful. Therefore, the estimated parameters of the linear model fit can be used as starting values for fitting the nonlinear model where the focus can be put on the recruitment phenomena. With the new nonlinear model, using the estimated values of \( R_1 \), \( R_2 \), \( C_s \) from the linear model (Figure 1 left), it is now possible to reproduce the nonlinear characteristics (Figure 1 right).

**Conclusions** Using this new model it is possible to fit nonlinear behavior due to alveolar recruitment separatedly from viscoelastic effects with minimized error.