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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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 neutrophilic infiltration at 96 hours. TNFα, IL-1β, 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 matrixkines. Histological assessment of injury revealed increased alveolar tissue fraction up to and including 96 hours post injury. Myofibroblasts were present in α-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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References

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

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Introduction
Trials comparing higher versus lower levels of positive end-expiratory pressure (PEEP) in adults with acute lung injury or acute respiratory distress syndrome (ARDS) were underpowered to detect small but important effects on mortality, overall or in any subgroups.

Methods
We searched MEDLINE, Embase, and the Cochrane Central Register for trials randomly assigning adults with acute lung injury or ARDS to higher versus lower levels of PEEP (minimal difference of 3 cmH₂O over first 3 days), while using low tidal volume ventilation, and comparing mortality. Data from 2,299 individual patients in three trials
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 (32.9%) in the higher PEEP group and 409 (35.2%) in the lower PEEP group (adjusted relative risk, 0.86; 95% confidence interval, 0.75 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 ventilation was started with 10 cmH\(_2\)O PEEP and 0 cmH\(_2\)O Paw for 60 breaths/minute, l/E: 1/2 on pressure-controlled ventilation (PCV) mode. After cannulation of the carotid artery was performed, a baseline blood gas sample was taken. Subsequently 0.5 ml of 10\(^5\) cfu/ml Pseudomonas aeruginosa was inoculated through the tracheotomy tube and PEEP was increased to 3 cmH\(_2\)O and ventilated for 30 minutes before randomization.

**Results**

After cannulation of the carotid artery was performed, a baseline blood gas sample was taken. Subsequently 0.5 ml of 10\(^5\) cfu/ml Pseudomonas aeruginosa was inoculated through the tracheotomy tube and PEEP was increased to 3 cmH\(_2\)O and ventilated for 30 minutes before randomization.

**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 \(P_w\) (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 of 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 \(R_s, R_c, C_s\) 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 separately from viscoelastic effects with minimized error.

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![Figure 1](abstract P184).