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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$PaO_2/FiO_2 \leq 150$ also had their extravascular lung water index (EVLWi) and pulmonary vascular permeability index (PVPI) monitored using the PiCCO system (Pulsion, Munich, Germany) when required by their attending physician. Statistical analysis was performed using the Spearman correlation coefficient (R_s) with $P \leq 0.05$ assumed to be significant.

Results Fourteen patients were enrolled in the study. In six of these patients, the EVLWi and PVPI were measured simultaneously. At baseline, the elastase level and the PVPI showed a strong and significant correlation ($R_s = 1.000$, $n = 6$, $P <0.05$). All of the plot data of the six patients showed strong correlations of the elastase level with the EVLWi ($R_s = 0.750$, $n = 25$, $P <0.01$) and the PVPI ($R_s = 0.811$, $n = 25$, $P <0.01$).

Conclusions The plasma neutrophil elastase level and the PVPI measured by PiCCO were strongly correlated in patients with pneumonia. This suggests that a rise in the blood level of elastase may elevate the PVPI, resulting in an increased EVLWi. (UMIN Clinical Trials Registry: ID UMIN000002803.)

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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 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, and 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 matrikines. Histologic 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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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
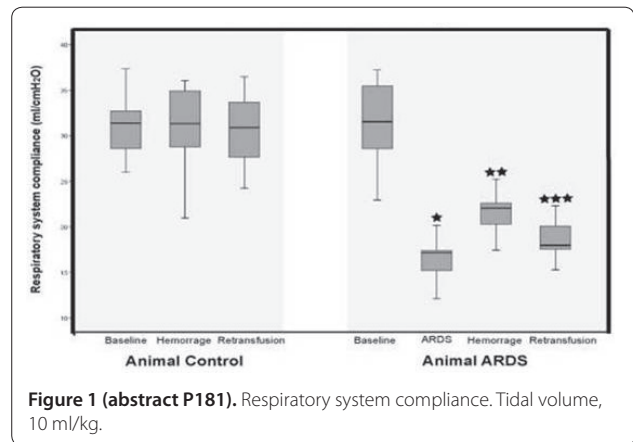

Figure 1 (abstract P181). Respiratory system compliance. Tidal volume, 10 ml/kg.

controversial. Pulmonary compliance depends in part on intrapulmonary blood and interstitial fluid volume. When compliance is severely reduced, small modification of 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 (C_{rs} = VT / (inspiratory airways pressure – PEEP)) of 14 domestic pigs. Animals were mechanically ventilated: tidal volume (VT) set at 10 ml/kg; respiratory rate at 15 bpm; PEEP at 0 cmH_2O. 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, C_{rs} (ml/cmH_2O) did not change during hemorrhage or re-transfusion (Figure 1). In the ARDS group, C_{rs} decreased with lung lavage (31.2 ± 5.7 (baseline) to 16.4 ± 3.0; *$P <0.01$). After hemorrhage C_{rs} increased (21.5 ± 2.9; **$P <0.001$ compared with lavage) and then decreased again after re-transfusion (18.7 ± 2.7; ***$P <0.05$). In the same group PaO_2/FiO_2 (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 of respiratory system compliance and oxygenation parameters. Reduction of intrapulmonary blood and interstitial fluid volume or thoracic cage compliance could be responsible for this effect.

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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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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 cmH_2O 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, 0.94; 95% confidence interval (CI), 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.

P183
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_2O P_{aw}, 0 cmH_2O PEEP, 60 breaths/minute, I/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_2O and ventilated for 30 minutes before randomization. Then rats were randomized into four groups: G1; SI was performed as 40 cmH_2O PEEP and 0 P_{aw} for 20 seconds, four times in an hour (15-minute intervals), G2; SI was performed as 20 cmH_2O PEEP and 0 P_{aw} for 40 seconds, four times in an hour (15-minute intervals), G3; SIGH was performed four times in 1 hour (15-minute intervals) as 40 cmH_2O P_{aw}, 3 mH_2O PEEP for 60 seconds, G4; control group that was ventilated with P_{aw} 10 cmH_2O, PEEP 3cmH_2O 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, PaO_2, $PaCO_2$, MAP, HR among groups. But PaO_2 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.

P184
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 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_1 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_1 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_2 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.
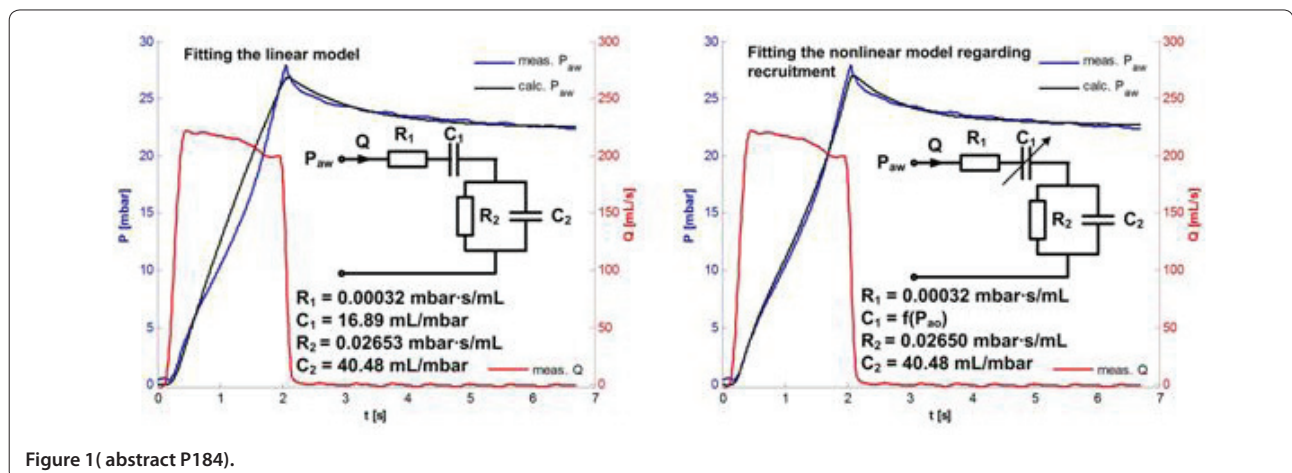

Figure 1(abstract P184).