**Evaluating the Fibroproliferative Response to Ventilator Induced Lung Injury**

Gerard F Curley, Maya Contreras, Brendan Higgins, Daniel O'Toole, John G Laffey  
Corresponding Author: curleygerard@gmail.com  
Department of Anaesthesia and Intensive Care, National University of Ireland, Galway, Ireland

**Introduction:** Acute Lung Injury (ALI), and its more severe subset the Acute Respiratory Distress Syndrome (ARDS), are a major cause of mortality in the Intensive Care Unit. 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. 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 contribute to our understanding of VILI and assist in developing strategies to hasten recovery from ARDS.

**Methods:** Male Sprague Dawley rats were anaesthetized, oro-tracheally intubated and subjected to injurious ventilation until a defined worsening of compliance was noted. The rats were then recovered, extubated and housed in individually ventilated cages for variable time periods to allow repair of VILI to occur. The level of ongoing injury/repair was characterised at time periods of 6 and 24 hours, 2, 4, 7 and 14 days, during harvest of the animals using blood gas analysis, compliance measurement, wet/dry ratio, BAL total protein, cytokines and cell count and histological analysis.

**Results:** Results demonstrated a time course dependent improvement in compliance and oxygenation, together with evidence of reduced lung oedema and clearance of neutrophilic infiltration at 96hrs. Tumour necrosis factor-α, and interleukins 1β, 6 and 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 (see figure) 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.

![Figure 1: Boxplots of TGF-β in broncho-alveolar lavage fluid at different time points post injury](image)

**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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