European Respiratory Society
Annual Congress 2012

Abstract Number: 748

Publication Number: P819

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: ALI (Acute Lung Injury) **Keyword 2:** Mechanical ventilation **Keyword 3:** Epithelial cell

Title: PI3K signalling may explain differential response of lung cells to mechanical stretch

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Body: Alveolar epithelial cells may be subjected to increased mechanical stretch (MS) during ventilation although low tidal volume is applied. High amplitude MS impairs PI3K activity and leads to apoptosis in alveolar type II (ATII) cells. The response of human pulmonary microvascular endothelial cells (HPMEC), fibroblasts (HPF), human A549 cells and rat ATII cells to MS is compare in this study. Stretching patterns (frequency/change in surface area) were chosen to mimic physiological breathing (P) and the effects of high frequency (hF), high amplitude (hA) and both (hFA). MS was compared with static cultures at 24h. Supernatant LDH, cell necrosis/apoptosis (Annexin-V binding/propidium iodide-staining) and cellular PI3K activity (measured as phosphorylated Akt-kinase, pAkt) were analyzed. MS increased the release of LDH in all cell types. This effect increased with the hF, hA and hFA stretching patterns. Viable HPMEC and ATII cells decreased significantly in response to MS with a minimum in the hFA and hA group; predominately due to apoptosis. A549 cells showed only a small decrease in viable cells with little change in necrotic and apoptotic cells. HPF, however, did not undergo apoptosis in response to MS. Cellular pAkt content was reduced in response to MS in HPMEC and ATII cells, unchanged in A549 cells and increased in HPF. PI3K stimulation increases the percentage of apoptotic cells. In contradiction with endothelial and epithelial cells, pulmonary fibroblasts do not undergo apoptosis and show increased PI3K in response to MS. In lung injury fibroblast may remain as a scaffold for the pulmonary structure leading the way for repair.