## S105 DOES VITAMIN D DEFICIENCY INCREASE RISK OF ACUTE LUNG INJURY POST OESOPHAGECTOMY?

doi:10.1136/thx.2010.150946.6

[1]R C A Dancer, [1]D Park, [1]V D'Souza, [2]F Gao Smith, [2]G D Perkins, [1]D R Thickett. [1]*University of Birmingham, Birmingham, UK;* [2]*University of Warwick, Warwick, UK*

**Introduction** Vitamin D has profound effects on the immune system and its deficiency has been implicated in increased risk of diseases such as tuberculosis and pneumonia. We have shown vitamin D levels to be lower in patients with Acute Lung Injury than in healthy or at risk controls. We hypothesised that vitamin D deficiency may be a risk factor for developing Acute Lung Injury (ALI) following transthoracic oesophagectomy.
**Methods** 25-OH vitamin D (tandem mass spectrometry) and 1.25-OH vitamin D (ELISA) were measured in plasma samples taken from patients prior to oesophagectomy. IL-6, RAGE and HMGB-1 were measured by ELISA. Extravascular Lung Water (EVLW) measurements were recorded using a PiCCO catheter.
**Results** All patients undergoing oesophagectomy had insufficient levels of 25-OH vitamin D (<75 nmol/l, median 25.5 nmol/l). 1.25-OH vitamin D levels ranged from 26 to 182 pmol/l (reference range 43–144 pmol/l). Patients who developed ALI more than 72 h post-op had lower levels of 25-Vitamin D (p=0.032). Very low levels of 25-OH vitamin D (<15 nmol/l) were significantly associated with elevated post-operative systemic inflammatory response (as demonstrated by higher plasma levels of IL-6 (p=0.006) and HMGB-1 (p=0.04)) with evidence of increased epithelial damage (elevated RAGE (p=0.03)). Levels of 25 vitamin $D_3$<15 nmol/l were associated with greater post-operative increases in extra vascular lung water (p=0.03). Patients with severe vitamin d deficiency (<20 nmol/l) had a 40% risk of developing post-operative ALI compared to 15% in those with less severe deficiency (p=0.03).
**Discussion** These results suggest that very low 25 vitamin D levels in oesophagectomy patients are associated with an elevated post-operative systemic inflammatory response, increased alveolar epithelial dysfunction and an increased risk of developing lung injury. These data support the rationale for clinical trials of vitamin D replacement as a preventative therapy for acute lung injury.

## S106 POLYMORPHISMS IN GENES ENCODING RAGE OR RAGE LIGANDS PREDISPOSE PATIENTS TO ADVERSE OUTCOMES FOLLOWING SURGERY NECESSITATING CARDIOPULMONARY BYPASS

doi:10.1136/thx.2010.150946.7

[1]N Zakeri, [1]B Creagh-Brown, [1]L R Hector, [1]R J Hewitt, [1]A L Lagan, [1]G J Quinlan, [2]P Pantelidis. [1]*Department of Critical Care Medicine, National Heart and Lung Institute, Royal Brompton Hospital NHS Foundation Trust, Imperial College, London, UK;* [2]*Interstitial Lung Disease Unit, National Heart and Lung Institute, Royal Brompton Hospital NHS Foundation Trust, Imperial College, London, UK*

**Background** Surgery necessitating cardiopulmonary bypass (snCPB) induces a systemic inflammatory response which can lead to organ dysfunction, including acute lung injury (ALI). Polymorphisms in inflammatory genes have been linked to adverse clinical outcomes following snCPB. The receptor for advanced glycation end products (RAGE) is an inflammation-perpetuating pattern recognition receptor. We investigated the hypothesis that polymorphisms in genes encoding RAGE or RAGE ligands predispose patients to a more severe systemic inflammatory response and the development of ALI after snCPB.
**Methods** In a nested unmatched case–control study 187 UK Caucasian patients undergoing cardiac surgery necessitating CPB were genotyped for eight biallelic single nucleotide polymorphisms (SNPs) in the *RAGE*, *S100A8* and *HMGB1* genes using sequence-specific primer polymerase chain reactions. Intensive care unit length of stay, duration of level 3 care, post-operative neutrophil and white blood cell count (WCC), C-reactive protein (CRP) and $PaO_2$:$FiO_2$ ratio were used as clinical outcome measures.
**Results** All SNPs conformed to Hardy–Weinberg equilibrium. Patients carrying the C alleles of rs3795391 and rs3806232 SNPs, in linkage disequilibrium in the *S100A8* gene, had a higher neutrophil and WCC (p=0.019, p=0.039 respectively) and a lower $PaO_2$:$FiO_2$ (p=0.01) on post-operative day 3. Median post-operative $PiO_2$:$FiO_2$ of patients carrying the C alleles versus those not was 123.5 mm Hg vs 204.4 mm Hg. Patients carrying the GG genotype of the rs2070600 (Gly82Ser) SNP in the *RAGE* gene had a higher neutrophil count on post-operative day 2 (p=0.025). Patients carrying the T allele of the *RAGE* rs1800624 (−374T/A) SNP had higher CRP levels on post-operative day 1 (p=0.015).
**Conclusion** SNPs in the *RAGE* and *S100A8* genes are associated with the intensity of the systemic inflammatory response and patient oxygenation levels in our cohort of patients following snCPB. Patients carrying the C alleles of the *S100A8* SNPs had significantly impaired oxygenation in the early post-operative period compared to patients carrying the TT genotype, suggesting a genetic influence on the degree of lung injury arising as a result of snCPB. Pre-operative genotyping for polymorphisms associated with adverse outcomes may be used to stratify patients' risk from snCPB, allowing the development of interventions designed to reduce post-operative morbidity and mortality.

## S107 COMPARISON OF HIGH-STRETCH VERSUS ATELECTASIS IN THE PATHOPHYSIOLOGY OF VENTILATOR-INDUCED LUNG INJURY USING THE MOUSE ISOLATED PERFUSED LUNG

doi:10.1136/thx.2010.150946.8

K Wakabayashi, M R Wilson, K P O'Dea, M Takata. *Section of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, London, UK*

**Introduction** Mechanical ventilation promotes pulmonary inflammation and oedema formation, a process known as ventilator-induced lung injury (VILI). Various aspects of ventilation have been proposed as injurious, including over distension of alveoli and the repetitive collapse and reopening of lung units associated with atelectasis. Here we attempt to elucidate the impact of these distinct entities on the pathophysiology of VILI, using a mouse isolated perfused lung, which enables us to study the effects of stretch versus atelectasis in the absence of extra pulmonary factors.
**Methods** Lungs were obtained from male C57BL6 mice, and allocated to one of three groups, that is, control, atelectasis or high-stretch. All the lungs were ventilated with respiratory rate of 80/min, and perfused at 25 ml/kg/min in a recirculating manner with non-blood buffer for 3 h. In the control group, low tidal volume (7 ml/kg) with positive end-expiratory pressure (PEEP; 5 $cmH_2O$) and regular deep inflation (DI; 25 $cmH_2O$, every 15 min) was applied. The atelectasis group received the same low tidal volume, but neither PEEP nor DI. In the high-stretch group, lungs were ventilated with high tidal volume (30–32 ml/kg) and both PEEP (3 $cmH_2O$) and DI. Perfusate and lung lavage samples were taken at the end of experiments for analysis of total protein and chemokines.
**Results** The lungs in the atelectasis and high-stretch groups developed similar, severe pulmonary oedema as represented by increases in protein levels in lavage fluid. High-stretch induced substantial increases in both perfusate and lavage fluid chemokines, compared to controls. In stark contrast, the atelectasis group showed similar low levels of chemokines in perfusate, with only slight increases in lavage fluid chemokines, compared to controls (Abstract S107 Table 1).