

Caffeine induced a concentration-dependent decrease in TGF $\beta$  activation in iHBECs but had no effect on TGF $\beta$  activation in lung fibroblasts. Furthermore, caffeine reduced expression of the TGF $\beta$ -inducible genes *PAI1* and *Col1A* and reduced *TGF $\beta$ 1* transcript in epithelial cells. Additionally, caffeine reduced TGF $\beta$ -induced proliferation of lung fibroblasts and reduced expression of pro-fibrotic genes including *COL1A* and *ACTA2*. Crucially, *ex vivo* treatment of fibrotic PCLS from bleomycin treated animals with caffeine caused a dose-dependent reduction in collagen deposition after five days. Caffeine had no effect on collagen deposition in PCLS isolated from saline treated animals nor did caffeine affect tissue viability in PCLS from either saline or bleomycin treated animals.

In conclusion, caffeine has anti-fibrotic effects in the lung via concomitant inhibition of epithelial TGF activation and fibroblast responses to TGF $\beta$ .

### S67 VITAMIN D DEFICIENCY DRIVES PULMONARY INFLAMMATION IN A HUMAN MODEL OF THE ACUTE RESPIRATORY DISTRESS SYNDROME INDUCED BY INHALED LIPOPOLYSACCHARIDE IN HEALTHY VOLUNTEERS

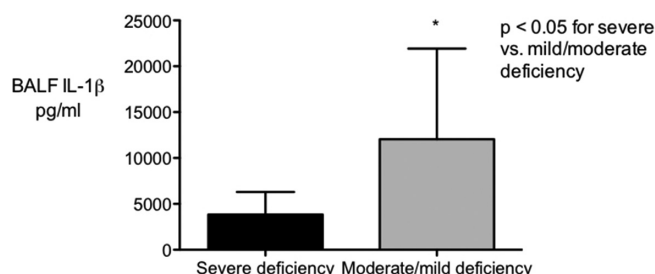
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10.1136/thoraxjnl-2015-207770.73

The acute respiratory distress syndrome (ARDS) is characterised by exaggerated alveolar inflammation. Vitamin D deficiency in an LPS induced murine model of ARDS results in exaggerated alveolar inflammation. However the role of vitamin D deficiency in pulmonary inflammation in humans is unclear. We hypothesised that in healthy volunteers with vitamin D deficiency, pulmonary inflammation would be increased following LPS inhalation.

**Methods** Healthy volunteers inhaled 50 micrograms of LPS and six hours later underwent bronchoalveolar lavage for measurement of cytokines. Plasma was collected at baseline and one day post LPS inhalation for measurement of vitamin D.

**Results** 28 participants were included. The mean age of volunteers was 26.2 +/- 5.5 years. All 28 patients were vitamin D deficient (plasma levels <50 nmol/l), with 89% (25/28) patients having severe vitamin D deficiency (<25 nmol/l). Vitamin D levels were significantly higher after LPS inhalation ( $p < 0.002$ ). Levels of IL-1 $\beta$  in BALF were significantly higher in those with severe deficiency than those with mild/moderate deficiency (Figure 1;  $p = 0.04$ ). Levels of IL-6, IL-8 or TNF- $\alpha$  did not differ between groups.



**Abstract S67 Figure 1** Bronchoalveolar lavage fluid (BALF) levels of IL-1 beta were significantly elevated in volunteers with severe plasma vitamin D deficiency (<25 nmol/l) compared to those with mild or moderate deficiency (25–50 nmol/l)

**Conclusions** Vitamin D deficiency was highly prevalent in this population of healthy volunteers. The rise in vitamin D levels post LPS exposure may represent mobilisation of vitamin D from fat stores during inflammation though vitamin D metabolism and kinetics are complex and may differ in healthy volunteers and the critically ill. Severe deficiency correlated with increased alveolar inflammation.

## Lung infection and primary ciliary dyskinesia

### S68 A LONGITUDINAL STUDY CHARACTERISING A LARGE ADULT PRIMARY CILIARY DYSKINESIA COHORT

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10.1136/thoraxjnl-2015-207770.74

Adult Primary Ciliary Dyskinesia (PCD) has not been well characterised. Patients have varied radiological severity of disease and lung function impairment and limited data is available regarding prognosis. In this retrospective study we describe and characterise a large adult PCD cohort, and identify determinates of disease progression using longitudinal lung function data.

We retrospectively analysed 151 adult patients at a single tertiary centre. Overall mortality was 4.6% over a 7-year median follow-up period. Lung function decline was estimated at 0.49% FEV<sub>1</sub>predicted/year. Older age at diagnosis showed moderate negative correlation with FEV<sub>1</sub>predicted at diagnosis ( $r = -0.30$ ;  $p = 0.01$ ) and increased *Pseudomonas aeruginosa* colonisation ( $p < 0.01$ ) but not longitudinal FEV<sub>1</sub>predicted ( $\beta = 0.001$ ; (95% CI:-0.35,0.35)). Within multivariate mixed models of FEV<sub>1</sub> adjusting for ciliary ultrastructure, HRCT scoring of severity of bronchial wall dilatation ( $p < 0.01$ ) and extent of bronchiectasis ( $p = 0.03$ ) showed evidence of modifying the decline in FEV<sub>1</sub> with age. Lung function decline additionally differed by ciliary ultrastructure ( $p = 0.04$ ) with patients with microtubular defects having the greatest decline.

Our study reveals a large proportion of adult PCD patients are diagnosed late with lower FEV<sub>1</sub> and increased *P. aeruginosa* colonisation at diagnosis. Increased disease burden on HRCT and microtubular defects on ciliary ultrastructure predicts progressive lung function decline. This study highlights the need for early diagnosis alongside prospective multi-centre disease-specific trials to confirm triggers for lung function decline and identify potential novel therapeutic strategies.

### S69 DEVELOPMENT OF AN *IN VITRO* ASSAY TO DETECT CHEMICALLY-INDUCED CHANGES IN CILIARY BEAT FREQUENCY

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10.1136/thoraxjnl-2015-207770.75

Techniques are well-established to quantify ciliary beat frequency (CBF), which is often reduced in patients with primary ciliary dyskinesia. This project aims to determine the impact of genetic