S39 SYSTEMIC BIOCHEMICAL MARKERS ARE IMPORTANT IN MORTALITY PREDICTION IN MESOTHELIOMA: A NOVEL PREDICTION MODEL

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doi:10.1136/thx.2009.127068m

Introduction Malignant pleural mesothelioma is frequently considered clinically to be localised to the chest, although it may often have significant systemic manifestations in advanced disease. Classification and Regression Tree (CART) analysis is able to create decision trees and classify risk groups by analysing the interaction between different variables and an outcome measure. We analysed clinical and laboratory data to identify prognostic factors for 1-year mortality in patients with mesothelioma in Portsmouth, UK, a dockyard city with high previous asbestos usage.

Methods Data from 323 histologically confirmed mesothelioma cases were retrospectively analysed using electronic demographic records, laboratory result databases and case note review. 24 routinely collected variables at the time of diagnosis (including histology, haematological, serum and pleural fluid biochemical results, co-morbidity and presenting symptoms) were analysed using CART modelling (utilising the V-fold cross validation technique) to establish prognostic indices for 1-year mortality.

Results Of the 323 cases, 273 (84%) were male, mean (±SD) age at the time of diagnosis was 68 (±10) years and mean body mass index (BMI) was 24.01 (±4.1) kg/m^2; at the time of data collection 265 (82%) of the cohort were dead. Overall median survival was 7.0 (interquartile range (IQR) 3–12) months. 72 (22%) patients had chemotherapy, and no patients were referred for trimodality therapy. CART identified six risk groups using five variables to best fit a prediction model with a C-statistic of 0.63. The best prognostic group had a serum albumin >37.5 g/l and urea <5.0 mmol/l (1-year mortality 25.0%); the highest risk group had a serum albumin ⩽37.5 g/l, alkaline phosphatase >100.0 IU/l, phosphate ⩽1.14 mmol/l and did not receive chemotherapy (1-year mortality 80.0%); a full breakdown of risk group parameters is provided in table 1.

Conclusions Simple, objective, biochemical markers taken at the time of diagnosis may provide important prognostic information for mortality from mesothelioma. These indices are likely to be reflective of underlying systemic and nutritional health. An awareness of these parameters may augment clinical and multidisciplinary team decisions, although the accuracy of the model precludes its use alone to inform treatment decisions.

Abstract S39 Table 1 Stratification of different risk groups to predict 1-year mortality in mesothelioma patients

	High risk		Medium risk			Low risk
	Risk 1	Risk 2	Risk 3	Risk 4	Risk 5	Risk 6
n/N (%: mortality)	16/20 (80.0%)	25/35 (71.4%)	86/133 (64.7%)	45/71 (63.4%)	16/40 (40.0%)	6/24 (25.0%)
Parameter						
Albumin (g/l)	⩽37.5	>37.5	⩽37.5	⩽37.5	⩽37.5	>37.5
Alkaline phosphatase (IU/l)	>100.0	–	>100.0	⩽100.0	>100.0	–
Urea (mmol/l)	–	>5.0	–	–	–	<5.0
Phosphate (mmol/l)	⩽1.14	–	>1.14	–	⩽1.14	–
Chemotherapy	No	–	–	–	Yes	–

n, number of deaths within a category; N, total numbers within a category.

Clinical studies into the pathogenesis of acute lung injury

S40 LIPOPOLYSACCHARIDE INHALATION DRIVES PULMONARY INFLAMMATION AND CAUSES ALVEOLAR EPITHELIAL AND ENDOTHELIAL ACTIVATION/INJURY IN AN IN VIVO HUMAN MODEL OF ACUTE LUNG INJURY

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doi:10.1136/thx.2009.127068n

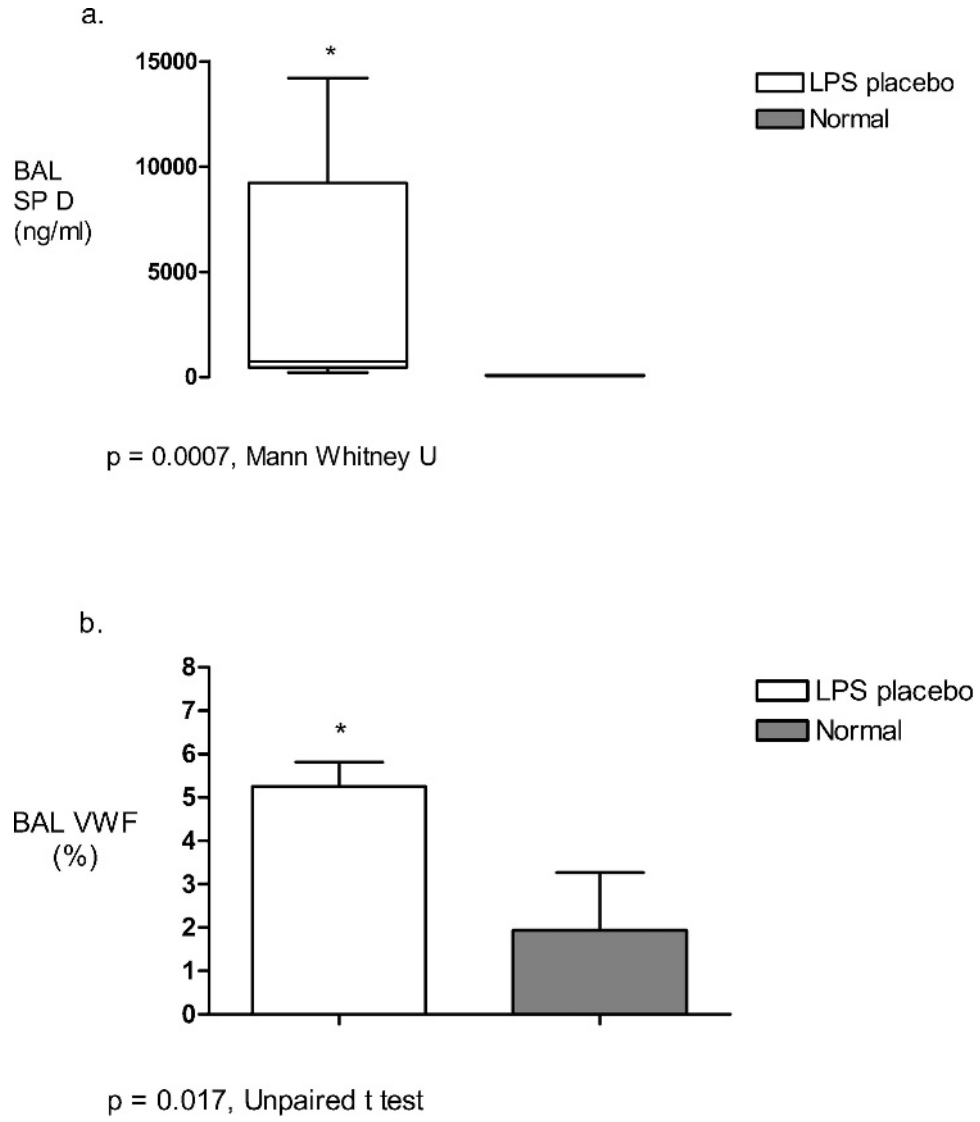
Acute lung injury (ALI) is an inflammatory process characterised by damage to the alveolar epithelial–capillary endothelial barrier leading to alveolar flooding. The objective of this study was to determine if lipopolysaccharide (LPS) inhalation, as an in vivo human model of ALI, causes alveolar epithelial and endothelial activation/injury.

Ten healthy subjects, enrolled in the placebo arm of a clinical trial,[1] who inhaled 50 μg of LPS, and 5 healthy controls were recruited. Bronchoalveolar lavage (BAL) was performed at 6 h and plasma sampling at 24 h after LPS inhalation. Surfactant protein-D (SP-D), an alveolar type 2 epithelial cell biomarker, von Willebrand factor (vWF), an endothelial cell biomarker, and calgranulin C reflecting neutrophil and/or macrophage activation were measured by ELISA. Cytokines were measured by cytometric bead array. The protein permeability index (PPI) (BAL protein/plasma protein ratio) was calculated as a marker of barrier integrity. Data are mean (±SD) or median (interquartile range).

LPS inhalation induced a significant increase in BAL SP-D (fig 1a) and BAL vWF (fig 1b). There was a significant increase in plasma SP-D (ng/ml) (107.3 (69.2–132.2) vs 35.4 (28.8–61.5), $p = 0.005$) but no change in plasma vWF levels. BAL calgranulin C (pg/ml) was also increased (176.8 (90.1) vs 5.1 (3), $p<0.001$). There was an associated increase in BAL interleukin-6 (IL-6) (pg/ml) (509.8 (264.0) vs (1.6 (0.5) $p = 0.001$), IL-8 (pg/ml) (389.4 (93.6) vs (28.8 (12.67) $p<0.0001$) and (monocyte chemoattractant protein-1 (MCP-1) (pg/ml) (562.4 (257.3) vs (13.7 (7.3) $p = 0.0004$). In contrast, only MCP-1 was detectable in plasma after LPS inhalation but was not increased compared with normal volunteers. PPI was significantly elevated after LPS inhalation compared with normal volunteers ($p<0.05$).

This is the first study to demonstrate alveolar epithelial and endothelial activation/injury due to LPS inhalation in vivo. It is likely that the proinflammatory response characterised by the local pulmonary release of inflammatory mediators induced by LPS inhalation causes the epithelial and endothelial activation/injury. This model of ALI shows an increase in a range of biomarkers implicated in ALI and is a valuable tool in early phase clinical trials of potential pharmacological therapies for ALI.

1. **Shyamsundar M** *et al*. *AJRCCM*, 2009;**179**:1107–1114.



Abstract S40 Figure 1 BAL, bronchoalveolar lavage; LPS, lipopolysaccharide; VWF, von Willebrand factor; SP D, surfactant protein-D.

S41 INCREASING PULMONARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN IS ASSOCIATED WITH RESOLUTION OF PULMONARY OEDEMA AND ICU SURVIVAL IN ACUTE LUNG INJURY

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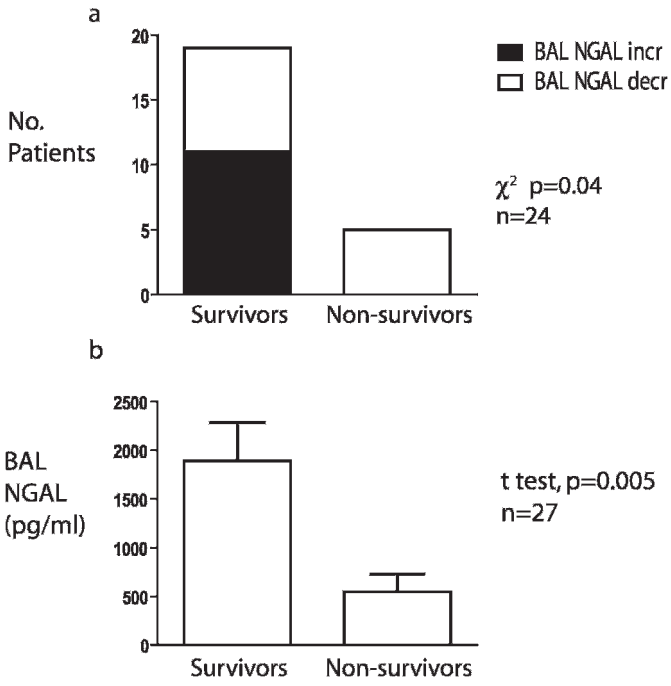
doi:10.1136/thx.2009.127068o

Background Matrix metalloproteinase-9 (MMP-9) has been implicated in the resolution of acute lung injury (ALI). Neutrophil gelatinase-associated lipocalin (NGAL) is a complex of lipocalin and MMP-9, secreted by neutrophils and epithelial cells. We investigated changes in bronchoalveolar lavage (BAL) fluid and plasma NGAL concentrations, reflecting epithelial and neutrophil production of MMP-9, in patients with ALI and correlated these with extravascular lung water (EVLW) and intensive care unit (ICU) mortality.

Methods Patients within 48 h of onset of ALI were recruited to a double-blind placebo-controlled trial of simvastatin for up to 14 days (HARP study). Plasma and BAL (where possible) were collected at baseline and at 72 h. EVLW indexed to predicted body weight (EVLWp) was measured in ICU patients by thermodilution (PiCCO). BAL from a group of healthy volunteers was used as a control (n = 5). NGAL was measured by a point of care rapid NGAL assay (BioSite Inc). Data were analysed by Mann–Whitney or t tests.

Results Simvastatin treatment did not alter NGAL concentrations, EVLWp or mortality. The following results are from both the simvastatin and placebo groups combined. BAL NGAL was significantly elevated in ALI compared with healthy controls (median 821 vs 13 pg/ml 8, p = 0.0006). Baseline BAL NGAL and EVLWp were similar in survivors and non-survivors. Patients whose BAL NGAL increased over the first 72 h had significantly lower EVLWp at day 3 than those whose BAL NGAL fell (12.7±1.4 vs 18.9±2.6 ml/kg, $p<0.05$, n = 24). All patients who increased BAL NGAL concentration over the 72 h period survived (fig 1a). Day 3 BAL NGAL was >3-fold higher in ICU survivors compared with non-survivors (fig 1b). Findings were similar when NGAL was corrected for BAL protein, indicating this is not simply a feature of oedema concentration upon re-absorption. Baseline plasma NGAL was similar in survivors and non-survivors. In contrast to BAL, ICU survivors had a non-statistically significant decrease in plasma NGAL at day 3 compared with non-survivors (p = 0.13).

Conclusion Increasing lipocalin-complexed MMP-9 (NGAL) in the pulmonary but not systemic compartment is associated with improved survival and clearance of pulmonary oedema fluid in ALI. These data further implicate pulmonary MMP-9 in the resolution of ALI.



Abstract S41 Figure 1 BAL, bronchoalveolar lavage; NGAL, neutrophil gelatinase-associated lipocalin,

S42 THE EFFECT OF EX VIVO LUNG PERFUSION ON PROINFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES IN THE HUMAN LUNG

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doi:10.1136/thx.2009.127068p

Background Ex vivo lung perfusion (EVLP) is an emerging technique for the re-conditioning of damaged donor lungs prior to transplantation. Previous work has demonstrated improvement in gas exchange in lungs subjected to this technique; however, the effect of EVLP on inflammation has not yet been examined. We hypothesised that a potential benefit of EVLP in re-conditioning donor lungs may be due to modification of the inflammatory profile.

Methods Five human donor lungs rejected clinically for transplantation were recruited. Three had cellular and two acellular perfusion for 6 h in a normothermic ex vivo setting. Circulating perfusate was sampled hourly and bronchoalveolar lavage (BAL) was performed before and after perfusion. The concentrations of the proinflammatory cytokine interleukin-8 (IL-8) and the anti-inflammatory cytokine IL-10 were measured in both perfusate and BAL using the sandwich ELISA technique.

Results There was a statistically significant increase of IL-8 concentration in the perfusate with a median after 1 h of perfusion of 1.20 ng/ml (range 0.49–5.56 ng/ml) increasing to 40.05 ng/ml (range 11.57–65.08 ng/ml) at 6 h ($p = 0.0012$). Similarly for IL-10, perfusate median at 1 h was 0.25 ng/ml (range 0.22–0.34 ng/ml) increasing to 0.48 ng/ml (range 0.38–1.90 ng/ml) at 6 h ($p = 0.0068$). There was no statistically significant difference in either cytokine in BAL preperfusion and postperfusion; however, there was a downward trend in IL-8 concentration postperfusion, with preperfusion median 49.61 ng/ml (range 4.51–135 ng/ml) reducing to 34.26 ng/ml (range 9.70–51.36 ng/ml) postperfusion. In contrast, IL-10 concentration in lungs subjected to acellular perfusion only appears to increase postperfusion (preperfusion median 0.025 ng/ml, postperfusion 0.40 ng/ml).

Conclusion The current study suggests that there is a significant effect of EVLP on inflammation in the human lung. The increasing levels of proinflammatory and antiinflammatory cytokines in perfusate over time is suggestive of a 'wash-out' effect of perfusion, possibly due to cytokines diffusing out of the lung tissue in response to binding to the circulating heparin. There is also an intriguing trend in the BAL, of decreasing proinflammatory and increasing anti-inflammatory cytokines. This effect could have a beneficial impact on outcomes following transplantation, as previous work has shown a correlation of high IL-8 levels in donor lung BAL with early graft failure.

S43 DEFECTIVE EFFEROCYTOSIS DUE TO ABERRANT INTRAPULMONARY STEROID METABOLISM CONTRIBUTES TO PERSISTENT INFLAMMATION IN ARDS

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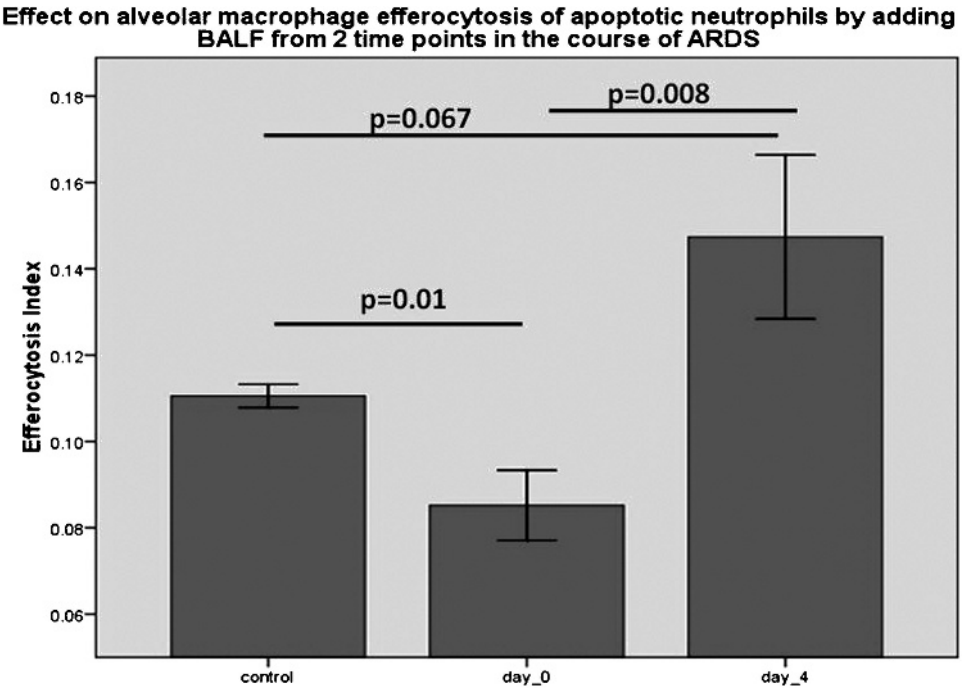
doi:10.1136/thx.2009.127068q

Introduction Efferocytosis, the removal of spent and apoptotic cells, is necessary for the resolution of inflammation. Failure of efferocytosis results in proinflammatory mediator release and further tissue damage. A defect in the removal of spent neutrophils by alveolar macrophages (AMs) in the acute respiratory distress syndrome (ARDS) may contribute to ongoing inflammation. Corticosteroids increase efferocytosis in other cell types. We have previously shown a decrease in cortisol levels in the bronchoalveolar lavage fluid (BALF) of patients with persistently severe ARDS. The aim of this study was to investigate whether corticosteroids and their intrapulmonary metabolism by hydroxysteroid dehydrogenase (HSD) influences efferocytosis in ARDS.

Methods An efferocytosis assay using fluorescently labelled apoptotic neutrophils was used in conjunction with established HSD activity assays and flow cytometry techniques.

Results Efferocytosis was decreased by BALF taken from patients at day 0 of disease, compared with saline controls ($p = 0.01$). Efferocytosis induced by BALF taken at day 4 of ARDS was higher than that of day 0 BALF ($p = 0.008$), but no different from that of control ($p = 0.067$). BALF had no effect on cell viability. Efferocytosis is upregulated by cortisol and cortisone. Efferocytosis upregulation by cortisone is suppressed by HSD inhibitors ($p = 0.037$). Salbutamol also upregulates efferocytosis in a dose-dependent manner (analysis of variance (ANOVA): $p = 0.001$), and has an additional effect when combined with cortisol. Alveolar macrophages from patients with ARDS have decreased HSD conversion of cortisone to cortisol at diagnosis of ARDS compared with day 4 (0.10 vs 0.57 pmol/10^6 cells/h, $p = 0.039$, $n = 12$). Annexin V/propidium iodide flow cytometry of ARDS BALF neutrophils ($n = 14$) demonstrates an increase in late apoptotic and necrotic cells compared with human lipopolysaccharide (LPS) challenge ($n = 20$).

Conclusions Local steroid metabolism by HSD is dysregulated early in ARDS. Low cortisol levels and defective HSD activity is associated in vitro with defective efferocytosis. ARDS BALF suppresses efferocytosis of apoptotic neutrophils, suggesting that the alveolar phagosome may be defective in ARDS. This hypothesis is supported by flow cytometry data suggesting that these changes may contribute to persistence of inflammation in ARDS.



Abstract S43 Figure 1 ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid.

S44 ONCOSTATIN-M IS PRODUCED BY INFLAMMATORY CELLS AND DRIVES CXCL8 FROM RESIDENT PULMONARY CELLS IN A MODEL OF ACUTE LUNG INJURY

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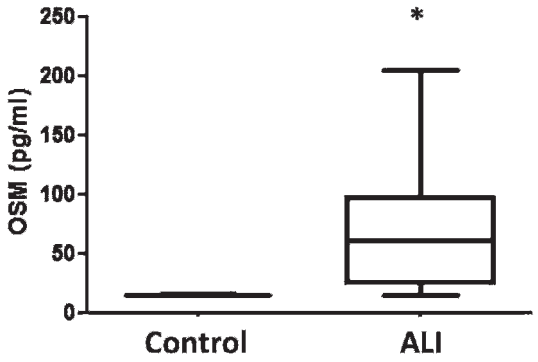
doi:10.1136/thx.2009.127068r

Background Acute lung injury (ALI) is characterised by uncontrolled inflammation in the alveolar space with resultant damage to the alveolar–capillary barrier. Oncostain-M (OSM) is a multifunctional cytokine secreted by inflammatory cells. Synergy between OSM and other inflammatory cytokines drives potent cytokine secretion in other diseases, but has not been shown in ALI.
Hypothesis OSM secretion by inflammatory cells in the alveolar space in ALI drives cytokine secretion.
Methods OSM was measured in bronchoalveolar lavage fluid (BALF) from patients with ALI within 24 h of onset. Human type II-like alveolar epithelial (A549) cells or lung fibroblasts were stimulated with OSM and/or tumour necrosis factor-α (TNFα). CXCL8 was measured by ELISA. Human neutrophils, monocytes and monocyte-derived macrophages (MDMs) were isolated from peripheral blood. Cells were stimulated with lipopolysaccharide (LPS) (0–100 ng/ml range) with or without mitogen-activated protein kinase (MAPK) inhibitors (MAPKis). OSM was measured by ELISA.
Results OSM is significantly upregulated in BALF in ALI (fig 1). OSM alone had no effect upon fibroblast CXCL8 production; however, in combination with TNFα, OSM significantly upregulated CXCL8 compared with TNFα alone (36.4 ± 0.9 vs 14.5 ± 1.2 ng/ml, respectively, $p \leqslant 0.05$). Compared with control, LPS induced a significant increase in neutrophil (10 ng/ml; 4.2 ± 2 vs 87.4 ± 14.8 pg/ml, $p = 0.000$), monocyte (100 ng/ml; 8.4 ± 7.4 vs 93.2 ± 28.4 pg/ml, $p = 0.002$) and MDM (100 ng/ml; 97.1 ± 5.7 vs 1646.6 ± 340.9 pg/ml, $p = 0.000$) OSM production. Only the p38 inhibitor SB203580 (10 μM) significantly reduced neutrophil OSM production ($22.8 \pm 1.8\%$ decrease vs media control; $p = 0.000$). Monocyte OSM production significantly decreased in a dose-dependent manner in response to each MAPKi ($p \leqslant 0.05$).
Conclusions OSM synergises with TNFα to drive epithelial and fibroblast CXCL8 secretion. LPS induces OSM secretion by inflammatory cells present during ALI. Neutrophil OSM production is p38 dependent, while monocyte and MDM OSM production is dependent on all three MAPK pathways. Inhibition of OSM production may attenuate the inflammatory response in ALI and may be a novel therapeutic target.

Funding: This work was funded by the Intensive Care Society, UK.



Abstract S44 Figure 1 Oncostain-M (OSM) is significantly upregulated in bronchoalveolar lavage fluid in acute lung injury (ALI).

S45 POLYMORPHISMS IN INFLAMMATORY PATHWAY GENES PREDISPOSE PATIENTS TO ADVERSE OUTCOMES AFTER CARDIOPULMONARY BYPASS SURGERY

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doi:10.1136/thx.2009.127068s

Introduction The systemic inflammatory response syndrome (SIRS) is a common consequence of surgery requiring cardiopulmonary bypass (CPB). The more serious sequelae of SIRS include acute lung injury (ALI) and other organ dysfunction. Inflammatory cytokines

play a central role in the pathogenesis of these syndromes. We hypothesised that variation in genes encoding the cytokines tumour necrosis factor (TNF), lymphotoxin α (LTA), interleukin-6 (IL-6) and IL-10 may predispose certain patients to SIRS and organ dysfunction following CPB.

Aim To determine the distribution of 14 biallelic single nucleotide polymorphisms (SNPs) from candidate genes in patients undergoing CPB surgery and investigate their relationship with adverse outcome measures.

Method A nested, unmatched case–control study conducted in the surgical theatres and adult intensive care unit (ICU) of a university hospital. DNA from 137 Caucasian patients undergoing complex cardiac surgery requiring CPB was genotyped by sequence-specific primer PCR. Length of stay in ICU, white cell count (WCC), C-reactive protein and postoperative PaO_2:FiO_2 were used as adverse outcome measures.

Results All SNPs conformed to Hardy–Weinberg equilibrium. Carriage of the IL-6-174C allele was associated with a lower postoperative PaO_2:FiO_2 263.5±86.8 mm Hg vs non-carriage 302.7±99.8 mm Hg, p = 0.028. The LTA +252 and LTA +723 genotype influenced the level of WCC on postoperative days 2 and 3 ($p<0.001$). WCC increased with a dose increase of the LTA +252A or LTA +723C alleles.

Conclusion We have found evidence for a genetic influence on the development of adverse outcomes after CPB. IL-6 alleles are associated with poor oxygenation after CPB. PaO_2:FiO_2 <300 mm Hg is one of three criteria used to diagnose ALI. Polymorphisms of IL-6 potentially influence the degree of lung injury arising as a result of CPB. Genetic variation in LTA influences the size of the white cell response to CPB. The intronic SNP LTA +252 has previously been associated with severe sepsis, and SNP +723 leads to a non-synonymous amino acid change that could alter protein function. Preoperative screening for the presence of polymorphisms associated with adverse outcome may allow stratification of high risk groups and development of interventions designed to limit postoperative morbidity and mortality.

Airway challenges

S46 EFFECTS OF ALLERGEN AND TRIGGER FACTOR AVOIDANCE ADVICE IN PRIMARY CARE ON ASTHMA CONTROL: A RANDOMISED CONTROLLED TRIAL

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doi:10.1136/thx.2009.127068t

Background Allergy contributes significantly to asthma exacerbation, yet avoidance of allergic triggers is rarely addressed in detail in regular asthma review in primary care.

Objective To determine whether structured, individually tailored allergen and trigger avoidance advice, given as part of a primary care asthma review, improves lung function and asthma control.

Methods In a randomised controlled trial 214 adults with asthma in six general practices were offered either usual care during a primary care asthma review or usual care with additional allergen and trigger identification (by skin prick testing and structured allergy assessment) and avoidance advice according to a standardised protocol by trained practice nurses. Main outcome measures were lung function, asthma control and asthma self-efficacy.

Results Both intervention groups were equivalent in demographic and asthma-related variables at baseline. At 3-month follow-up, patients receiving the allergen and trigger avoidance review showed significant improvements in lung function (assessed by blinded research nurses) compared with those receiving usual care. Adjusted post-treatment means: forced expiratory volume in 1 s (FEV_1) intervention 2.58 litres (2.52–2.63) vs control 2.44 (2.38–2.50) $p<0.01$; lung age 58.8 years (56.6–60.6) vs 62.0 (59.8–64.3) $p<0.05$, respectively. No significant differences were found in self-report measures of asthma control. Asthma-specific self-efficacy improved in both groups but did not differ between groups.

Conclusion Allergen and trigger identification and avoidance advice, given as part of a structured asthma review delivered in primary care by nurses results in clinically important improvements in lung function but not self-report of asthma control.

Trial registration number ISRCTN45684820.

S47 DISCONNECT BETWEEN STANDARDISED FIELD-BASED TESTING AND MANNITOL CHALLENGE IN SCOTTISH ELITE SWIMMERS

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doi:10.1136/thx.2009.127068u

Introduction and Objectives Elite swimmers have high rates of rhinoconjunctivitis and exercise-induced bronchospasm (EIB). Moreover, exposure to chlorine and chlorine metabolites is known to induce hyper-reactivity. In track and winter sports athletes, prolonged high-volume gas exchange is thought to generate an osmolar bronchial challenge through drying and cooling of the airways. Mannitol challenge is an osmolar challenge and thought to be a reliable surrogate of EIB in athletes. Elite swimmers also generate high levels of gas exchange, but, unlike other athletes, their environment is warm, humidified and chlorinated. We sought to assess the effects of chlorine and exercise on the unified airway of national level elite swimmers.

Methods The Scottish National Youth Squad underwent exhaled tidal (FE_{NO}) and nasal (N_{NO}) nitric oxide measurement, peak nasal inspiratory flow (PNIF) and forced expiratory volume in 1 s (FEV_1) before, immediately after and 4–6 h postswimming. A standardised sport-specific exercise test was carried out during an intensive lactate set. Swimmers also performed mannitol challenge and a health questionnaire.

Results 61 swimmers were assessed: 8/59 (14%) of swimmers had a positive mannitol challenge; 9/57 (16%) of swimmers had a positive exercise test. Only one swimmer was positive to both. Swimmers with a positive mannitol had a significantly higher baseline FE_{NO} than those with a positive exercise challenge. A significant decrease in FE_{NO} was observed prechlorine exposure vs immediate-post-chlorine and delayed-postchlorine exposure: mean (95% CI) 18.7 ppb (15.9 to 22.0) vs 15.9 ppb (13.3 to 19.1, $p<0.01$) and 13.9 ppb (11.5–16.7, $p<0.01$), respectively. There were no significant differences in N_{NO}. Mean (SEM) PNIF increased from 142 (6) l/min at baseline to 163 (6) l/min immediately postexposure ($p<0.01$). Delayed postexposure PNIF was not significantly different from pre-exposure.

Conclusions No association was found between mannitol and standardised sport-specific exercise challenge in elite swimmers. Mannitol but not excercise was associated with a high baseline FE_{NO}. Thus mannitol may identify swimmers with a ''traditional'' inflammatory asthmatic phenotype, while field-based exercise challenge may identify a swimmer's specific bronchoconstrictor response to hyperventilation in a chlorine-rich environment. A sustained fall in FE_{NO} following chlorine exposure suggests that a non-cellular, perhaps neurogenic, response may be involved in this group of athletes.