Final report: Utility of a panel of acute lung injury biomarkers following lung resection – a pilot study

Introduction

Biochemical markers of acute lung injury (ALI) may facilitate earlier diagnosis, identification of patients at risk, may serve as a predictor of clinical outcome or as a guide to therapeutic strategies. A wide range of potential biomarkers have been evaluated. Fremont et al recently evaluated 21 potential biomarkers in general intensive care patients with trauma, from which they identified a "top seven" panel of biomarkers (receptor for advanced glycation end products (RAGE), procollagen peptide III (PCP-III), brain natriuretic peptide (BNP), angiopoietin-2 (ANG-II), interleukin-10 (IL-10), tumour necrosis factor alpha (TNFa), and interleukin-8 (IL-8)) which in combination had a high diagnostic accuracy in differentiating ALI from controls [1].

One lung ventilation (OLV), a necessary anaesthetic technique to facilitate surgical access during thoracic surgical procedures results in exposure of the ventilated lung to volutrauma, atelectotrauma and high inspired oxygen concentrations; conditions mimicking ventilator associated lung injury. Biochemical evidence of pulmonary inflammation is detectable in all patients following lung resection. These observations have lead to one-lung ventilation being utilised as a model of lung injury [2].

We analysed the same "top 7" biomarkers identified by Fremont et al [1] in a thoracic surgical population in order to (a) classify the response of this biomarker panel to OLV and (b) to determine any correlation between biomarker levels and PaO_2:FiO_2 in the early post-operative period.

Methods

In a previous study*, with research ethics committee approval and after obtaining informed consent we collected plasma samples pre-, immediately post- and 24 hours post-operatively from 22 patients undergoing thoracic surgery for resection of primary lung cancer. Biomarker levels at each time point were evaluated by enzyme immunoassay using commercially available kits. Results were tested for normality, log-transformed as necessary and compared using a paired t-test or Mann-Whitney U as appropriate. Correlation was determined using Pearson's or Spearman's rank correlation coefficient as appropriate. Analysis was carried out using Minitab (v16) and SPSS (v19) software.

Results

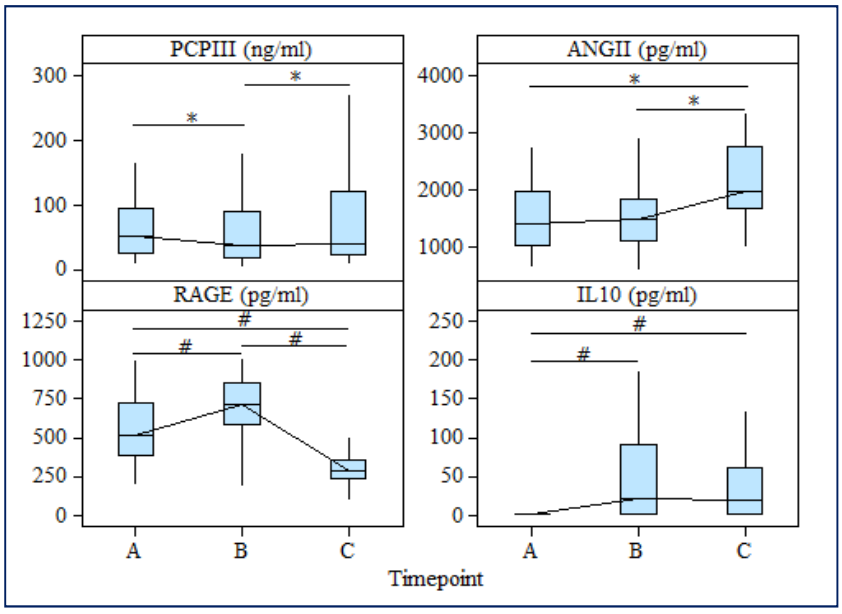

Fig 1. Plasma biomarker levels pre- (A), post- (B) and 24 hours post-operatively (C). Raw data displayed. Median, IQR and full range. * P<0.01 (log transformed, paired-t test), # P<0.01 (Mann-Whitney U test).

Biomarker response to OLV: There were no significant differences in BNP nor IL8 levels between time points. RAGE, PCP III, ANG-II, and IL-10 levels demonstrated significant changes between time points (Fig 1). TNF-alpha was not detectable in any sample.

Correlation with PaO2:FiO2 ratio: PCP-III levels correlated negatively with post-operative PaO_2:FiO_2 ratio observed six hours post-operatively (PaO_2:$FiO_{2\ six\ hours}$). Correlation existed immediately post-operatively (r= -0.52, p=0.02), at 24 hours post-operatively (r= -0.50, p=0.04) and was also evident between pre-operative PCP-III levels and PaO_2:$FiO_{2\ six\ hours}$ (Fig 2A). RAGE levels immediately post-operatively correlated with PaO_2:$FiO_{2\ six\ hours}$ (Fig 2B). There

was no association between IL-10 levels, ANG-II, IL-8, BNP and PaO_2:FiO_2 six hours.

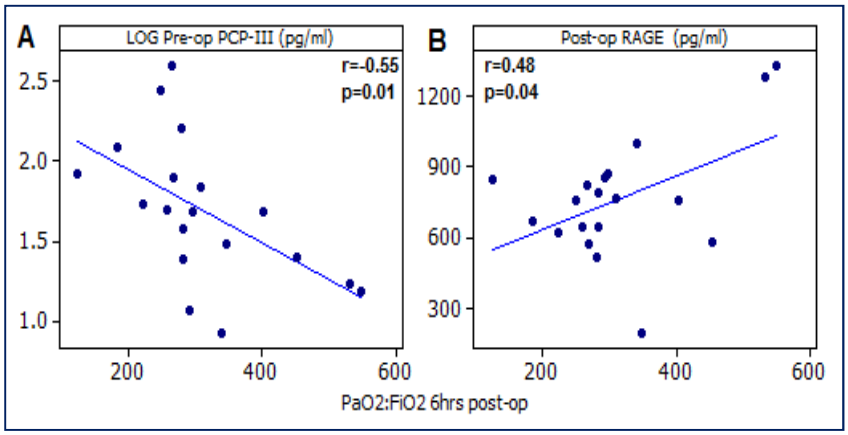

Fig 2. Pearson correlation between (A) pre-op PCP-III, (B) immediate post-op RAGE and PaO_2:FiO_2 six hours.

Discussion

We report significant changes in plasma levels of ANG-II, RAGE, PCP-III and IL-10 in response to one lung ventilation and lung resection. *Limitations:* This is a pilot study conducted in stored samples; as such there was no a priori analysis plan nor power calculation. In addition we carried out single assays of each biomarker and made multiple statistical comparisons.

Though it is possible they represent α-error, the associations observed between PCP-III, RAGE and PaO_2:FiO_2 six hours warrant further consideration. The positive correlation between plasma RAGE and PaO_2:FiO_2 six hours was unexpected; a number of studies of RAGE in the wider intensive care environment have demonstrated a negative relationship between RAGE and PaO_2:FiO_2 six hours and outcome [3]. PCP-III has been reported as an 'early biomarker' of ALI [4]. Our observation of a correlation between pre-operative (hence pre-insult) plasma PCP-III levels and PaO_2:FiO_2 six hours suggests that PCP-III is a marker of susceptibility to, rather than severity of ALI. We are planning a prospective study in order to further explore these associations.

We conclude that OLV may be a useful model in ALI biomarker research. In addition biomarkers may prove a useful monitor during the early post-operative period following lung resection. Further research is required to characterise the nature and clinical significance of the observed biomarker responses to OLV.

Dissemination

This data has been presented in part to the Association of Cardiothoracic Anaesthetist Autumn Meeting, and the Glasgow and West of Scotland Society of Anaesthetists / Glasgow Anaesthetic Research Club Annual Research Competition. The abstract will appear in Anaesthesia (in press).

Acknowledgement

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References

[1] Fremont RD, et al. Acute lung injury in patients with traumatic injuries: utility of a panel of biomarkers for diagnosis and pathogenesis. J Trauma 2010; 68(5): 1121-7. [2] Proudfoot AG, et al. Human models of acute lung injury. Disease Models & Mechanisms 2011; 4: 145-53. [3] Calfree CS, et al. Plasma receptor for advanced gycation end-products and clinical outcomes in acute lung injury. Thorax 2008; 63: 1083-9. [4] Chesnutt AN, et al. Early detection of type III procollagen peptide in acute lung injury. Am J Respir Crit Care Med 1997; 156: 840-45.

**Stored samples referred to are from the "Endogenous Antioxidant Capacity and Oxidative Stress, Nitrosative Stress and Endothelial Dysfunction after Thoracic Surgery" study. REC reference 10/S0709/43. Funded by the National Institute of Academic Anaesthesia and the Intensive Care Society (BS).*