European Respiratory Society
Annual Congress 2013

Abstract Number: 2063
Publication Number: 354

Abstract Group: 1.1. Clinical Problems
Keyword 1: Biomarkers **Keyword 2:** COPD - diagnosis **Keyword 3:** No keyword

Title: Differences in plasma and sputum biomarkers between COPD and COPD-asthma overlap

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Body: The pathophysiological features of COPD-asthma overlap are poorly understood and there has been no study of plasma or sputum biomarkers in overlap patients. In order to clarify the similarities and differences between COPD-asthma overlap and COPD or asthma, we have investigated four potential biomarkers of COPD: surfactant protein A (SP-A), soluble receptor for advanced glycation end-products (sRAGE), myeloperoxidase (MPO) and neutrophil gelatinase-associated lipocalin (NGAL). SP-A and sRAGE are pneumocyte-derived markers. MPO and NGAL are neutrophil-derived molecules but NGAL can be also expressed by respiratory epithelial cells. Plasma levels of SP-A and sRAGE and induced sputum levels of MPO and NGAL were measured by EIA/ELISA in 134 subjects: non-smokers (n=26), smokers (n=23), asthma (n=32), COPD (n=39), and COPD-asthma overlap patients (n=14). Comparisons between groups were evaluated using repeated measures analysis of variance followed by Fisher's protected least significant difference test post hoc comparison. In patients with overlap and COPD sputum MPO and plasma SP-A were significantly elevated whereas plasma sRAGE levels were reduced compared with asthma patients, but there was no significant difference in these three markers between overlap and COPD. In contrast, sputum NGAL in overlap patients (mean ± SEM, 9.1 ± 2.2 μg/ml) was significantly higher than that in COPD (4.5 ± 0.6 μg/ml) ($p = 0.00016$) and also than in asthma, smokers, and non-smokers ($p < 0.00001$). Increased induced sputum levels of NGAL might be a characteristic feature of overlap, suggesting enhanced neutrophilic airway inflammation and/or airway epithelial injury in COPD-asthma overlap.