

European Respiratory Society Annual Congress 2013

Abstract Number: 7246

Publication Number: P5156

Abstract Group: 4.3. Pulmonary Circulation and Pulmonary Vascular Disease

Keyword 1: Pulmonary hypertension **Keyword 2:** Biomarkers **Keyword 3:** No keyword

Title: Evaluation of angiotensin-2 and thrombomodulin as biomarkers for pulmonary hypertension

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Body: Introduction: Angiotensin-2 (Ang-2) was shown to be increased in plasma of idiopathic pulmonary arterial hypertension (IPAH) patients (Kümpers, P et al. European Heart Journal 2010; 31:2291–2300). On the other hand, thrombomodulin (TM) is significantly decreased in patients with IPAH and with associated forms of pulmonary arterial hypertension (Sakamaki, F et al. Circulation 2000; 102:2720-25). Aims and objectives: To investigate whether Ang-2 and TM have potential as biomarkers for clinical use in Pulmonary Hypertension (PH). Methods: Blood samples from patients with IPAH (n=40), PH associated with collagen vascular disease (CVD, n=40), pulmonary venous hypertension (PVH, n=40), chronic thromboembolic PH (n=40), and non-PH controls (n=40) were taken during right heart catheterization. Ang-2 and TM level was measured by ELISA in plasma and correlated with survival and hemodynamics. Results: Ang-2 is significantly higher in plasma from CVD patients (median 4.8, IQR 10.2 ng/ml) compared to non-PH controls (median 3.3, IQR 1.7 ng/ml, p<0.001). Ang-2 plasma levels correlate with pulmonary vascular resistance (r=0.40, p<0.001) and mixed venous oxygen saturation (r=0.513, p<0.001). Patients with Ang-2 plasma levels above the median have a poor prognosis (1-,3-,5-year survival 89, 86, 67 vs. 97, 90, 83%, p=0.145). There is no difference in plasma levels of TM between the patient groups and non-PH controls, and no association of TM with clinical parameters or prognosis. Conclusions: TM is not a biomarker for diagnosis, prognosis or severity of disease in our cohort. Ang-2 plasma levels are associated with disease severity and prognosis.