

## Platelets and Chronic Thromboembolic Pulmonary Hypertension

Roela Sadushi-Kolici, Max-Paul Winter, Cihan Ay\*, Michael Schemper<sup>1</sup>, ‡Simon Panzer, Diana Bonderman, Ioana-Alexandra Tilea, Nika Skoro-Sajer, and Irene Marthe Lang

Department of Internal Medicine II, Division of Cardiology, \*Clinical Division of Haematology and Haemostaseology, Department of Medicine I, <sup>1</sup>Center for Medical Statistics, Informatics and Intelligent Systems, Section for Clinical Biometrics, and ‡Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna

### Background.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a late sequelae of venous thrombosis with obstruction of pulmonary arteries by fibrotically transformed thrombus. Platelet function in CTEPH is poorly studied.

### Methods

In this prospective cohort study data were collected from CTEPH patients that consented at the time of diagnosis for a series of laboratory follow up visits after pulmonary endarterectomy (PEA), off anticoagulation. Platelet adhesion and aggregation were analyzed using cone and platelet analyzer. Circulating heterotypic aggregates between monocytes and platelets, and leukocytes and platelets were measured by flow cytometry. Soluble P-selectin and soluble CD40L were determined by enzym-immuno assay. Further high-sensitive CRP (hs-CRP) was analyzed. Patients with PAH, acute venous thromboembolism (VTE) and healthy subjects

served as controls.

## Results

Between June 1992 and January 2013, 176 CTEPH (mean age 59.2 years, 55.7% females), and 75 PAH patients (mean age 48.7 years, 81.3% female) registered in the Vienna PH database, fulfilled inclusion criteria. Of CTEPH patients, 53 were consented and completed a series of follow up visits over a period of  $3\pm 2$  years. At the time of database closure 18 (34%) patients had undergone PEA, and 35 (66%) patients remained non-operated.

MPA-formation, LPA-formation platelet surface coverage and average size were also significantly elevated without a significant reduction after PEA. In the non-operated group, elevated levels were sustained at follow-up. Baseline concentrations of sP-selectin ( $P<0.001$ ), and hsCRP ( $P <0.001$ ) were significantly elevated in CTEPH patients compared to PAH patients. After PEA a significant reduction of levels for sP-selectin ( $P =0.005$ ), and hs-CRP ( $P =0.035$ ) was observed.

Soluble P-selectin plasma levels were analyzed in 176 CTEPH patients, in 75 PAH patients, in 116 patients with acute VTE, and in 129 healthy controls.

Baseline plasma levels of logs P-selectin were significantly higher in CTEPH compared with PAH ( $P<0.001$ ), acute VTE ( $P<0.001$ ), and healthy controls ( $P<0.001$ ).

Soluble P-selectin, WHO functional class, mean right atrial pressure, and non-operability status were multivariable predictors of outcome.

Conclusion.

Among stable patients with CTEPH, platelet function and platelet activation tests revealed a steady state of activation. Soluble P-selectin is increased in plasma of CTEPH patients, and predicts survival/freedom from lung transplantation. Data suggest that platelet activation is involved in the pathogenesis of CTEPH.