Pulmonary hypertension

Clinical and pathophysiological studies

Akademisk avhandling

som för avläggning av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum Medicinaregatan 3, Göteborg ,
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av
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Avhandling baseras på följande delarbeten:

I. **Assessment of pulmonary vascular resistance by Doppler echocardiography in patients with pulmonary arterial hypertension**. Selimovic N, Rundqvist B, Bergh CH, Andersson B, Petersson S, Johansson L, Bech-Hanssen O.
J Heart Lung Transplant 2007 Sep; 26(9):927-34

II. **Pulmonary hemodynamics as predictors of mortality in patients awaiting lung transplantation.** Selimovic N, Andersson B, Bergh CH, Martensson G, Nilsson F, Bech-Hanssen O, Rundqvist B.
Transpl Int 2008 Apr; 21(4):314-9.

III. **Increased serum levels of growth factors and interleukin-6 across the pulmonary circulation in patients with pulmonary arterial hypertension.** Selimovic N, Andersson B , Bergh CH, Sakiniene E, Carlsten H, Rundqvist B.
Submitted.

IV. **Endothelin-1 across the lung circulation in patients with pulmonary arterial hypertension and influence of epoprostenol infusion.** Selimovic N, Bergh CH, Andersson B, Sakiniene E, Carlsten H, Rundqvist B.
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ABSTRACT

Pulmonary hypertension (PH) is a common abnormality, most often associated with various cardiopulmonary diseases. Pulmonary arterial hypertension (PAH) is a devastating pulmonary vascular disease characterised by the proliferation of endothelial, smooth-muscle cells and fibroblasts. The processes that initiate the pathological changes seen in PH are still unknown. Pulmonary hypertension is defined by increased pulmonary artery mean pressure over 25 mm Hg at rest. Right heart catheterisation is required to confirm the diagnosis and to estimate the severity of PH.

The aims of this thesis were to evaluate whether Doppler echocardiography can be used to determine pulmonary vascular resistance (PVR) in patients with PAH; to evaluate the association between PH in patients with lung diseases awaiting lung transplantation (LTx) and mortality; to assess circulating levels of growth factors, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor β1 (TGF-β1), interleukin-6 (IL-6) and endothelin-1 (ET-1) across the lung circulation in patients with PAH and their association with the severity of disease; to examine the influence of intravenous epoprostenol on the arterial to venous ET-1 ratio in PAH patients.

Forty-two patients with PAH underwent Doppler echocardiography simultaneously (n=22) and non-simultaneously (n=60) with right heart catheterisation. Retrospectively, 177 patients with advanced lung disease accepted for lung transplantation were studied. Blood samples for the analysis of growth factors, ET-1 and IL-6 were obtained simultaneously from the pulmonary artery (PA) and the radial artery (RA) in patients with PAH (n=44) during right heart catheterisation and were compared with control subjects (n=20).

The correlation coefficient between catheter and simultaneous/non-simultaneous Doppler echocardiography was 0.93/0.92 for PVR. In multivariate analysis, PVR and forced vital capacity (FVC) % of predicted were independently associated with death in patients on the waiting list for LTx. Serum levels of VEGF, PDGF, TGF-β1, ET-1 and IL-6 were significantly higher in patients with PAH as compared with controls. There was a consistent step-up of VEGF, PDGF and TGF-β1 across the lungs in PAH patients whereas arterial and PA serum levels of growth factors, ET-1 and IL-6 were similar in the controls (p=NS). IL-6 appeared as a predictor of mortality in multivariate analysis. There were significant correlations between serum levels of ET-1, hemodynamic data and clinical variables.

In conclusion, Doppler echocardiography can be used for estimating of PVR in patients with PAH and may reduce the need for invasive follow-up in these patients. Patients with increased PVR and a lower FVC % of predicted awaiting LTx should be considered for a higher organ allocation priority. The finding of increased circulating levels of growth factors indicates increased release and/or decreased clearance of growth factors at the lung vascular level. These changes may contribute to vascular remodelling in PAH. IL-6 emerged as an independent predictor of adverse outcome in patients with PAH. The ET-1 RA/PA ratio of unity indicates that the clearance and release of ET-1 across the lungs are balanced in controls, PAH patients and during intravenous epoprostenol infusion in treatment-naïve PAH patients. ET-1 serum levels correlated with hemodynamic and clinical markers of PAH severity.

Keywords: pulmonary hypertension, echocardiography, right heart catheterisation, pulmonary vascular resistance, pulmonary function tests, lung transplantation, mortality on the waiting list, vascular remodelling, growth substances, inflammation, endothelin.

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