**Abstract for half-way PhD thesis control 2019-03-01**

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**Title:** Blood-borne biomarkers in pulmonary arterial hypertension pathogenesis, diagnosis, risk stratification and treatment response

**Background.** In pulmonary arterial hypertension (PAH), distal pulmonary arteries are subjected to vasoconstriction and remodeling. Although the underlying mechanisms promoting PAH are still not completely understood, many intriguing abnormalities have been identified. Among those, disturbed receptor tyrosine kinase (RTK) signaling and altered cellular metabolism are known to promote vascular remodeling.

**Aim and method.** The present thesis investigates plasma proteins related to disturbed mechanisms in PAH development. The first two papers focus on RTK signaling, whereas the third sheds light on metabolic substances. Plasma biomarkers were measured in PAH patients, at diagnosis and follow-up, using PCR, proximity extension assays and/or ELISA techniques, and were studied in relation to risk stratification and/or treatment response in PAH. The aim was to identify potential plasma biomarkers to be used in PAH diagnosis, risk assessment or treatment response evaluation.

**Preliminary results**

**Paper I:** Plasma soluble fms-like tyrosine kinase-1 (sFlt-1) decreased in PAH patients between diagnosis and follow-ups, with changes in sFlt-1 correlating to changes in pulmonary vascular resistance (PVR).

**Paper II:** Plasma stem cell factor (SCF) was lower in PAH patients, compared to healthy controls, where it was strongly correlated with hemodynamics. PAH patients at high risk exhibited lower SCF levels compared to those with intermediate or low risk of early mortality, as classified according to ESC/ERS PAH risk stratification guidelines.

**Paper III (submitted):** Plasma fibroblast growth factor 23 (FGF-23) was, compared to controls, elevated in PAH patients, in both those with adequate and declined renal function. FGF-23 levels correlated to hemodynamics as well as to patient risk status as calculated according to ESC/ERS PAH risk stratification guidelines. These correlations were present even after adjusting for renal function.

**Implications:** The present projects provide information on new potential plasma biomarkers in PAH, with a potential utility of SCF and FGF-23 for risk assessment and sFlt-1 for treatment response evaluation in PAH. Moreover, these substances are potential culprits in PAH pathology that deserve closer investigation in larger future studies.
Published and submitted papers:


**Paper II.** Bouzina H, Rådegran G (2018). Low plasma stem cell factor combined with high transforming growth factor-alpha identifies high-risk patients in pulmonary arterial hypertension. ERJ Open Research. 2018