HALFWAY REVIEW REPORT

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Modulators of hypoxic pulmonary vasoconstriction and pulmonary hypertension – Implications for new treatment strategies

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Pulmonary hypertension (PH) is classified into five different groups; 1.) pulmonary arterial hypertension (PAH), 2.) PH due to left heart diseases, 3.) PH due to chronic lung disease and/or hypoxia, 4.) chronic thromboembolic PH and 5.) PH due to unclear multifactorial mechanisms. PAH, specifically, is a disease primarily of small pulmonary arteries, characterized by excessive vasoconstriction and vascular remodeling, including endothelial- and vascular smooth muscle cell proliferation, intimal fibrosis, inflammation, in-situ thrombosis and vascular obstruction by plexiform lesions. The subsequent increase in pulmonary vascular resistance leads to right heart failure and ultimately death. PAH is treated by drugs that induce pulmonary vasodilatation, but prognosis is
nonetheless very poor \(^5\)\(^7\). Furthermore, as incidence rates are low \(^6\)\(^8\)\(^11\) and early symptoms unspecific, patients are often diagnosed in late stages of the disease \(^6\)\(^7\)\(^9\)\(^11\)\(^12\).

The present PhD project aimed to initially characterize the population of patients with idiopathic-, heritable- or connective tissue disease-associated PAH in Lund 2000-2010 with regards to survival, prognostic markers, treatment regimens and outcome in relation to different treatment regimens. Second, an \textit{in vivo} pig model for hypoxic pulmonary vasoconstriction (HPV) was established. HPV is a fundamental physiological mechanism, as it in focal hypoxia optimizes ventilation/perfusion matching to optimize blood oxygenation \(^13\), but in global hypoxia, such as at high altitude, HPV may lead to PH, acute right heart failure and pulmonary edema \(^14\)\(^15\). The model was set up to study mechanisms behind pulmonary vasoconstriction and the effect of pulmonary vasodilatory compounds to identify new potential pulmonary vasodilatory treatments for PH related to hypoxia and PAH, as there may be overlapping pathobiological mechanisms in HPV and PAH. Third, blood samples from patients with PAH, stored in the Lund Cardio Pulmonary Register (LCPR) or the Systemic Sclerosis Biobank, will subsequently be analyzed to evaluate new treatment regimens and potential biomarkers, related to the PAH pathobiology, for screening, early diagnosis and non-invasive follow-up of patients with PAH.


**Methods:** Retrospective analysis of survival rates, prognostic markers, treatment regimens and treatment response, utilizing patient file data from patients diagnosed with idiopathic-, hereditary- and connective tissue disease-associated PAH in Lund 2000-2010.

**Results:** Survival rates were despite modern treatments poor (3-year survival of 54 % for the entire cohort), but comparable to data from large, international registers. 86.8 % of patients were diagnosed late in WHO functional class III-IV. The prognostic utility of WHO functional class, 6-minute walking
distance (6MWD) and mean right atrial pressure at baseline were validated. Only 6MWD and pulmonary vascular resistance index (PVRI) were found to predict outcome at follow-up. 37.5 % of patients on first-line single therapy required escalated treatment already at first follow-up. The proportion of patients alive on single therapy at three years from diagnosis was only 24 %. Hemodynamic effects of PAH-targeted treatments were greater (greater decrease in PVRI and improved cardiac index) with initial combination therapy than with the recommended single therapy.


**Methods:** Intravenous administration of the dual endothelin receptor antagonist tezosentan to anesthetized, mechanically ventilated pigs before and during exposure to acute hypoxia at F\textsubscript{O\textsubscript{2}} 0.10.

**Results:** When administered during normoxia, tezosentan decreased mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) so that the mPAP increase to acute hypoxia was attenuated by approximately 70 % and the PVR increase was abolished. When administered during acute hypoxia, tezosentan decreased mPAP by approximately 62 % and normalized PVR.


**Methods:** Intravenous administration of the cyclooxygenase-2 inhibitor nimesulide or the thromboxane A\textsubscript{2} receptor antagonist daltroban to anesthetized, mechanically ventilated pigs during exposure to acute hypoxia at F\textsubscript{O\textsubscript{2}} 0.10.

**Results:** When administered during acute hypoxia, nimesulide decreased mPAP by approximately 10 % and PVR by approximately 4 %. Daltroban, administered during acute hypoxia, resulted first in a
transient peak increase in mPAP. Thereafter, mPAP decreased to a level approximately 11 % below the hypoxia baseline. PVR was not significantly altered by daltroban, even though pulmonary arterial wedge pressure and cardiac output (CO) was unaltered by the treatment.


**Methods:** Intravenous administration of the positive inotropic- and vasodilator drug levosimendan to anesthetized, mechanically ventilated pigs during exposure to acute hypoxia at F_iO_2 0.10.

**Results:** When administered during acute hypoxia, levosimendan decreased mPAP by approximately 9 % and PVR by approximately 19 %. At the same time, levosimendan increased stroke volume and prevented a hypoxia-induced decrease in CO.

**CONCLUSIONS**

I. Survival among PAH patients are still poor with current treatment regimens and new treatments are hence warranted. Specifically, single therapy seems insufficient in most patients with PAH. First-line combination therapy may instead result in a more rapid and potent hemodynamic improvement, including a larger drop in PVRI and improved CI. A lower PVRI at follow-up was furthermore associated with better outcome in PAH patients. The strongest prognostic marker, both at diagnosis and at follow-up, was 6MWD. In addition, a majority of PAH patients are diagnosed in late stages of the disease underlining the need for new strategies to enable earlier diagnosis.

II. Hypoxic pulmonary vasoconstriction is potentiated by endothelin-1 and a cyclooxygenase-2-derived vasoconstrictor, presumably thromboxane A_2.

III. Intravenously administered tezosentan can induce potent pulmonary vasodilatation and could potentially, as endothelin-1 is involved in the pathogenesis of various forms of PH,
including acute hypoxia-induced PH, be used to treat PH of different etiologies, for instance in the setting of an intensive care unit or peri-operatively. During acute hypoxia-induced PH, levosimendan induces pulmonary vasodilatation and alleviate right ventricular afterload, at the same time as it prevents a cardio-depressive effect of acute hypoxia. Levosimendan could be a new means to optimize the treatment of acute hypoxia-induced PH.

**Planned projects for finalization of the thesis:**

In paper 5, a potential role for adenosine diphosphate in the modulation of HPV are investigated. In paper 6, angiogenic- and inflammatory plasma biomarkers for screening, early diagnosis and non-invasive follow-up of patients with idiopathic- or systemic sclerosis-associated PAH are explored. New findings with regards to angiogenic- and inflammatory biomarkers in PAH may furthermore give new insights into the pathobiological mechanisms behind PAH and thereby contribute to the development of new treatment strategies.
References


