Summary

This thesis aimed to obtain more insights into the neurohormonal dysfunction in PAH, and to investigate the effects of targeting the neurohormonal activation in PAH by novel therapeutic strategies.

In Chapter 2, we investigated the protein changes involved in altering RV cardiomyocyte diastolic dysfunction in patients with PAH. We observed that reduced PKA-mediated phosphorylation of the giant sarcomeric protein titin contributed to RV cardiomyocyte stiffness. In addition, reduced phosphorylation of the sarcomeric protein troponin I and altered expression levels of Ca\(^{2+}\) handling proteins contribute to RV diastolic dysfunction in PAH. We speculate that excessive neurohormonal activation leading to downregulation of β-adrenergic receptor signaling and decrease PKA signaling play an important role in increasing the RV diastolic stiffness in PAH.

In Chapter 3, we investigated the relationship between parasympathetic activity and RV function in idiopathic/hereditary PAH-patients, and the potential therapeutic effects of parasympathetic activity stimulation by pyridostigmine in an experimental PAH-rat model. By using a translational approach we provided evidence that in PAH-patients reduced parasympathetic activity was associated with reduced RV function. Moreover, nicotinic acetylcholine receptor was upregulated in RV myocardial tissue of PAH-patients who underwent heart/lung transplantation. Chronic parasympathetic nervous system stimulation in experimental PAH delayed disease progression, improved RV function, which was related with a reduction of RV inflammation, fibrosis, and normalization of nicotinic acetylcholine receptor expression. Furthermore, pyridostigmine treatment reduced RV afterload and pulmonary vascular remodeling, which was associated with its direct anti-proliferative and anti-inflammatory effects.

Renal denervation is a potential therapy which aims to abolish afferent and efferent renal nerves signaling, and therefore inhibits both neurohormonal systems (SNS and RAAS). In Chapter 4, the effect of renal denervation on RV function and pulmonary vascular remodeling was investigated in two experimental PAH-models. We were able to demonstrate that renal denervation reduced RV diastolic stiffness and improved the pulmonary vascular remodeling. The beneficial effects of renal denervation could be associated to partial RAAS suppression, as renal denervation revealed down regulation of AT1-receptors in the pulmonary vasculature and reduction of MR-expression in the RV.
Previously we have reported opposite effects of exercise training in two experimentally induced PAH-phenotypes. We demonstrated that exercise training was beneficial in rats with stable-PAH. However, it was detrimental in progressive-PAH. In Chapter 5, we aimed to investigate whether changes in adrenergic and cholinergic signaling could contribute to the opposite effect of exercise training observed in progressive and stable PAH. We were able to demonstrate that different β-adrenergic and cholinergic signaling response in the RV may contribute to the detrimental effect of exercise training in progressive-PAH. Exercise training improved norepinephrine reuptake and reduced norepinephrine breakdown only in stable-PAH. In addition, exercise training resulted in opposite PKA-mediated phosphorylation of sarcomeric proteins, improving β-adrenergic receptor signaling in stable-PAH. Furthermore, exercise training increased the cholinergic signaling in stable-PAH, whereas this was impaired in progressive-PAH. Therefore, we propose that the cardiovascular autonomic function was in balance after exercise training in stable-PAH, while in progressive-PAH, a predominant increase in the sympathetic activity may contribute to the detrimental effects of exercise training.

Taken together this thesis demonstrated that neurohormonal dysfunction may contribute to RV dysfunction and pulmonary vascular remodeling in PAH. However, further clinical studies should investigate whether the neurohormonal dysfunction is present during early PAH progression, and whether it could distinguish the patients who would respond to exercise training. In addition, we provided evidence that targeting the neurohormonal system may be a potential therapy for PAH. Although no side effects were observed in our experimental studies, we should be aware that neurohormonal inhibitors may have some side effects. Therefore, further clinical studies should investigate the safety and efficacy of targeting the neurohormonal dysfunction in PAH-patients.