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### **Exercise training, Beta-blocker treatment and Muscle function in Pulmonary Arterial Hypertension**

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## Summary



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Pulmonary Arterial Hypertension (PH) is characterized by excessive pulmonary vascular remodelling, resulting in elevated pulmonary artery and right heart pressures. Eventually, the right ventricle cannot adapt to the increase in afterload, and PH-patients die as a consequence of overt right heart failure. The main symptoms of the patients are reduced exercise tolerance, shortness of breath and other symptoms related to right heart failure such as oedema. This thesis aimed to obtain more knowledge of the pathophysiology of these symptoms and investigate the effects of two different therapeutic strategies.

In **Chapter 2** we investigated if exercise training could be beneficial to improve exercise capacity in PH. As exercise training is still contra-indicated because of fear that the right ventricle of PH-patients could not cope with a further increase in right ventricular (RV) afterload during exercise, we assessed the effects of exercise training in an animal model (monocrotaline (MCT) rat model) for PH. We hypothesized that the effect of exercise training was dependent on the adaptation of the right ventricle to increased afterload and we therefore induced two types of PH, a stable PH with preserved cardiac function (low dose (40 mg/kg) of MCT) and a progressive PH with right heart failure (high dose (60 mg/kg) of MCT). After two weeks of MCT, all rats had developed PH (assessed by echocardiography) and the exercise training was initiated. After 4 weeks of exercise training, we observed opposite effects of exercise training in stable and progressive PH. In stable PH, exercise training was beneficial as it improved exercise capacity and RV capillarization. However, in progressive PH, exercise training was detrimental: exercise training accelerated the progression towards right heart failure and was associated with manifest RV inflammation.

Encouraged by the findings that exercise training was beneficial in stable PH rats, we performed a clinical study in **Chapter 3** to assess the effects of exercise training in patients with idiopathic PH who were clinically stable and had no change in therapy for at least three months prior to inclusion. Eventually, nineteen patients were enrolled in this study, who underwent an exercise training program (three times a week, for a period of 12 weeks) in a rehabilitation center located within five kilometres from their homes. Before and after 12 weeks of training, maximal and submaximal exercise capacity and quadriceps muscle function were assessed at the VU University Medical Center. Moreover, in a subset of 12 patients we were able to obtain quadriceps muscle biopsies before and after training to analyse the effects of exercise training on skeletal muscle morphology in more detail. Our study revealed that exercise training could improve submaximal exercise capacity and quadriceps muscle function (both strength and endurance) in patients with stable PH. Interestingly, the enhanced quadriceps muscle function after exercise training was associated with improvements in oxygen handling of the quadriceps muscle fibers.

In **Chapter 4** we investigated whether alterations in myofilament phosphorylation and function could underlie the opposite effects of exercise training discussed in **Chapter 2**. We hypothesized that exercise training in progressive PH induced an overload of catecholamines (suggested by the observed RV inflammation), thereby altering beta-adrenergic receptor signalling and affecting myofilament phosphorylation and function. Histological analyses revealed that in addition to the previous reported increase in lymphocytes, exercise training in progressive PH also induced infiltration of macrophages and granulocytes specifically in the right ventricle. Moreover, opposite effects of exercise training were again observed in myofilament phosphorylation where exercise training increased phosphorylation in stable PH and decreased phosphorylation in progressive PH of the myofilament proteins troponin I, troponin T and myosin binding protein C. Furthermore, reduced myofilament phosphorylation in progressive PH was associated with increased protein phosphatase 1 expression. Interestingly, we were able to analyse the functional consequences of the altered myofilament phosphorylation by isolation of single cardiomyocytes. These functional measurements revealed that exercise training was able to improve active force in both stable and progressive PH. However, in progressive PH this increase in active force was at the expense of passive force indicating severe diastolic dysfunction. The role of diastolic dysfunction in progressive PH rats and patients will be investigated further.

As we observed signs of catecholamine overload in progressive PH rats who developed overt right heart failure, we subsequently investigated the effects of beta-blocker therapy in **Chapter 5**. Beta-blockers are often used as therapeutic strategy for the treatment of patients with left heart failure and are able to restore the detrimental effects of catecholamines. However, beta-blockers are contra-indicated for the treatment for PH as it is feared that patients can not cope with the transient myocardial depressant effects of beta-blockers. On the other hand, this fear is substantiated on studies using high dose of  $\alpha$ -selective (first generation) beta-blockers, who only assessed acute effects of beta-blockers. We therefore hypothesized that chronic use of a low-dosed cardio-selective beta-blocker (bisoprolol 10 mg) could have beneficial effects on survival and RV function in rats with progressive PH. Rats were randomized in bisoprolol or vehicle 10 days after MCT-injection. Echocardiography and pressure volume relations were used to assess the effects of bisoprolol on arterial-ventricular coupling and diastolic function. Bisoprolol delayed the progression of right heart failure and improved survival. Bisoprolol had no effect on RV afterload, however it improved RV contractility significantly, resulting in a partially restored arterial-ventricular coupling. Moreover, diastolic function was significantly improved after bisoprolol treatment. Interestingly, the improvements in RV function were associated with decreased RV fibrosis and RV inflammation. The clinical applicability of bisoprolol for the treatment of patients with PH will be further evaluated in a clinical phase I/II setting.

Respiratory muscle dysfunction is suggested to be associated with increased sensation of dyspnoea in patients with PH. Especially, inspiratory muscle function seems impaired in PH-patients. As patients with PH hyperventilate continuously, we hypothesized in **Chapter 6** that over-activity of the diaphragm muscle (main muscle of inspiration) could induce alterations in contractile properties and morphology resulting in reduced inspiratory muscle function. As obtaining diaphragm muscle biopsies of patients with PH is hampered by ethical difficulties, we investigated diaphragm muscle function and morphology of rats with progressive PH. Telemetry revealed that breathing frequencies of PH rats were significantly elevated. Furthermore, force generating capacity of diaphragm muscle strips was significantly reduced, indicated by lower twitch and tetanic force and shifted force-frequency curve in PH rats. Subsequent histological analyses revealed manifest atrophy of the diaphragm muscle fibers, which can even further affect force generating capacity of the diaphragm muscle. Interestingly, we were able to extrapolate our pre-clinical findings to patients who died of PH, as manifest atrophy was also present in diaphragm muscle fibers of PH patients compared to controls. Importantly, these alterations in diaphragm muscle function were specific to the diaphragm as skeletal muscle function was unaltered in PH-rats. Future research will investigate the causal relation between over-activity and diaphragm muscle function in PH by use of pharmaceutical interventions.

