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

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Conclusions and Future Perspectives



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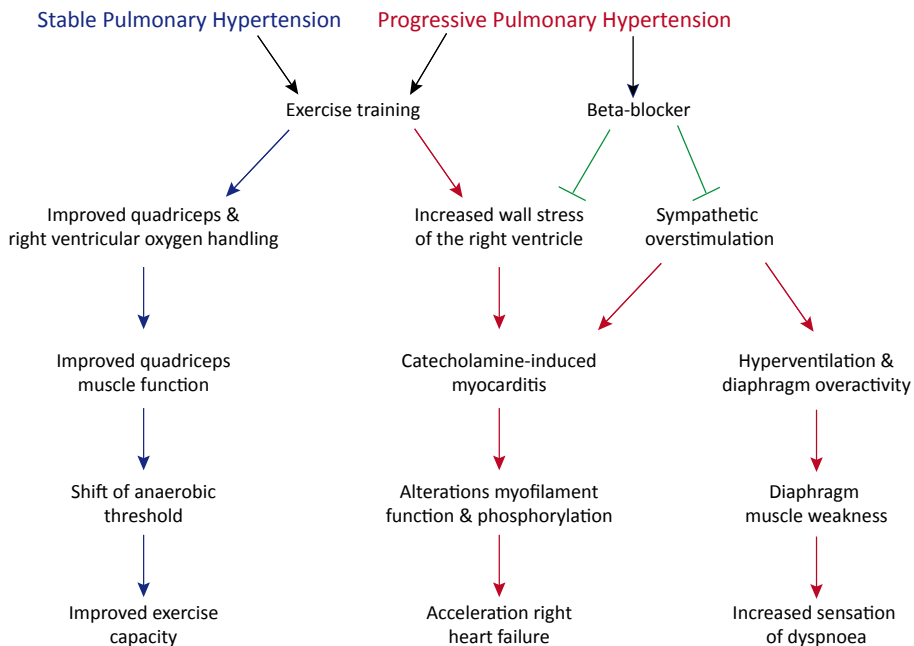
CONCLUSIONS

Figure 1 gives an overview of the findings of this thesis, and demonstrates the knowledge we have obtained on the pathophysiology of the main aspects of patients with pulmonary hypertension (exercise capacity, right heart failure, and dyspnoea) and provide possible new therapeutic strategies to improve exercise capacity and right heart failure in Pulmonary Hypertension (PH). In addition, we show that besides the pulmonary vasculature and right ventricle, also the diaphragm muscle is affected in PH.

Exercise training is currently implemented in the recent treatment guidelines as therapeutic strategy to improve exercise capacity of patients with PH.¹ However, we demonstrated that exercise training can also have profound detrimental effects, and therefore caution is still warranted. Larger clinical trials (currently ongoing in Clamart, Paris) should determine how potential responders of exercise training can be distinguished from non-responders to training. Our studies on exercise training (Chapters 2-4) suggests that right ventricular (RV) adaptation and RV wall stress might be important factors that determine the (unfavourable) response of exercise training. In this respect, right ventricular (RV) hemodynamic indices may

Figure 7.1 Schematical overview of the main findings of this thesis

The possible mechanisms and effects of therapies are illustrated. Exercise training can have opposite effects in stable (blue arrows) and progressive (red arrows) pulmonary hypertension (Chapter 2-4). Beta-blockers can improve right ventricular function in progressive PH and even delays the progression towards right heart failure (Chapter 5). Diaphragm muscle weakness is present in progressive PH, which may be a consequence of increased diaphragm muscle activity (Chapter 6). In future, the effects of beta-blocker mediated inhibition of sympathetic overactivity on RV myofilament and diaphragm muscle function should be further elucidated.



be of high value, especially measures of RV wall stress like NT-pro BNP plasma levels, or RV end diastolic diameters. In addition, cardio-pulmonary exercise test combined with echocardiography will give essential information about the acute response of the right ventricle to the exercise-induced increase in afterload. This could be an important prognostic factor to distinguish a “responder” from a “non-responder” and detect PH-patients that will benefit of exercise training.

The gained knowledge on the development of right heart failure, the effects of β -blocker therapy and the finding of diaphragm muscle weakness have all been subject of three new project proposals of whom two will be discussed below. Furthermore the post-doc project of Frances de Man, which she will perform at the laboratory of prof. Humbert and dr. Eddahibi (top experts on the field of vascular biology and pulmonary hypertension) in Paris, will also be discussed below.

FUTURE PERSPECTIVE

Diastolic dysfunction in Pulmonary Arterial Hypertension: Titin as therapeutic target

In several longitudinal studies, diastolic dysfunction has been shown as an independent prognostic factor in PH-patients.² Diastolic dysfunction in left heart failure is mainly determined by the myofilament protein titin and collagen deposition.^{3,4} Interestingly, we observed in rats with manifest right heart failure a significant increase in cardiomyocyte passive stiffness (**Chapter 4**), suggesting alterations in titin. Moreover, bisoprolol could partially restore diastolic function (**Chapter 5**). In future research, we will investigate by which mechanism bisoprolol could improve diastolic function, by focusing on the role of collagen deposition and titin on cardiomyocyte passive stiffness.

Moreover, we will investigate whether findings of passive stiffness and myofilament phosphorylation in PH rats can also be extrapolated to clinical PH. Until now, all clinical research on right ventricular dysfunction in PH, has been performed on heart specimens obtained during autopsy. However, the often long time between time of death and autopsy, is detrimental for cardiomyocyte function and hampers analysis of functional characteristics of the right ventricular cardiomyocytes. Therefore, in collaboration with prof. Marc Humbert, we will perform cardiomyocyte measurement as described in **Chapter 4** on RV cardiomyocytes obtained at cardio-pulmonary transplantation. This will give us highly important and unique information about the effects of PH on intrinsic cardiomyocyte properties, which could only be derived before in animal models.

Bisoprolol in patients with Pulmonary Arterial Hypertension

Notwithstanding the substantial evidence of their beneficial effects in LHF, the use of beta-blockers is still contra-indicated for patients with PH,¹ as it is thought that these patients do

not tolerate its (transient) myocardial depressant effects. However, in **Chapter 5** we have demonstrated that if introduced carefully, the cardio-selective β -blocker bisoprolol improves cardiac function and decelerates the progression towards right heart failure in rats. To assess if bisoprolol therapy is also beneficial in patients with PH, a phase I/II clinical trial will be initiated by the VU university medical center to assess its safety and efficacy.

Cross-talk between smooth muscle and endothelial cells as therapeutic target

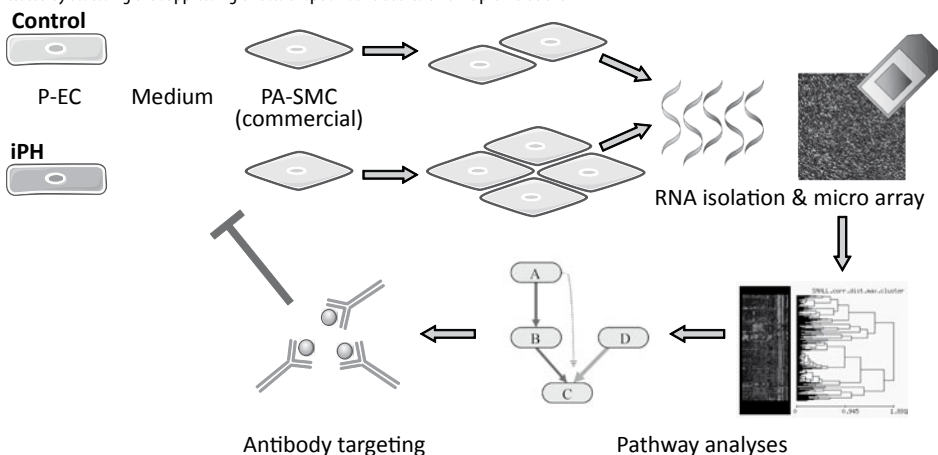
Even under optimal medical treatment, pulmonary vascular resistance cannot be restored to normal levels, and prognosis of idiopathic PH-patients (iPH) remains poor. Therefore, it is of clinical importance and of basic scientific interest to unravel new molecular signalling pathways involved in pulmonary artery smooth muscle cell (PA-SMC) hyperplasia.

Eddahibi and co-workers were the first to demonstrate the additional value of investigating the *cross-talk* between endothelial cells (P-EC) and PA-SMC in iPH, over investigating PA-SMC *only*. They showed that PA-SMC hyperplasia is either the result of abnormal P-EC signalling and/or intrinsic cellular alterations of the PA-SMC itself.^{5,6}

So far, studies mainly focussed on signalling pathways that are already known to induce PA-SMC hyperplasia in other disease states.^{6,7} This approach, however, only allows identification of a minority of pathways that are potentially involved in PA-SMC hyperplasia in iPH. An alternative approach is to perform a genome-wide search for molecular changes in PA-SMC of iPH-patients using microarray techniques. Recent technological developments have enabled the translation of gene-expression profiles to key signalling pathways, thereby revealing

Figure 7.2 Schematical overview of the study approach.

Human P-EC will be isolated from lung specimens of patients with iPH and control subjects. Commercial PA-SMC will be exposed to the medium of P-EC of iPH or control, which will lead to differences in PA-SMC proliferation. By microarray techniques, we will analyse the underlying differences in gene-expression profiles, to unravel new signalling pathways and new paracrine factors. The relevance of these factors will be tested by assessing the suppressing effects of specific antibodies on SMC proliferation.



many yet unknown pathways at once.⁸ Identification of new signalling pathways will greatly aid the development of novel therapeutic strategies for iPH-patients.

Therefore, we wish to investigate which signalling pathways are involved in PA-SMC proliferation either via abnormal P-EC signalling or intrinsic cellular alterations of the PA-SMC by using P-EC and PA-SMC from lung specimens of patients undergoing lung transplantation and commercially available cells (see experimental setup Figure 2). This project proposal has been granted by the European Respiratory Society/Marie Curie Joint Research Fellowship MC 1120-2009.