SUMMARY / SAMENVATTING
NOVEL TREATMENT STRATEGIES FOR RIGHT HEART FAILURE IN PULMONARY ARTERIAL HYPERTENSION
LESSONS FROM THE LEFT HEART

The right ventricle as a potential treatment target

Pulmonary arterial hypertension (PH) is a rare disease, which is characterized by excessive remodeling of the pulmonary vasculature, resulting in increased pulmonary vascular resistance and right ventricular (RV) afterload. This leads to extensive RV remodeling and ultimately to right heart failure.

Unfortunately, no definite cure exists. Nevertheless, in the last decade several new drugs were introduced for the treatment of PH that selectively lowers the pulmonary vascular resistance, thereby secondarily improving right heart function, resulting in significant clinical improvement. However, even under maximal treatment, the prognosis of PH-patients remains grim, with a 5-year survival of approximately 50%.

Although it is widely recognized that the degree of symptoms (like breathlessness, fatigue, peripheral edema) and survival in patients with PH are strongly related to the severity of RV dysfunction, right heart failure was first presumed an inevitable consequence of PH. As a result, the right ventricle was not considered a potential target for therapy. However, recently it has been recognized that the adequacy of RV compensatory response (i.e. preservation of stroke volume) is quite variable amongst individuals, and this has triggered the interest for therapies that could directly improve right heart function.

In this thesis, we explored novel treatment strategies that directly target the right ventricle, using a well-established rat model for PH. First, methodology (such as RV pressure-telemetry, echocardiography of the right ventricle, RV pressure-volume measurements and cardiac magnetic resonance imaging) was optimized for rats to monitor right heart function in vivo. Details on the functional characteristics of the PH-rat model are found in chapter 2. Subsequently, we evaluated the effects of exercise training, β-blocker therapy, and RV-pacing (chapters 3 to 5). A general discussion of the results from this thesis is found in chapter 6.

Exercise training

Exercise training in PH is considered a promising adjunct to medical treatment. However, it is still unclear whether training is beneficial for all PH-patients. We hypothesized that RV adaptation plays a pivotal role in the response to training.

Two different dosages of monocrotaline were used in rats to model stable PH with preserved cardiac output, and progressive PH developing right heart failure. Two weeks after injection, PH was confirmed by echocardiography, and treadmill training was initiated. Rats were trained for four weeks, unless manifest right heart failure developed earlier. At end of study protocol, all rats were functionally assessed by endurance testing, echocardiography and invasive pressure measurements. Lungs and hearts were further analyzed for quantitative histomorphologic analyses.
In stable PH, exercise training was well-tolerated and markedly increased exercise endurance. Moreover, RV capillary density increased significantly. However, in progressive PH exercise training worsened survival and increased pulmonary vascular remodeling. In addition, training induced widespread leukocyte infiltration into the right ventricle.

In our rat model, exercise training is found to be beneficial in stable PH, but detrimental in progressive PH. Future studies are necessary to address the clinical implications of our findings.

**Beta-blocker therapy**

The use of β-blockers is currently strongly discouraged in PH, because of their acute negative inotropic and chronotropic effects. However, use of β-blockers in chronic (left) heart failure is safe and significantly reduces mortality. We investigated whether chronic low-dose treatment with bisoprolol (a cardioselective β₁-adrenergic receptor antagonist) has beneficial effects on mortality and cardiac function in experimental PH.

Progressive PH in rats was induced by a single injection of monocrotaline. By pressure-telemetry in PH-rats, the lowest dose of bisoprolol was determined that blunted heart rate response during daily activity. Ten days after monocrotaline-injection, echocardiography was performed, and PH-rats were randomized for bisoprolol-treatment. At end-of-study (body mass loss >10%), echocardiography was repeated with additional pressure-volume measurements. After euthanization, heart and lungs were harvested for histomorphological analyses.

Echocardiography confirmed PH-status at start-of-treatment. Bisoprolol delayed disease progression and improved survival. Compared to control, RV systolic pressure and arterial elastance (Ea; measure of vascular resistance) more than tripled in PH. RV afterload was unaffected, however bisoprolol-treatment increased RV contractility (Ees) and elastance (Eed), and partially restored RV ventriculo-arterial coupling (Ees/Ea) and cardiac output. Histology revealed significantly less RV fibrosis and less RV myocardial inflammation in bisoprolol-treated PH-rats.

In experimental PH, treatment with bisoprolol improves survival and RV function. These promising results suggest a therapeutic role for β-blockers in PH that warrants further clinical investigation.

**Cardiac resynchronization by RV-pacing**

Right heart failure in PH is associated with mechanical ventricular dyssynchrony, which leads to impaired RV function, and - by adverse diastolic interaction - to impaired left ventricular (LV) function as well. However, therapies aiming to restore synchrony by pacing are currently not available. In a proof-of-principle study, we determined the acute effects of RV-pacing on ventricular dyssynchrony in PH.

Chronic PH with right heart failure was induced in rats by injection of monocrotaline. To validate for PH-related ventricular dyssynchrony, PH- and control-rats were examined by cardiac magnetic resonance imaging, twenty-three days after monocrotaline- or sham-injection. In a
second group, the effects of RV-pacing were studied in detail, using Langendorff-perfused heart preparations.

In PH, septum bulging was observed, coinciding with a reversal of the trans-septal pressure gradient, as observed in clinical PH. RV-pacing improved RV systolic function, compared to unpaced condition. In addition, RV-pacing markedly decreased adverse diastolic interaction and was able to resynchronize time of RV and LV peak-pressure. Finally, RV-pacing had no detrimental effects on LV function or coronary perfusion, and no LV pre-excitation occurred.

Taken together, we demonstrate that in experimental PH, RV-pacing improves RV function and diminishes adverse diastolic interaction. These findings provide a strong rationale for further in vivo explorations.

Parallels between left and right heart failure treatment

Right heart function is the main determinant of prognosis in PH. Yet, no treatments are currently available that directly target the right ventricle.

In this thesis, we demonstrate that well-established therapies for left heart failure (exercise training, β-blocker therapy, cardiac resynchronization) might also be relevant for right heart failure, in spite of important structural, functional and developmental differences between the left and right ventricle. However, before they can be implemented in clinical PH-management, safety and efficacy should be evaluated first. Well-designed clinical studies are warranted, as they could provide us supporting evidence for use of novel therapeutic modalities that are relatively easy at hand, to treat this devastating disease. Future will reveal whether going “left” is a step in the “right” direction.