Summary and future perspective

Pulmonary arterial hypertension (PAH) is a disease, which involves the small pulmonary vessels. In the past few years the efforts done to understand the pathobiology underlying this disease improved treatment and outcome. However prognosis remains grim in PAH. It has been recognized that mortality of PAH patients is directly associated to the function of the right ventricle; i.e. right heart failure in end-stage disease.

During progression of the disease there is a transition from an adapted right ventricle, able to maintain its function in relation to the pressure overload, to a failing ventricle. Insight in this process and the role of the left ventricle, the atria and large pulmonary vessels are limited.

The studies described in this thesis were aimed to improve our understanding of right ventricular failure in patients with pulmonary arterial hypertension and provide accurate measures for an early detection of right ventricle failure. Chapter 1 of this thesis gives an overview of the insights on the pathobiology, pathogenesis, and genes involved in PAH. Furthermore, the classification, diagnostic work-up and treatment of PAH are viewed.

The effect of pulmonary hypertension on the right ventricle is the increased afterload, which elevates myocardial wall stress. Brain natriuretic peptide and its biological inactive equivalent N-terminal pro-brain natriuretic peptide (NT-proBNP) are released by the cardiomyocytes due to increased wall stress. It has been shown that brain natriuretic peptide and NT-proBNP can monitor disease and treatment effects, and both are significant prognostic markers in PAH. However, insight into changes in right ventricular structure and systolic function in relation to NT-proBNP are unknown. **Chapter 2** presents a study about the temporal relationships of NT-proBNP with right ventricular structure and systolic function in thirty pulmonary hypertension patients. The results of the study showed that relative changes in NT-proBNP during treatment were correlated to the relative changes in right ventricular end-diastolic volume index \( r = 0.59, p < 0.001 \), right ventricular mass index \( r = 0.62, p < 0.001 \) and right ventricular ejection fraction \( r = -0.81, p < 0.001 \). Elevated NT-proBNP levels over time reflects right ventricular dilatation concomitant to hypertrophy and deterioration of systolic function, and should be interpreted as a sign of right heart failure.

It has been recognised that systolic function is important in the overloaded right ventricle, however there is little insight in right ventricular diastolic function. There are arguments that right ventricular diastolic function may be impaired in pulmonary hypertension patients. First, due to increased right ventricular afterload myocardial relaxation and filling may be impaired. Second, right ventricular compensatory hypertrophy to increased afterload reduces ventricular
compliance and may impair diastolic function. Therefore the aim of the study presented in chapter 3 was to investigate whether right ventricular diastolic function is impaired in pulmonary hypertension patients, and whether this impairment is related to right ventricular mass and afterload. Phosphodiesterase-5-inhibitor sildenafil was used to investigate whether an acute reduction of afterload improves right ventricular diastolic function. Finally, the relation between right ventricular diastolic function and cardiac parameters that reflect disease severity in pulmonary hypertension was assessed. Twenty-five patients and 11 controls were studied. Isovolumic relaxation time (IVRT), normalized early (E), atrium-induced (A) peak filling rate, and E/A, described diastolic function. Compared to controls, patients had impaired right ventricular diastolic function in terms of prolonged isovolumic relaxation time (IVRT) (133.5 ± 53.2 ms vs. 29.3 ± 20.8 ms, \( p < 0.001 \)), decreased normalized early peak filling rate (E) (3.0 ± 1.6 s\(^{-1}\) vs. 6.4 ± 2.5 s\(^{-1}\), \( p < 0.001 \)) and E/A (1.1 ± 0.7 vs. 5.3 ± 4.9, \( p < 0.001 \)), and increased atrium-induced peak filling rate (A) (3.0 ± 1.4 s\(^{-1}\) vs. 1.5 ± 0.9 s\(^{-1}\), \( p = 0.001 \)). IVRT was related to right ventricular mass (\( r = 0.56, p = 0.005 \)) and pulmonary vascular resistance (\( r = 0.74, p < 0.0001 \)). In patients right ventricular diastolic dysfunction is related to right ventricular mass and afterload. Sildenafil improved right ventricular diastolic and systolic function. IVRT was correlated to, NT-proBNP (\( r = 0.70, p < 0.001 \)), and inversely related to cardiac index (\( r = -0.70, p < 0.001 \)) and right ventricular ejection fraction (\( r = -0.69, p < 0.001 \)). Whether this effect is secondary to a reduction in afterload or a direct effect of sildenafil on the cardiomyocytes remains to be further investigated. Right ventricular diastolic function improves by reducing afterload. The correlations between diastolic function and prognostic parameters showed that impairment of the diastolic function is a major contributor to right ventricle failure.

Although the right ventricle is the main player in right ventricle failure, there is increasing evidence that the role of the left ventricle is largely underestimated in pulmonary hypertension. The hallmark of pulmonary hypertension on echocardiography is paradoxal septal movement; i.e. leftward ventricular septal bowing, which results from a transseptal pressure gradient in diastole. The phenomenon by which the right ventricle directly influences left ventricular filling is known as direct ventricular interaction. The aim of the study presented in chapter 4 was to determine the effect of direct ventricular interaction on stroke volume. Forty-six PAH patients and 18 control subjects were studied. Magnetic resonance imaging measured stroke volume, right and left ventricular volumes, left ventricular filling rate and interventricular septum curvature. Transesophageal echocardiography measured left
atrial filling. The results showed that compared to control subjects, patients had decreased stroke volume (28±13 vs. 41±10 ml/m², p< 0.001), left ventricular end-diastolic volume (46±14 vs. 61±14 ml/m², p< 0.001) and left ventricular peak filling rate (216±90 vs. 541±248 ml/s, p< 0.001). Among patients stroke volume did not correlate to right ventricular end-diastolic volume or mean pulmonary artery pressure, but did correlate to left ventricular end-diastolic volume (r = 0.62, p< 0.001). Leftward ventricular septal bowing was correlated to left ventricular filling rate (r = 0.64, p< 0.001) and left ventricular end-diastolic volume (r = 0.65, p< 0.001). From these data can be concluded that ventricular interaction mediated by the interventricular septum impairs left ventricular filling contributing to decreased stroke volume.

The characteristic leftward ventricular septal bowing in pulmonary hypertension is the result of a transeptal pressure gradient during diastole as described earlier. The mechanism underlying this phenomenon is interventricular asynchrony. The mechanism was explored and described in Chapter 5. The aim of the study was to investigate whether the nature of the asynchrony lies in the difference in duration of shortening of the two ventricles; i.e. left-to-right delay in myocardial shortening, or in the onset of shortening. In addition, the functional impact of asynchrony was determined by assessing the association with left ventricular septal bowing and filling, and stroke volume. In 21 PAH patients, MRI myocardial tagging was applied. The onset time and peak time of circumferential shortening were calculated, for the left ventricular free wall, septum and right ventricular free wall. The Laplace law estimated right ventricular wall tension. The results showed that myocardial shortening of both ventricles start simultaneously, and that the time to peak shortening was different for the left ventricular free wall, septum and right ventricular free wall respectively (293±58, 267±22 and 387±50 ms). Maximum leftward ventricular septal bowing was at 395±45 ms, coinciding with septal overstretch and peak time of the right ventricle. The left-to-right delay in peak time was not correlated with the QRS width, but was associated with right ventricular wall tension (r = 0.54, p = 0.01). The left-to-right delay in peak time correlated with leftward septal curvature, and correlated negatively with left ventricular end-diastolic volume (r = 0.50, p = 0.02) and stroke volume (r = 0.49, p = 0.02). Based on these findings we conclude that in PAH left to right asynchrony is caused by lengthening of right ventricular shortening and that right ventricular peak time coincides with septal overstretch and maximal leftward ventricular septal bowing. Furthermore, we observed that there is still myocardial shortening of the right ventricular free wall while the pulmonary valves are already closed, underscoring the ineffectiveness of right ventricular systolic function in end stage PAH.
The role of the right atrium in pulmonary arterial hypertension and especially the interaction with right ventricular function is largely unknown. Due to changes in right ventricular structure and function the right atrium has to adapt to compensate for diastolic and systolic function. Under physiological conditions the right atrium transfers large volumes at low pressures and can be quantified by, 1) The conduit volume; i.e. the amount of blood that flows directly from the veins into the right ventricle, 2) Reservoir volume: the blood being stored during ventricular systole. Conduit-to-reservoir volume quantifies right atrial function. In Chapter 6 the adaptive capacity of the right atrium in relation to right ventricular structure and function was studied. On average, the 14 patients had larger right atria than the 11 controls (42 [31-55] vs. 25 [17-30] ml/m², p = 0.001), comparable reservoir volume (27 [20-30] vs. 25 [21-28] ml/m², p=0.792), and decreased conduit volume (4 [2-9] vs. 13 [10-18] ml/m², p = 0.003). In PH conduit-to-reservoir volume ratio is reduced (0.14 [0.08-0.92] vs. 0.61 [0.39-0.72], p = 0.002), and atrial contractile function is enhanced (43 [33-63] vs. 27 [18-29] %, p = 0.002). In patients, right atrial maximum volume was related to right ventricular end-diastolic volume index (r = 0.63, p = 0.022). Conduit-to-reservoir volume ratio was related to right ventricular ejection fraction (r = -0.71, p = 0.005), and inversely related to right ventricular isovolumic relaxation function (r = -0.63, p = 0.015. In pulmonary hypertension, the right atrium is larger, conduit-to-reservoir volume ratio smaller and atrial contractile function is enhanced, probably as a result of a compensatory mechanism for impaired right ventricular diastolic and systolic function.

Prognosis in PAH has improved over the last years. This can be attributed to better insights in the pathobiology of the disease. However, monitoring disease and predicting prognosis remains challenging. Since decreased total compliance of the pulmonary vascular bed is associated with increased mortality in PAH, we hypothesized that proximal pulmonary artery stiffness, the relative area change (RAC), assessed non-invasively by MRI can predict prognosis. In chapter 7 Eighty-six subjects were studied and underwent right heart catheterization and an MRI-scan to assess area distensibility (ΔA/ΔP·A) and RAC. Patients were followed up to 48 months. Kaplan-Meier plot and Cox proportional hazards regression analyses assessed the predictive value of area distensibility and RAC. In 70 patients, the diagnosis PAH was confirmed and 16 subjects served as controls. In comparison with controls, proximal pulmonary arteries of patients were distended (685±214 vs. 411±153 mm², p<0.001), less distensible (ΔA/ΔP·A: 0.46±0.38·10⁻² mmHg⁻¹ vs. 3.69±1.96·10⁻² mmHg⁻¹, p<0.0001), and RAC was smaller (20±10 vs. 58±21 %, p<0.0001). RAC showed an inverse
curvilinear relation with mean pulmonary artery pressure ($R^2 = 0.47$). Eighteen patients (26%) died because of cardiopulmonary causes. Patients with a pulmonary artery RAC ≤ 16% had a worse prognosis than those with a value >16% (log-rank, $p < 0.001$). The RAC predicted mortality better than area distensibility. From these data can be concluded that in PAH patients increased pulmonary artery pressure causes distension and possibly wall remodelling, both resulting in stiffening of the proximal pulmonary artery. In addition, our results showed that pulmonary artery relative area change is a good predictor of mortality.

In chapter 8 we summarize the pathophysiological mechanisms involved in right ventricular failure in end stage PAH and the clinical consequences of these insights on the management of these patients.

**Future perspective**

The studies described in this thesis view some of the mechanisms involved in right ventricular failure in PAH. Since the awareness that both morbidity and mortality are determined by right ventricular function, both basic and clinical investigators are encouraged to focus on the right ventricle(1). There is a field waiting to be explored. The study described in chapter 3 adds to our knowledge of NT-proBNP in pulmonary hypertension. Since this cardiac hormone is released under influence of myocardial stress, studies investigating NT-proBNP in relation to exercise are challenging. Furthermore, the diagnostic value of NT-proBNP in the diagnosis of early PAH in high-risk groups of patients for developing pulmonary hypertension, such as in scleroderma and BMPR-2 mutation carriers, should be evaluated in prospective studies. Finally, given the many treatment possibilities in pulmonary hypertension, there is a need of a single simple measure to guide therapy and support the decision to switch from oral to intravenous treatment. Based on the results of chapter 2 a goal oriented treatment approach seems to be justified, taking NT-proBNP level of 1685 pg/ml as a cut-off value (2).

Multicenter prospective studies are currently designed to evaluate the feasibility and clinical value of such a goal.

The role of right ventricular diastolic function needs furthermore investigation in a larger study group. The predictive value should be compared to other known MRI parameters (3). In addition, the occurrence of right ventricular diastolic dysfunction in relation to the progression of pulmonary hypertension is of interest. Right ventricular diastolic dysfunction may precede systolic dysfunction. Therefore, isolated right ventricular diastolic dysfunction; i.e. in the absence of systolic dysfunction or compensated systolic function, may be an early sign of right ventricular failure. The clinical and prognostic role of non-invasive echocardiographic
and MR measures of the diastolic right ventricular function in pulmonary hypertension should be further explored.

Interventricular mechanical asynchrony, the mechanism of leftward ventricular septal bowing, might potentially be eligible for myocardial pacing in those patients waiting for lung transplantation. Restoring synchronous ventricular function, may improve biventricular systolic and diastolic function. Preclinical studies are a requisite to explore the effects of biventricular pacing on cardiac function. Currently, the possible beneficial role of restoration of ventricular synchrony by pacemaker technology is under investigation in our institute.

There is still a need for new end-points in clinical trials. Although expensive, MRI is potentially, the tool to monitor end evaluate therapy in clinical trials. Measures of right ventricular structure, function, pulmonary artery stiffness, can be obtained in a single MRI session. In addition, techniques to measure pulmonary perfusion are currently under investigation and the first results are encouraging (4).

The complex coupling between the right ventricle and the pulmonary vascular tree is still not well understood. Mathematical modelling of this interaction is a promising way to extend our knowledge of right ventricular failure. Current research performed at our institute is underway to develop these models.

Finally, to understand the molecular basis of the transition of right ventricular adaptation to failure, and find adequate treatments to prevent such a transition, animal studies are a requisite. There are strong arguments that hypoxia of the cardiomyocyte might play a key-role in the process of right ventricular adaptation to failure. This hypothesis is currently under investigation in several pulmonary hypertension animal models and will be tested in patients by means of PET measurements. Based on the findings of these studies, future studies will focus medical therapies able to prevent the transition of right ventricular adaptation to failure.

References

