CHAPTER 10

Insights into the progression of right ventricular failure in pulmonary arterial hypertension: summary and future perspectives

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10.1 SUMMARY

10.1.1 Introduction

PULMONARY ARTERIAL HYPERTENSION (PAH) is characterized by excessive pulmonary vascular remodelling, resulting in elevated pulmonary artery and right heart pressures. Although pulmonary pressure rise is the distinctive characteristic of this disease, the patients’ functional capacity and survival is predominantly determined by right ventricular (RV) function. Knowledge about the role of the RV in health and disease historically has lagged behind that of the left ventricle. The RV has generally been considered a mere bystander, a victim of pathological processes. Consequently, in PAH comparatively little attention has been devoted to how RV dysfunction is best detected and measured. Little attention has also been paid to what specific molecular and cellular mechanisms contribute to adaptation of right ventricular function or failure, as well as how RV dysfunction evolves structurally and functionally in the course of the disease, or what interventions might best preserve RV function. The studies described in this thesis aimed to improve our understanding of the mechanical principles underlying the progression of RV failure in PAH.

10.1.2 Right ventricular geometric shortening in PAH

In Chapter 2, we evaluated regional transverse shortening of the RV myocardium, defined as movements of the RV free-wall to the septum, in a group of PAH patients and control subjects. As yet, tricuspid annular plane systolic excursion (TAPSE) has been well studied in pulmonary hypertension (PAH) as a surrogate for RV function. This measure quantifies the longitudinal shortening of the RV and its clinical and prognostic value has been well established by echocardiography. However, TAPSE ignores the septal contribution to RV ejection. We hypothesized that in PAH, transverse movements of the RV free wall towards the septum are important in RV ejection. From 101 PAH patients, MRI four-chamber cine images were analyzed to quantify RV transverse shortening at seven levels along an apex-to-base axis.
For each level, regional absolute and fractional transverse shortening were computed and related to rvef. Regional transverse wall movements provide important information of rv function in pah. Our results showed a close relation between transverse motion at mid-rv reveals and global right ventricular function as measured by rvef.

Encouraged by the findings that rvef is better reflected by rv transverse shortening than longitudinal shortening in pah, we performed the study of chapter 3 to assess which of these geometric shortening parameters provides the best reflection of rv functional decline over time in a cohort of pah patients with progressive right ventricular failure. We reviewed 42 consecutive pah patients who underwent right heart catheterization and cardiac mri at baseline and after 1-year follow-up. Based on the survival after this one-year run-in period, patients were classified into two groups: survivors (26 patients); subsequent survival of more than 4 years, and non-survivors (16 patients): subsequent survival of less than 4 years. Four-chamber cine imaging was used to quantify rv longitudinal shortening, rv transverse shortening, and rv fractional area change between end-diastole and end-systole. Our study revealed that a progressive decline in rv transverse shortening and rv fractional area change is associated with mortality in these pah patients. Interestingly, this decline in right ventricular function was predominantly the consequence of increased leftward septal bowing.

### 10.1.3 Interventricular asynchrony and RV wall stress in PAH

Recent research demonstrated the presence of interventricular mechanical asynchrony in severe pah patients. This asynchrony is caused by prolonged duration of shortening and delayed peak shortening of the rv free wall compared with that in the left ventricular free wall and interventricular septum. This rv free wall shortening even continued after pulmonary valve closure and appeared to be related to leftward septal bowing during lv early diastole. In chapter 4 we investigated whether in pah the prolonged period between pulmonary valve closure and tricuspid valve opening is associated with increased relaxation period (representing rv diastolic dysfunction). Therefore, this prolonged isovolumic period in pah cannot be considered as a mere reflection of rv diastolic dysfunction, as had been the assumption until now, but is a parameter of prolonged contraction duration.

The underlying mechanism of this prolonged contraction duration of the rv free wall is unknown in pah. In chapter 5 we hypothesized that rv end-systolic wall stress plays a key role in this interventricular mechanical asynchrony in pulmonary arterial hypertension. Thirteen consecutive patients with chronic thromboembolic pulmonary hypertension underwent magnetic resonance imaging myocardial tagging before and after pulmonary endarterectomy. For the left ventricular free wall, septum and rv free wall, the time to peak of circumferential shortening (t\textsubscript{peak}) was calculated. Pulmonary artery pressure was measured by right heart catheterization. Then, for the rv free wall, the rv systolic wall stress was calculated by the Laplace law. Post-operatively, the left to right free wall delay in t\textsubscript{peak} decreased to normal reference values. The rv wall stress decreased to values which were not different from the normal reference values. Moreover, the reduction of l-r delay in t\textsubscript{peak} was associated with the reduction in rv wall stress, but not with the reduction in systolic pah, reduction in rv radius or increase in rv wall thickness. These observations support the role of increased rv wall stress as a cause for the interventricular asynchrony in pah.

Since elevated myocardial wall stress induces an increased release of n-terminal pro-brain natriuretic peptide (nt-probnp), we subsequently investigated the prognostic value of serial nt-probnp measurements a large group of pah patients in chapter 6. We retrospectively analyzed all available nt-probnp plasma samples in 198 patients who were diagnosed with who group pah from january 2002 to january 2009. At the time of diagnosis, median nt-probnp levels were significantly different between survivors (610 pg/ml; range, 6 to 8714) and nonsurvivors (2609 pg/ml; range, 28 to 9828) (p < 0.001). In addition nt-probnp was significantly associated (p < 0.001) with other parameters of disease severity (6 minutes walking distance; functional class). Receiver operating curve analysis identified ≥ 1256 pg/ml as the optimal nt-probnp cut-off for predicting mortality at the time of diagnosis. Serial measurements allowed calculation of baseline nt-probnp (i.e., the intercept obtained by back-extrapolation of the concentration-time graph) providing a better discrimination between survivors and non-survivors than nt-probnp at time of diagnosis alone (p = 0.010). Furthermore, a decrease of nt-probnp of more than 15 percent per year is associated with long term survival.

### 10.1.4 Main pulmonary artery flow and size

The rv stroke volume directly reflects right ventricular (rv) function in response to its load, and contains prognostic information in pah as described in earlier studies. Since most of the mri protocols used in pah measure pulmonary artery flow, sv can be assessed by measuring flow in the main pulmonary artery (pa). Previous studies have shown that this method is accurate to measure sv from pa flow in healthy subjects. In chapter 7 we investigated the accuracy of pulmonary artery (pa) flow for measuring sv in pah. Thirty-four pah patients underwent both cmr and right-sided heart catheterisation. Cmr-derived stroke volume was measured by pa flow, left (lv) and right ventricular (rv) volumes, and, in a subset of nine patients also by aortic flow. These stroke volume values were compared to the stroke volume obtained by the invasive direct fick method. The sv value, as derived from pa flow, appeared to have limited accuracy in pah patients. lv volumes and aorta flow are to be preferred for the measurement of sv.

As we observed that in pah patients the flow profile in the main pulmonary artery differs from that seen in healthy subjects, we subsequently studied the retrograde flow in the pulmonary artery in pah patients in chapter 8. We hypothesized that early onset of retrograde flow in the main pulmonary artery is indicative for the presence of pulmonary hypertension. Thirty-eight pah patients and 17 non-pah subjects underwent cmr and right heart catheterisation. The onset time of the retrograde flow, as a fraction of the cardiac cycle duration, was compared with the mean pulmonary artery pressure. A negative relation between onset time of retrograde flow and pulmonary artery pressure was found. Furthermore, the relative onset time of retrograde flow in pah patients was significantly smaller than those

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found in non-PH subjects. In addition, a cut off value for relative onset time (fraction of R-R interval) of 0.25 distinguished PAH patients from all non-PH subjects hypertension (PAH) and is used for non-invasive detection as described earlier. However, it is unclear how the size of the PA behaves over time and whether it is related to pressure changes. In Chapter 9 we evaluated the PA size during follow-up in treated patients with PAH and tested whether it reflects pulmonary vascular hemodynamics. Fifty-one patients with PAH who underwent at least two right-sided heart catheterizations together with cardiac MRI were included in this study. Another 18 patients who had normal pressures at RHC were included for comparison. From RHC, we derived PA pressures and cardiac output. From the MRI images we derived PA diameter and ascending aorta diameter. The PA diameter was significantly larger in patients with PAH than in patients without PAH. A ratio of the PA diameter and ascending aorta diameter more than 1 had a positive predictive value of 92% for PAH. Mean follow-up time was 942 days, and there was a significant dilatation during this period. However, the change of the PAD did not correlate with the changes in pressure or cardiac output. A moderate correlation between PAD and follow-up time was found.

10.2 Future Perspectives

10.2.1 Right Ventricular Geometric Shortening in PAH: the importance of the septum
The RV longitudinal shortening, when taken as a measure of RV function, ignores the septal contribution to RV ejection (Chapter 2) which may become important to maintain overall RV function. A further reduction of RV function is due to progressive leftward septal displacement (Chapter 3). Because transverse shortening incorporates both free wall and septal displacement, this parameter can be used to monitor the decline of RV function. The clinical value of the transverse measures would be even stronger if these could be measured also by using echocardiography. Thus further development of right ventricular echocardiography, already a widespread tool in the non-invasive work-up and follow-up of patients with left ventricular dysfunction, is advised.1

10.2.2 Diastolic Function in Pulmonary Arterial Hypertension: how to measure?
Diastolic function of the RV in PAH is a concept that has not been well studied. There is modest evidence of impaired diastolic RV function in PAH. Further studies are needed to investigate the presence of relaxation impairment and the relative contribution to the progression of RV dysfunction in PAH patients. The gold standard for the assessment of diastolic dysfunction is to measure the load independent diastolic elastance as obtained by invasive pressure-volume relations.2

However, this measurement is rather invasive and not suitable for serial follow-up measurements. Although tissue Doppler imaging has been well validated as a modality to measure left ventricular diastolic function, few studies have used it to examine RV diastolic function. The prolonged post-systolic isovolumic period, as previously interpreted as a reflection of diastolic function, is not a sign of diastolic dysfunction (Chapter 4). This raises the question which measure should be used to accurately assess RV diastolic function non-invasively. One option is diastolic myocardial strain rate derived from MRI myocardial tagging.3 Alternatively, 3D velocity-encoded MR imaging might aid in the assessment of right ventricular diastolic function and the clinical implications in patients with PAH.

10.2.3 Interventricular asynchrony: target for treatment?
Interventricular asynchrony is often observed in progressive stages of PAH-induced right ventricular failure.4-6 The underlying cause of this interventricular asynchrony is an increase in pulmonary resistance and subsequently the increase in RV wall stress (Chapter 5). So, the principal target of therapy is the pulmonary microvasculature. However, as the RV adaptation capacity plays a central role, the RV itself may well be a target for treatment. This suggests that additional therapeutic methods, that improve the efficiency of RV contraction, may be beneficial in these patients. One option is resynchronization with biventricular pacing, such that the asynchrony in LV and RV peak shortening is reduced.6,7 An alternative treatment option would be to lower RV wall stress pharmacologically that will limit the variability and load dependence of relaxation.

10.2.4 N-terminal pro B-type natriuretic peptide in PAH: serial measurements
Measurement of the B-type natriuretic peptides is currently recommended by guidelines, despite a lack of appropriate validation in the PAH population.11 With regard to NT-proBNP, a value above 1400 pg/ml was associated with poorer survival in 55 patients with several types of pulmonary hypertension, all receiving PAH targeted therapies.12 The REVEAL registry has identified a similar cut-off (1500 pg/ml) associated with worse outcomes.13 We observed in 198 PAH patients a comparable cut-off value of 1256 pg/ml for predicting mortality at the time of diagnosis. Moreover, our result shows that decreasing NT-proBNP levels during follow-up by more than 15% per year (Chapter 6) is an important treatment goal in pulmonary arterial hypertension. Prospective, goal-oriented strategies are warranted to test whether this treatment goal is achievable in PAH patients and whether this will alter the prognosis. Investigators undertaking cohort studies or therapeutic trials in PAH should be encouraged to incorporate serial NT-proBNP measurements in study designs.

10.2.5 Pulmonary Artery Dilatation: chance of PA dissection or rupture?
Pulmonary artery dilatation is a characteristic in PAH and further dilatation seems to be a process most likely due to a change of the intrinsic vessel properties independent of pulmonary hemodynamics (Chapter 9). Dissection and rupture of a dilated pulmonary artery is a rare, but deadly, event which is most difficult to predict in PAH.14 These complications are possibly related to the size of the pulmonary arteries. Better identification of risk factors for pulmonary artery rupture or dissection may help to select the high-risk patients as candidates for heart-lung transplantation, since the outcome is very poor of patients who develop these complications.
References


