8.1 Discussion

VU University Medical Center PAH patient cohort

Although PAH is a rare disease, the VU University Medical Center was the first hospital in the Netherlands to provide effective pharmacological treatment with epoprostenol for this group of patients in the late 1990s. Therefore, a large population of PAH patients has concentrated around the VU University Medical Center. Since 1999, the patients have been systematically entered into a growing database of patients with pulmonary hypertension, diagnosed and treated in the VU University Medical Center. At the same time, the project started, which aimed to determine the clinical value of monitoring PAH patients with MRI. This resulted in a unique patient cohort, providing the opportunity to learn more about the clinical outcome of PAH patients and to study the effects of PAH on the right ventricle, during treatment.

Right ventricular parameters that indicate right ventricular failure measured by MRI

The studies of this thesis are all based on this patient cohort. Long-term follow-up of these patients have pointed out which changes take place in the right ventricle during progressive right ventricular failure and lead to a worse prognosis. The most important parameters that indicated right ventricular failure where dilatation of the right ventricle, a decreased left ventricular volume, a low stroke volume and an increased heart rate (Figure 8.1). Importantly, right ventricular hypertrophy, did not appear to be an important prognostic marker. This is a remarkable finding since an increased PAP and PVR lead to an increased strain on the right ventricle, and in turn to myocardial hypertrophy to compensate. Next to right ventricular hypertrophy, PAP is also known to have little prognostic value.\(^1,2\) Therefore, in patients with PAH, it seems that instead of the severity of PAH, the capacity of the right ventricle to adapt and maintain cardiac output determines prognosis. Already in 1999, Quaife et al.,\(^3\) used a model of concentric and eccentric right ventricular hypertrophy to explain differences in outcome (Figure 8.2). Patients with a favorable adaptation had predominantly hypertrophy and little dilatation (concentric...
remodeling), whereas patients with an unfavorable adaptation had predominantly right ventricular dilatation (eccentric remodeling). It is important to learn which circumstances lead to a favorable remodeling. In this thesis, it is shown that a targeted therapeutic intervention can lead to improvement of right ventricular function and reverse remodeling. Currently, a multinational European Union-funded Framework 6 EURO-MR project is underway to study cardiac MRI as end-point in longitudinal follow-up studies and clinical trials of treatment effect. If this international study also demonstrates improvement in right ventricular structure and function after a therapeutic intervention and that patients with progressive worsening of right ventricular structure and function, despite treatment, have a worse prognosis, then there is a strong rationale to use MRI for evaluation of PAH patients. Therefore, we expect that MRI will emerge as modality for the clinical follow-up of patients with PAH.

**Figure 8.1** Assessment of treatment effect using cardiac MRI in PAH patients.
Alternative non-invasive techniques to monitor right ventricular failure in PAH

Other non-invasive techniques besides cardiac MRI that might be used as a modality to monitor PAH patients are also described in this thesis. Of these techniques, probably the most promising are acetylene absorption, or other rebreathing techniques, such as the Innocor system, since they provide the opportunity to measure cardiac output and stroke volume in a simple manner, which can be done in the lung function laboratory for instance. These techniques can give valuable information at low cost. Several studies have been published regarding these techniques. In the future, long-term follow-up study of patients with PAH with serial assessment of stroke volume by rebreathing techniques are required to determine the clinical value of this technique in PAH.

8.2 SUMMARY

Pulmonary arterial hypertension (PAH) is characterised by obstruction and narrowing of the small pulmonary arteries. This results in increased pulmonary vascular resistance which in turn leads to chronic right ventricular pressure overload. Although in the early stage of the disease, the right ventricle is able to adapt, at a certain stage during the course of the disease the right ventricle is no longer able to further adapt to the increased pulmonary artery pressure and starts to fail. The cause of death in PAH is right heart failure. Thus monitoring the right ventricle is of importance to evaluate response to treatment and predict prognosis.

Right ventricular function and structure is currently best measured by cardiac MRI. Cardiac MRI provides detailed images of the right ventricle with high accuracy and good reproducibility. In this way, small changes in right ventricular structure and function can be detected by cardiac MRI, which is crucial because at present, most therapeutic interventions have a modest efficacy.

In Chapter 2 we assessed the prognostic value of right ventricular structure and function parameters as assessed by means of MRI and compared outcomes of these measures with hemodynamic measurements and the 6 minute walk test. In this study we found that a baseline right ventricular stroke volume index less than 25 mL/m², right ventricular end-diastolic vol-
ume more than 84 mL/m$^2$, and a left ventricular end-diastolic volume less than 40 mL/m$^2$, are predictors of a worse outcome. In addition, further dilation of the right ventricle, a decrease in left ventricular diastolic volume and a further decrease in right ventricular stroke volume at 1-year follow-up, was related to a worse prognosis and thus treatment failure.

If stroke volume is an important parameter to monitor, it can be hypothesized that heart rate will be of equal importance, since in a patient with a failing right ventricle cardiac output can only be maintained by means of an increase in heart rate. In addition, in left heart failure it is well known that an increased heart rate is a marker for a worse prognosis. In Chapter 3 we used ECG measurements to assess heart rate in PAH patients. We demonstrated that an increased heart rate is associated with a poor prognosis and that a persistent elevated heart rate during treatment is predictive of treatment failure in PAH.

Based on the findings of Chapter 2 we assessed in Chapter 4 what change in stroke volume can be considered as a clinical relevant change. To study this, we used 6 minute walk distance as a reference. The 6 minute walk test is worldwide accepted as an important tool to monitor treatment effects in PAH, since it measures the main symptom of PAH, which is limited exercise tolerance. Earlier studies revealed that the 6 minute walk test reflects prognosis in pulmonary hypertension. Using this method as a reference method we found that a change of 10 ml can be considered clinically relevant. The relevance of this finding is that not only stroke volume, more than 6 minute walk distance, reflects the state of the right ventricle in PAH, but also that this measurement can be performed in patients who are unable to perform exercise in a highly reproducible manner. In Chapter 5, we used cardiac MRI to monitor the effects of addition of sildenafil on patients stable on bosentan therapy. Cardiac index and right ventricular ejection fraction improved after addition, whereas right ventricular hypertrophy decreased, together with a decrease in right ventricular volume. This study not only showed favourable effects of combination therapy but also showed that MRI is a sensitive tool to detect clinical relevant changes in a small sample size. Moreover, the results were concordant with the changes in 6 minute walk test and NT-proBNP.

In Chapter 6, we explore a possible contributing mechanism to right ventricular failure. Due to chronic right ventricular overload, the right ventricle changes and resembles the left ventricle. In left ventricular failure it is well known that ischemia can play an important role. Gomez et al. was the first to demonstrate right ventricular ischemia in patients with pulmonary hypertension. However, for the right ventricle, much less is known about the role of ischemia in right ventricular failure. In experimental studies on acute right ventricular failure, it was found that right ventricular function was limited by coronary perfusion. In pulmonary hypertension there are two reasons why coronary perfusion might be insufficient. There is an increased oxygen demand of the hypertrophied right ventricle and the driving pressure of the right coronary artery, which supplies the right ventricle, is decreased. This is because systemic blood pressure in pulmonary hypertension is low. In Chapter 6 we described the application of MRI to measure flow in the right and left coronary artery in PAH. We found that in patients with pulmonary hypertension, the right coronary artery flow that is normally constant over the cardiac cycle, becomes biphasic and resembles the flow pattern of the left coronary artery. In addition, we found that right coronary artery flow is decreased in proportion to the amount of right ventricular hypertrophy. This result fits with the early observation of Gomez et al. who showed by means of nuclear techniques that right ventricular ischemia is present in end stage disease.
Finally in Chapter 7, we describe alternative noninvasive methods to measure decreased flow in the pulmonary circulation in patients with pulmonary hypertension. These include perfusion measurement of the pulmonary vasculature by MRA or CTA, electrical impedance tomography, acetylene diffusion technique and exhaled NO. These methods are under development and used for research purposes. Some of these techniques might find clinical applications for patients with pulmonary hypertension.

### 8.3 CONCLUSION AND FUTURE PERSPECTIVE

In this thesis we provide a starting point for the use of cardiac MRI to monitor treatment effect. Given the fact that PAH patients die from right ventricular failure, early recognition of this condition is required in order to add combination therapy, perform balloon atrial septostomy or list for lung transplantation in time. Results of this thesis showed that MRI can provide this information and is of additional value to other clinical and functional parameters measured in patients with PAH. In the future, large multicenter studies that use cardiac MRI to monitor treatment effect are required to validate the parameters of right ventricular failure presented in this thesis.

Echocardiography is an important step in the noninvasive work-up of patients with suspected PAH, before right heart catheterisation is performed. Also, echocardiography is frequently used in the follow-up of patients with PAH. Prognostic markers of right ventricular failure that can be measured by echocardiography with sufficient reliability and reproducibility to detect meaningful changes during treatment should be sought and validated as is performed for cardiac MRI. For these studies, cardiac MRI can act as a reference tool to detect right ventricular failure.

Despite the fact that stroke volume, heart rate and left and right ventricular volumes are important markers of prognosis in PAH, they do not fully explain the large variation in clinical presentation and prognosis of our PAH patients. Clearly, the strategy of the right ventricle to adapt to the increased afterload is different for individual PAH patients. Further insight into these differences in adaptation of the right ventricle in pulmonary hypertension and elucidation of the mechanisms that lead to progressive right ventricular failure should be investigated to develop specific therapies that can benefit patients with PAH.

### References


