SUMMARY

In patients with pulmonary arterial hypertension (PAH) the lumen of the small pulmonary arteries is narrowed due to abnormal proliferation, hypertrophy and vasoconstriction. This remodelling process leads to an increase in pulmonary artery pressures and pulmonary vascular resistance. At first, the right ventricle (RV) will be able to adapt to this increase in pressures by increasing its wall thickness (hypertrophy) and the RV can thereby maintain its cardiac output. However, as the disease process continues and pulmonary pressures increase even more, this hypertrophic process is not sufficient to ensure sufficient cardiac output. RV dilatation will occur and in the final stage the RV will begin to fail. As the status of the RV dictates prognosis, evaluating and monitoring RV function is of great value in PAH.

Pulmonary hypertension (PH) due to left heart disease (post-capillary PH) cannot be effectively treated with pulmonary vasodilators. In those patients, no hemodynamic evaluation by means of a right heart catheterization (RHC) is required when echocardiography points towards the presence of left heart disease. However, in many cases echocardiography results are inconclusive and patients are referred to tertiary PAH centres for a RHC. As such, optimizing the noninvasive identification of post-capillary PH will lead to a reduction of the number of RHC performed and reduce patient burden.

In this thesis we focused on the right- and left side of the heart in PH and investigated several hypotheses concerning RV monitoring by CMR in response to PAH-specific drugs and aimed for diagnostic optimization.

Part 1. The right ventricle in pulmonary arterial hypertension: response to treatment

Over the years, the RV has earned its place in the PH field as major determinant of patient mortality. Unfortunately, no treatment is currently known to specifically target the RV and the positive effects of PAH-specific medication on RV function are most likely linked to a reduction in RV afterload\textsuperscript{1}. The difficulty with addressing RV specific effects of currently available drugs is that all widely used noninvasive markers of RV function are load dependent. Nevertheless, markers of RV dysfunction are highly relevant because irrespective of their load dependency, they offer valuable information on patient response to PAH-specific drugs and subsequent clinical outcome\textsuperscript{2-4}. One of the first papers reporting on the prognostic value of a change in RV volumes in the follow-up of PAH patients was the study by Van Wolferen et al. demonstrating the relation between increased RV end-diastolic volumes and survival\textsuperscript{5}. Based on this study and others reporting on the prognostic value of RV function, monitoring
RV volumes and function by CMR has become standard of care in the VU medical centre. In the first part of this thesis we conducted two studies aiming to shed light on the response of the RV to current approved PAH therapies as assessed with CMR.

In chapter 2 we tested the hypothesis that upfront dual combination therapy would lead to a stronger decrease in RV volumes and improvement in RV function when compared to monotherapy. This hypothesis was based on results of the landmark AMBITION study in which the superiority of an upfront dual combination strategy over monotherapy was proven. In that event-driven study, upfront combination therapy with ambrisentan and tadalafil significantly reduced the risk of the occurrence of a clinical failure event by 50% when compared to monotherapy alone. In addition, a decrease in NT-proBNP levels was observed with dual combination therapy. This is of particular interest as NT-proBNP can be considered a surrogate for RV wall stress and could therefore by associated with improved RV functional outcome as well. However, RV function was not addressed in the AMBITION study and that is why we studied RV functional changes after both mono- and dual combination therapy. Indeed, upfront combination therapy was associated with a greater improvement in RV volumes and function, as measured by CMR. This was paralleled by a significant decrease in RV wall stress, only in the combination therapy group.

Previously, it has been shown that any deterioration in RV volumes and function can precede clinical worsening even in seemingly clinical stable PAH patients. As such, we developed a standardized, goal-orientated treatment strategy aimed at stabilizing RVEF. In chapter 3 first experiences with this treatment strategy are reported. We found that escalating PAH-specific therapy at a time of a deterioration in RVEF led to subsequent improvements in RVEF and clinical stability. However, in patients with a low RVEF at baseline (RVEF <35%) clinical worsening did occur, despite a stable RVEF. This led to the hypothesis that in order to prevent ultimate disease progression we cannot be satisfied with a stable RVEF but should strive for a RVEF above a certain threshold. Additionally, in patients with a RVEF at baseline <35% aggressive treatment strategies including upfront triple therapy can be considered.

Part 2. Pulmonary hypertension due to left heart failure: optimizing diagnostic- and therapeutic care

As set out in chapter 4, a diagnosis of HFpEF can be an important clinical challenge, also in the setting of PH. As patients with HFpEF mainly present with symptoms of dyspnoea on exertion, diagnostic tools incorporating exercise measures may enhance an accurate diagnosis of HFpEF. Nowadays, resting echocardiography measures including E/e’ especially lack sensitivity for the identification of diastolic dysfunction
in HFpEF. Exercise echocardiography (E/e’) or RHC (PAWP) may enhance sensitivity for unmasking diastolic abnormalities in patients with normal resting values and thereby contribute to improved diagnostic care.

Computed tomography angiography (CTA) is often performed in the early diagnostic work-up for PH to rule out interstitial lung disease or pulmonary embolisms as a cause for PH. As it is known that in PAH patient right atrial (RA) size is often increased, whereas in HFpEF-PH the left atrium (LA) is enlarged we investigated how atrial dimensions can help in the discrimination between these two conditions. First, we demonstrated in chapter 5 that the CMR-derived ratio of LA size over RA size is relatively constant during the cardiac cycle while LA dimensions varied over time. We subsequently tested the diagnostic value of the LA/RA ratio in patients with PAH and PH due to HFpEF by using non-gated CTA images in a cohort of 95 patients. The LA/RA ratio accurately discriminated between PAH and HFpEF-PH and could therefore be of value in guiding early clinical- and diagnostic decision making in patients with suspected PH.

A major step towards optimizing diagnostic care for patients with PH consists of the noninvasive identification of post-capillary PH. Previously, several attempts have been made to improve the diagnosis of post-capillary by developing multiparametric risk scores. However, none of these scores were externally validated, prohibiting their use in daily clinical care. In chapter 6 we were first to externally validate two risk scores aimed at facilitating a noninvasive diagnosis of either pre-or post-capillary PH. A score developed by Bonderman et al used the absence of a right ventricular strain pattern on ECG with low NT-proBNP levels to exclude pre-capillary PH. However, when this score was tested in an external cohort of patients derived from non-PAH expert centers, sensitivity of the score was only 89% and pre-capillary PH could not be sufficiently ruled out. In contrast, the score developed by Jacobs et al (OPTICS score) had a specificity of 100% for the identification of post-capillary PH and 1 out of 5 patients in whom a RHC was performed could be identified as post-capillary PH by using the score. The OPTICS score can therefore reduce the number of patient referrals and RHCs performed at tertiary PH centers.

As up to 80% of patients with HFpEF will develop PH and the development of PH confers a worse outcome, targeting the pulmonary vasculature may hold promise. While PAH-specific drugs do not seem to be beneficial in patients with HFpEF without PH or in patients with isolated post- and pre-capillary PH, these drugs might be of use in the setting of combined post- and pre-capillary PH (Cpc-PH). However, data on the hemodynamic and cardiac specific effects of PAH-specific drugs in patients with HFpEF and Cpc-PH is not widely available. A clear understanding of the effect of
pulmonary vasodilators in Cpc-PH could pave the way for novel randomized trials and optimal patients selection. That is why studied the effect of these drugs on both RV- and LV afterload and cardiac function in chapter 7. We found that although PAH-specific drugs in HFpEF patients with Cpc-PH successfully lowered RV- and LV afterload, this occurred at the cost of an increase in LV filling pressures. This is of particular interest as it has been recently demonstrated that higher LV filling pressures with exercise correlate closely with severity of dyspnea and reduced exercise capacity. Taken together results from this study indicate that when aiming to reduce RV afterload by PAH-specific drugs, care should be taken in monitoring LV filling pressures.

Can and should we use RV parameters to guide treatment decisions? Overall it has been shown that the initiation of PAH treatment has a positive effect on RV function. As changes in RV volumes and function are considered relevant