Summary and future perspectives
Introduction

THIS THESIS AIMS to improve our understanding of the hemodynamic characteristics of the right ventricle (RV) and the pulmonary arteries under physiological conditions and in disease states, with a focus on pulmonary hypertension (PH). Currently, parameters that accurately describe the circulatory behavior are limited in clinical practice, because clinical and ethical concerns strongly restrict hemodynamical measurements possible in human. We applied methodologies to accurately estimate parameters of the cardiovascular system, with a potential of clinical application, as well as methodologies directed to improve our understanding of the circulatory behavior. Since PH is as much a disease of the lungs as it is of the heart, this thesis is divided into two parts. The first part focuses on modeling and measurements of cardiac function, whereas the second part is dedicated to arterial function. This chapter summarizes the most important findings in this thesis and concludes with a paragraph on recommendations for future studies.

Part 1. Cardiac function

Right Ventricular Geometric Shortening in PAH

In a clinical setting, RV ejection fraction (RVEF) is a widely accepted measure used for quantification of RV pump function. This measure can be estimated non-invasively, using e.g. MRI. However, the estimation is time consuming and depends on geometric assumptions. A simpler approach is to approximate RVEF by measuring the tricuspid annular plane systolic excursion (TAPSE). This measure quantifies the longitudinal shortening of the RV and its clinical value has been studied extensively in PH. Transverse wall motion has been examined less frequently, despite the importance of transverse movements of the RV free wall towards the septum in RV ejection. Therefore, Chapter 2 addresses the contribution of longitudinal and transverse shortening to blood ejection in 101 PH patients who underwent MRI four-chamber cine imaging. We quantified longitudinal and transverse shortening, as well as RVEF. Our results revealed that transverse shortening was significantly reduced in PH compared with control subjects. This reduction was larger than for longitudinal shortening. Moreover, results indicated that measures of transverse shortening at mid RV had a significant relationship with RVEF, which was stronger than for measures of longitudinal shortening. Therefore, we concluded that transverse measures might be a better predictor of RV function in PH than TAPSE.

These promising results encouraged us to perform the study of Chapter 3, in which we evaluated the progression of RV longitudinal and transverse shortening in 42 PH patients during follow-up. RV transverse shortening consists of two components: movement of the RV free-wall and movement of the interventricular septum. Because of the
importance of transverse shortening to ejection, as shown in the previous chapter, we also evaluated the progression over time of these components individually. Patients were classified into two groups based on survival after a one-year run-in period: survivors (26 patients, who had a subsequent survival of more than 4 years), and non-survivors (16 patients, who had subsequent survival of less than 4 years). Our results indicate that a progressive decline in RV transverse shortening is associated with mortality in PAH patients. However, progressive RV failure in PAH is associated with a parallel decline in RV longitudinal and transverse free wall displacement until a ‘floor’ effect is reached for both. The end-stage decline in RV function is due to a progressive leftward septal displacement, rather than due to a further decrease in RV free wall transverse or longitudinal displacement.

In Chapter 4 the interaction between the vascular system and the RV was investigated in PAH patients, with a focus on the prognostic value of clinically available measures. In this context, RVEF was used as a measure of RV function and pulmonary vascular resistance (PVR) for arterial function. This study was motivated by the observation that loading conditions can be normalized in patients with PAH after lung transplantation and in patients with chronic thromboembolic pulmonary hypertension after pulmonary endarterectomy. Although PVR can be reduced by means of PAH-specific medications, PVR remains elevated in the vast majority of patients and prognosis remains unsatisfactory. Therefore, in this study we explored the relation between changes in PVR, changes in RVEF and survival in PAH patients under PAH-targeted medical therapy. Results clearly indicated that RVEF could deteriorate despite a reduction PVR. The reduction in RVEF was strongly associated with a poor outcome, irrespective of a change in PVR.

Time varying elastance

The previously discussed geometric measures provide important information on the functional state of the RV and prognosis of a patient, but are not inherent ventricular characteristics since they are dependent of the loading conditions of the heart (preload, afterload). A load-independent measure of RV pump function can be very useful in various situations, such as assessment of the effect of therapeutic interventions on the RV and monitoring of heart function relative to the arterial function (i.e. arterio-ventricular coupling). Time-varying elastance is such a measure of pump function, which defines ventricular stiffness as a function of time for a complete cardiac cycle. Although this measure is proposed as “load independent”, in Chapter 2 we showed that loading conditions, however, do affect time-varying elastance. We observed that the time to reach maximal elastance increased with increased ventricular pressures. To take this load dependency into account, we normalized the time course of all beats relative to four cardiac phases (i.e. isovolumic contraction, ejection, isovolumic relaxation, filling). With this
normalization, isophase lines were obtained that connect points in pressure-volume loops of different beats at the same normalized time relative to a cardiac phase. These lines are different from isochrone lines that mark points at the same time in a cardiac cycle. We concluded that the normalization resulted in a less load dependent and a more accurate description of time-varying elastance.

One particularly useful point of time varying elastance is the end-systolic elastance ($E_s$). This measure is proposed as an index of cardiac contractility. In clinical routine, determination of $E_s$ is hampered by the requirement of invasive vena cava occlusion. This concern has been addressed by the introduction of a single-beat method allowing for determination of $E_s$ via estimation of maximum isovolumic pressure ($P_{max}$), which is the peak pressure a ventricle can generate without ejecting. Isovolumic pressure can be estimated from a single ejecting ventricular pressure wave, and together with end-systolic RV pressure and stroke volume, $E_s$ can be computed. The approach had been proposed initially for the left ventricle (LV). However, some assumptions are made regarding the shape of the non-ejecting isovolumic pressure wave, which do not resemble physiology. Therefore, in Chapter 3, we proposed an improved method to derive $P_{max}$ using a more physiological shape of an isovolumic pressure wave. We determined the wave shape by clamping the pulmonary artery in PH and control rats and used this template to compute $P_{max}$ from ejecting beats in both PH and control rats. We also compared the accuracy of several other single-beat methods with our single beat method. Results indicated that all methods enable estimation of $P_{max}$ with reasonable accuracy, but differences in estimates of $P_{max}$ obtained from these methods increased with increasing severity of PH. Using our method the bias in estimates of maximum isovolumic pressure was almost independent of the disease condition. Furthermore, with our method isovolumic pressure wave shapes were obtained that better reflect physiology.

**Part 2. Vascular function**

Modeling the pulmonary vascular bed

Proportional relationships were reported between mean pulmonary artery pressure (mPAP), and the systolic (sPAP) and diastolic (dPAP) pressures in the pulmonary artery. It was found that these relationships are maintained in both health and various disease conditions, including PH\(^{1,2}\). This phenomenon is thought to be a unique intrinsic property of the pulmonary circulation because it has not been observed in the systemic circulation. Recently, Lankhaar et al.\(^3,4\) empirically showed in a cohort of normal subjects and patients with PAH, that pulmonary resistance (R) and compliance (C) are related by an inverse hyperbolic relationship. The product of these components was found to be approximately
constant (this product is called RC-time because the dimension is time). This constant RC-time might, in part, be the underlying mechanism of the proportional relations between the systolic, diastolic and mean pressure. To study these unusual strong relationships we conducted the study described in Chapter 7 to elucidate whether the underlying mechanisms of these proportionalities were primarily due to vascular or ventricular characteristics. In this study we used an arterial-ventricular interaction model in which the vascular bed was represented as a three-element Windkessel model and in which we modelled the RV using a time-varying elastance model. Simulation results indicated that satisfactory agreement was obtained with the true measurements in patients. Furthermore, with this model we were able to derive that the proportional relations are a direct consequence of the constant RC-time, without any effect of the RV function, except for negligible influence of heart rate.

Chapter 8 is focused on the mathematical estimation of Windkessel parameters in general. The original Windkessel model was proposed by Otto Frank in 1895 and consists of a lumped distensible element and a lumped peripheral resistance. In later research, this classical two-element Windkessel model was extended with a third element to account for the impedance of the proximal part of the arterial bed, and a fourth element to account for the inertia of the blood. An important requirement of a good model is that all parameters can be estimated from available data. Therefore, in this study it was investigated how well the three- and four-element Windkessel parameters could be estimated from pressure and flow data. In this study we employed a new algorithm based on subspace model identification (SMI). The robustness and accuracy of this technique to estimate Windkessel parameters were investigated using noise-corrupted pressure and flow simulation data. The use of simulation data has the advantage that parameters are known in advance. It was concluded that for a three-element Windkessel model, SMI is a very robust method to estimate parameters. However, application to a four-element Windkessel model was less accurate because of insufficient excitation power to accurately estimate the inerance term (fourth element). Therefore, based on the simulation results, the use of the three-element Windkessel model is preferred over the use of a four-element Windkessel model.

Pulmonary blood perfusion

The possibilities of MRI to study anatomy and function of the RV are widely recognized. In contrast, knowledge of application of MRI for assessing anatomy and function of the pulmonary vascular bed is less widespread. The conventional method to visualize pulmonary arteries is using contrast angiography, which allows accurate assessment of vessel anomalies. An important drawback of angiography is that it is unable to determine
parenchymal perfusion. Dynamic contrast-enhanced MRI is a technique that can be used for visualization of both pulmonary arteries and lung parenchyma in a non-invasively manner using the relative nontoxic gadolinium contrast and without radiation exposure. Moreover, it allows for absolute parenchymal perfusion quantification.

Quantification of perfusion is based on the central volume principle and requires a deconvolution of the measured arterial input function and a tissue concentration curve, which is a mathematical approach used to derive a residue function. The residue function is an important characterization of a tissue and directly provides perfusion parameters: blood flow, blood volume and mean transit time. Since deconvolution is an ill-posed problem, constraints should be applied to treat this problem. However, it is uncertain which method is most accurate in estimating blood perfusion. Therefore, in Chapter 9 several deconvolution techniques were investigated in simulation data to test the accuracy and robustness in estimating perfusion parameters. Among these techniques were model-dependent methods, which make assumptions of the underlying residue functions (i.e. exponential and Fermi shaped residue function), and model-independent methods, which do not rely on assumptions (i.e. deconvolution by truncating the smallest singular values, Tikhonov regularization and parameterization using B-splines + Tikhonov regularizations). Results indicated that the model-independent approach with B-splines and Tikhonov regularization had a reasonable accuracy in blood perfusion estimates and that it provided less biased results than all model-dependent approaches. Based on our simulations, this technique was considered most promising for application on experimental data.

In Chapter 10 the same deconvolution techniques were applied to experimental perfusion data obtained in five healthy control subjects and 16 patients. This study was performed to explore the effects of a delay and dispersion of the contrast bolus. This is an important issue since perfusion quantification is based on the assumption that the response of a tissue to an injected tracer is proportional with the dose. However, this assumption is only true when an arterial input function is measured directly at the inlet of a tissue. Since this is not possible in the lungs, the input function is usually measured in the main pulmonary artery resulting in a delay and dispersion of the contrast bolus when it arrives at the lung parenchyma. Without delay correction, pulmonary blood flow was underestimated up to 50%. In contrast, the effect of dispersion on perfusion estimates was almost negligible, which could be a consequence of the short transit time of blood. Based on our results we concluded that deconvolution with Tikhonov regularization and parameterization of the residue function with B-splines is the optimal way to estimate perfusion parameters. It is a computationally simple procedure that does not rely on assumptions and produces robust estimates of perfusion parameters.
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Future perspectives

Cardiac function
As shown in Chapters 2 and 3, measures of RV transverse shortening reflect RV dysfunction more accurately than measures of longitudinal shortening, which are commonly used in a clinical setting. Since measurement of RV transverse shortening incorporates both free wall and septum displacement, it may also useful for monitoring the decline of RV function in end-stage PAH, as further RV dysfunction is mainly determined by increased leftward septal displacement. Estimation of transverse measures might thus be a valuable addition to the standard work-up and follow-up of PH. The clinical value might even be improved when these measures can be determined using echocardiography, which is a standard modality in the evaluation of patients with RV dysfunction. Future research should also be directed to the development of methods to (semi) automatically quantify RV transverse shortening, in order to improve the reproducibility and to make estimation more feasible in clinical practice.

In Chapter 4 we evaluated a new single-beat method to estimate $P_{\text{max}}$ using experimental data measured in rat. Together with RV end-systolic pressure and stroke volume, this estimate can be used to determine end-systolic elastance. The next step would be to prove the validity and clinical value in PH patients. This would be especially useful for assessment of the effect of therapeutic interventions on the RV or for monitoring heart function relative to the arterial function (i.e. arterio-ventricular coupling). In this study, the methods were validated in rat using high fidelity catheters, which provide accurate pressure recordings. In clinical practice, RV pressure measurements are conventionally measured using fluid-filled catheters (e.g. Swan-Ganz catheters). It is known that these catheters have poor frequency characteristics and may result in under- or overdamped pressure measurements. Future studies should also assess the validity of these catheters to obtain $P_{\text{max}}$ estimates, which would increase its clinical applicability even more.

Vascular function
Using a mathematical model of the cardiovascular system, it was found that the constant RC-time was the underlying mechanism of the remarkable proportionalities between pulmonary pressure components (Chapter 7). It was hypothesized that this constant product could also explain various other pulmonary vascular characteristics, such as proportional relations between mean and oscillatory RV power. This study provides a strong rationale to elucidate the physiological mechanism behind this constant RC-time in the pulmonary circulation. Two mechanisms were hypothesized. The first mechanism
is that an increase in resistance leads to an increase in pressure (Ohm’s law), which results in a decrease in compliance as a consequence of the nonlinear pressure-diameter relation of pulmonary arteries\(^9\). This would imply that the constant RC-time results from elastic properties of the arteries. The second mechanism is based on the assumption of a rather uniform distribution of resistance and compliance over the vascular bed. This is in contrast to the systemic circulation where the large arteries (in particular the aorta) are the most compliant vessels\(^10\) and the small arteries and arterioles mainly determine the vascular resistance. Validation of these mechanisms require a distributed model of the pulmonary vascular bed accounting for anatomical and mechanical vessel characteristics.

The other chapters of this thesis are dedicated to quantitative assessment of lung parenchymal perfusion using MRI perfusion measurements. Because of the robustness of the method, future studies should consider application of Tikhonov-regularized deconvolution with parameterization of the residue function by B-splines, either for estimating global or regional perfusion parameters. In these studies, delay correction of the contrast bolus should be performed to avoid underestimation of parenchymal blood flow. Furthermore, care should be paid to avoid T2* saturation effects to maintain a linear association between observed signal intensity and contrast concentration. In our study, absence of saturation effects could not be guaranteed, which may have affected the accuracy of estimated blood flow. Given the recent advances in MRI parallel imaging techniques, saturation effects are less likely to occur as lower contrast doses are needed, while achieving a higher contrast to noise ratio. Therefore, pulmonary perfusion analysis could be a promising tool and the clinical value of perfusion MRI should be investigated in larger patient groups.

References

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