Chapter 11

SUMMARY AND CONCLUSIONS

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The general introduction of this thesis describes the characteristics of the right ventricle. An overview of right ventricular anatomy and function is provided. The clinical importance of right ventricular function has been recognized in patients with pulmonary hypertension, congenital heart disease, and left-sided heart disease. It has been demonstrated that right ventricular function is an important determinant of morbidity and mortality in these cardiopulmonary diseases. Accurate assessment of the right ventricle and understanding of its mechanics is therefore an essential part in the evaluation and management of patients at risk for right ventricular dysfunction. Although there are limitations due to the complex right ventricular geometry, conventional 2-dimensional echocardiography remains mainstay in the evaluation of the right ventricle. Advanced echocardiographic and electrocardiographic techniques including 2-dimensional speckle-tracking imaging and vectorcardiography, derived from the 12-lead electrocardiogram, have introduced new possibilities to evaluate right ventricular mechanics. The purpose of this thesis was to provide more insight into right ventricular mechanics and hemodynamics by echocardiography and electrocardiography.

In *Part I* of this thesis right ventricular mechanics are evaluated in patients with (suspected) pulmonary hypertension. As reviewed in **Chapter 2**, pulmonary hypertension is characterized by a spectrum of pathological lesions in the pulmonary vasculature, depending on the underlying cause. Pulmonary hypertension leads to right ventricular overload and eventual right ventricular failure. Early detection of elevated pulmonary arterial pressures and right ventricular dysfunction is paramount to treatment. Imaging modalities including echocardiography, cardiac MRI and computed tomography angiography as well as electrocardiography and right heart catheterisation can be used in the diagnostic workup of pulmonary hypertension. Depending on the underlying aetiology, several treatment options are available.

In **Chapters 3 – 5** right ventricular mechanics and function are characterized by 2-dimensional speckle-tracking analysis. Speckle-tracking echocardiography allows angle-independent evaluation of myocardial strain and does not rely on geometric assumptions. Previous studies showed that right ventricular longitudinal strain is more impaired in patients with pulmonary hypertension compared to normal controls. However, in certain subgroups of pulmonary hypertension, such as patients with chronic obstructive pulmonary disease, poor apical acoustic windows can be problematic. In **Chapter 3**, the feasibility of right ventricular longitudinal peak systolic strain measurement in the subcostal view was assessed in patients evaluated for pulmonary hypertension, including a large group of patients with pulmonary disease. This chapter demonstrates that the measurement of right ventricular peak systolic strain in the subcostal view is feasible and comparable to right ventricular peak systolic strain measured in the apical four-chamber view, even in patients with right ventricular enlargement, dysfunction or poor acoustic windows in the apical four-chamber view. Moreover, multivariate analysis demonstrated that right ventricular longitudinal peak systolic strain measured in the apical-four chamber view and in the subcostal view provides significant diagnostic information on right ventricular dysfunction. As such, the subcostal view provides a good alternative for right ventricular strain assessment in patients suspected of pulmonary hypertension and poor apical acoustic windows. In **Chapter 4**, the prognostic value of right ventricular longitudinal strain was assessed in a heterogeneous group of patients with pulmonary hypertension. Right ventricular

performance has been recognized as an important prognostic marker in patients with pulmonary hypertension. The results of this study show that patients with right ventricular longitudinal peak systolic strain ≥ - 19% had more than 3-fold risk of all-cause mortality. Furthermore, right ventricular longitudinal peak systolic strain provided incremental value over other well-known clinical and echocardiographic parameters of mortality, such as age, NYHA functional class and left ventricular ejection fraction. Therefore, the measurement of right ventricular longitudinal peak systolic strain as a parameter of right ventricular function should be part of risk stratification of patients with pulmonary hypertension. **Chapter 5** describes the assessment of interventricular dyssynchrony in patients with pulmonary hypertension. Chronic increased right ventricular pressure is associated with leftward deviation of the interventricular septum and altered interventricular septal function. These changes may distort left ventricular geometry and impair diastolic filling. In this chapter, interventricular dyssynchrony was evaluated by two-dimensional speckle-tracking echocardiography in patients with pulmonary arterial hypertension and patients with pulmonary hypertension due to left heart disease. The results show that right ventricular dyssynchrony is significantly associated with left ventricular dyssynchrony and impaired left ventricular ejection fraction. In addition, patients with pulmonary hypertension and right ventricular dyssynchrony had significantly larger right ventricular dimensions and worse function compared to patients with a synchronous contraction pattern. The results of this chapter raise the question whether pacing strategies aiming at restoring interventricular synchrony may improve clinical performance.

Part II of this thesis describes the relevance of right ventricular hemodynamics in ischemic heart disease, including patients with first ST-segment elevation myocardial infarction (STEMI) treated by percutaneous coronary intervention and end-stage heart failure patients supported by left ventricular assist device (LVAD). **Chapter 6** reports the incidence of elevated systolic pulmonary arterial pressure following first STEMI treated with percutaneous coronary intervention. STEMI may cause left ventricular systolic and diastolic dysfunction, which could result in elevated left ventricular filling pressures and consequently into elevated systolic pulmonary arterial pressure. In this chapter, systolic pulmonary arterial pressure was evaluated in patients with a first STEMI treated with percutaneous coronary intervention at baseline and at 12 months follow-up. The results demonstrate a low incidence of newly developed elevated systolic pulmonary arterial pressure at 12 months follow-up. Importantly, the development of new elevated systolic pulmonary arterial pressure during follow-up after STEMI was associated with a 4-fold adjusted increased risk for all-cause mortality. This indicates that routine echocardiographic surveillance of systolic pulmonary arterial pressure should be implemented during follow-up after STEMI, possibly resulting in improved clinical management of STEMI patients.

In **Chapter 7**, current treatment options in end-stage heart failure are reviewed. Chronic heart failure is a challenging syndrome associated with high mortality and morbidity, despite significant improvements in treatment modalities. The golden standard therapy for end-stage heart failure is heart transplantation. However, there is a persistent shortage of donor hearts. In order to improve clinical outcome, novel treatment options, including surgical treatments, cardiac resynchronisation therapy, and mechanical cardiac support have been introduced. A promising novel treatment option is the LVAD. LVADs are mechanical circulatory pumps that aim to support the circulation and improve end-organ perfusion. Continuous improvements in the design of the LVAD have led to

improved survival and quality of life in end-stage heart failure patients. However, adverse events, including right ventricular failure, remain a concern. **Chapter 8** evaluates the safety and efficacy of implantation of a continuous-flow LVAD as destination therapy in end-stage heart failure patients. The patient population selected for this study were patients with NYHA class IIIb or IV heart failure symptoms despite optimal medical therapy and who were ineligible for heart transplantation. This chapter shows a 6-month survival rate of 75% and significant improvement in functional capacity and in quality of life during follow-up. However, adverse events, including right ventricular failure, were also observed. These findings underline the necessity of a structured screening program with comprehensive assessment of indications and contraindications. The findings of this chapter demonstrate that continuous-flow LVAD therapy is a promising treatment option for end-stage heart failure patients.

In *Part III* of this thesis the use of vectorcardiography is evaluated in patients with pulmonary hypertension. Early detection of pulmonary hypertension is essential in order to improve outcome. Electrocardiography is a widely available, simple, and non-invasive diagnostic test. However, the 12-lead electrocardiogram has proven to be of little diagnostic value in the detection of pulmonary hypertension. In contrast, the electrocardiogram-derived vectorcardiogram demonstrated to be an accurate diagnostic method to detect elevated right ventricular pressures. In **Chapter** 9, the clinical performance of two different applications of the vectorcardiogram, the Butler-Leggett QRS amplitude criteria and the ventricular gradient projected on a direction optimized for detection of right ventricular pressure overload (VG-RVPO) were evaluated. The results show that the combination of the VG-RVPO and the Butler-Leggett QRS amplitude criteria accurately detects elevated mean pulmonary arterial pressure, validated by right heart catheterisation. It should be mentioned however that the VG-RVPO added most to the diagnostic accuracy, whereas the contribution of the Butler-Leggett QRS amplitude was limited. Finally, **Chapter 10** further extends these results by comparing the differences in morphology between the vectorcardiogram synthesized by the Kors matrix and the vectorcardiogram synthesized by the INVD matrix in a patient population suspected of pulmonary hypertension. Both matrices demonstrated equal diagnostic accuracy in the detection of elevated systolic pulmonary arterial pressure, even though there were significant differences in morphologic parameters between the two matrices. The results of both chapters suggest that the use of vectorcardiographic criteria could be systematically used to detect elevated pulmonary pressures in the screening of patients that are likely to develop pulmonary hypertension such as systemic sclerosis patients.

CONCLUSIONS AND FUTURE PERSPECTIVES

Traditionally, the right ventricle was often appropriately named the 'forgotten ventricle' as it was considered to have no significant contribution to the circulation. Over the past decades, awareness of the involvement of the right ventricle in both common and rare cardiovascular diseases has grown. Recent developments in echocardiography and electrocardiography have contributed to further insight into the pathophysiology of the right ventricle as well as its relation to the pulmonary circulation and the left ventricle. Because echocardiography is accessible, non-invasive, and inexpensive it is an ideal technique for the assessment of the right ventricle and can be used for screening patients at risk of right ventricular dysfunction as well as monitor therapeutic responses.

Furthermore, advanced echocardiographic techniques such as 2-dimensional speckle-tracking imaging may add to a better understanding of right ventricular mechanics. Integrated application of echocardiographic and electrocardiographic techniques could provide further understanding into the different pathophysiological aspects of right ventricular function. These insights could be used to identify risk factors, prognostic factors and monitor response to therapy through serial assessment in patients at risk for right ventricular dysfunction and failure such as patients with pulmonary hypertension, heart failure and those undergoing cardiac surgery. Furthermore, a better understanding of the mechanisms that lead to right ventricular remodeling may aid to the development of right ventricular specific therapies that improve survival in patients with right ventricular dysfunction.