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Chapter 9

Summary, Conclusions and Future Perspectives
Summary

The general introduction of this thesis in chapter 1 provides background information on the physiology of right ventricular (RV) overload with specific attention for high risk populations. RV performance is influenced by its preload, afterload and contractility and by interdependency with the left ventricle. RV overload can develop in a broad spectrum of diseases that cause either volume or pressure overload of the right ventricle. Especially increases in pressure load are not well tolerated by the thin walled and highly compliant right ventricle. RV dysfunction will develop when the right ventricle cannot sufficiently compensate for the aggravated loading conditions. RV dysfunction can cause symptomatic RV failure; a clinical syndrome of impaired cardiac output that results in exercise intolerance, fatigue, fluid retention and arrhythmia. RV failure is a progressive and ultimately fatal disorder. Assessment of RV overload includes physical examination, electrocardiography, echocardiography, magnetic resonance imaging and invasive pressure measurement. The diagnosis pulmonary hypertension is applied to a level of RV afterload that is equivalent to an invasively measured mean pulmonary artery pressure of 25 mmHg or higher. Although RV overload is a rare problem in the general population, it is a major determinant of morbidity and mortality in high risk populations, such as patients with left sided heart disease, congenital heart disease and pulmonary arterial hypertension. This thesis focusses on various diagnostic and treatment processes of RV overload in the above named high risk populations.

Part I: Right Ventricular Overload in Left Sided Heart Disease

In chapter 2 and 3 the relation between RV dysfunction and outcome after surgical left ventricular restoration was assessed. Surgical left ventricular restoration improves clinical status and survival in selected patients. However, the restoration of LV geometry and function can alter RV pre- and afterload and the position of the interventricular septum. It can therefore be hypothesized that surgical left ventricular restoration affects postoperative RV function. Preoperative as well as postoperative RV dysfunction might therefore influence outcome after surgical left ventricular restoration. The objective of the study presented in Chapter 2 was to evaluate the association between baseline preoperative RV dysfunction and outcome in heart failure patients undergoing surgical left ventricular restoration. RV function was assessed with echocardiography. RV dysfunction was defined as RV fractional area change less than 35%, tricuspid annular plane systolic excursion less than 16 mm and/or RV longitudinal peak systolic strain of -20% or higher in accordance with current guidelines. In total 139 ischemic heart failure patients were included. Based on the above named echocardiographic criteria, RV function was impaired in respectively 21%, 20% and 26% of
patients. Within 30 days after surgery 15 patients died, yielding a survival ratio of 89%. All 3 parameters of impaired echocardiographic functioning were independently associated with increased 30-day mortality, after adjusting for left ventricular ejection fraction, non-elective surgery and procedural aortic cross-clamping time. In 39% of patients 1 or more echocardiographic criteria of RV dysfunction were present. On patient level, the coexistence of several criteria for impaired RV function had an incremental worse effect on 30-day survival. It was therefore concluded that pre-existent RV dysfunction in ischemic heart failure patients undergoing surgical left ventricular restoration is frequent and associated with increased postoperative mortality. Comprehensive preoperative echocardiography is essential to characterize RV function and can optimize patient selection for surgical left ventricular restoration.

In chapter 3 alterations in echocardiographic functioning after surgical left ventricular restoration were assessed. From the original population described in the previous chapter, 86 patients had echocardiographic follow-up approximately 2 years after surgical left ventricular restoration. At 2 year follow-up clinical functioning and left ventricular ejection fraction had improved. However, impaired RV function at follow-up (defined as RV fractional area change less than 35%) was present in 40% of patients and was associated with higher preoperative EuroSCORE (European System for Cardiac Operative Risk Evaluation) II, longer aortic cross-clamping time, higher prevalence of pulmonary hypertension and an increase in left ventricular filling pressures. Moreover, patients with impaired RV function experienced worse heart failure symptoms at 2 year follow-up assessment and suffered from decreased survival at future follow-up. It was therefore recommended that the potential risk of RV dysfunction after SVR should be taken into account when deciding to perform SVR. Awareness for RV impairment after surgical left ventricular restoration may facilitate timely diagnosis and management in these patients.

In chapter 4 the effect of pump speed in patients with a left ventricular assist device (LVAD) was investigated. All patients had an LVAD for destination therapy, which means that patients were ineligible for future heart transplantation. In this population optimal functioning of the LVAD and preservation of RV function are major determinants of survival.\textsuperscript{13,14} RV function is affected by the speed of the LVAD pump, since speed settings influence RV pre- and afterload as well as the position of the interventricular septum.\textsuperscript{15,16} Optimal LVAD pump speed can be determined on echocardiographic criteria. To date, routine assessment of optimal pump speed is only recommended in the early postoperative period and when clinically indicated.\textsuperscript{15,17} It is, however, unknown whether LVAD pump speed should be routinely re-evaluated in stable patients over time.
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Therefore, the objective of this study was to assess whether routine echocardiographic re-assessment of optimal pump speed is indicated in stable LVAD patients. Furthermore, the effect of routine LVAD pump speed optimization on clinical status and RV function was assessed. A prospective study was performed in which 17 stable LVAD patients underwent echocardiographic assessment at different pump speeds to determine the optimal speed. In 8 patients (47%) LVAD pump speed could be optimized. In these patients RV function (RV fractional area change and longitudinal peak systolic strain) improved at 3 months follow-up and pro-BNP (a marker of ventricular wall stress) declined. Complications related to the increased LVAD speed were not observed. No significant changes at follow-up were found in patients without indication for speed adjustment. It was therefore concluded that routine evaluation of optimal LVAD pump speed reveals the potential of speed optimization in a substantial proportion of stable LVAD patients and can improve RV function.

Part II: Right Ventricular Overload in Congenital Heart Disease

In chapter 5 the long-term follow-up of patients with a systemic right ventricle was described. Between approximately the 1960’s and 1980’s patients born with a transposition of the great arteries underwent atrial reconstruction.\(^\text{18,19}\) The result is a right ventricle that supports the systemic circulation. The purpose of the study was to assess the long-term follow-up of patients with a systemic right ventricle after atrial reconstruction. In 76 adult patients the association between baseline characteristics, survival and the development of complications and present clinical status was assessed. The present study demonstrated that current survival exceeds 50 years after atrial correction for transposition of the great arteries. Patients who underwent the Mustard procedure after the age of 1 year had worst survival characteristics. Furthermore, the incidence of supraventricular tachycardia, ventricular arrhythmia and heart failure increased during follow-up. These complications resulted in reduced functional capacity and need for re-interventions. Especially a higher age at atrial correction was associated with increased risk for long-term development of ventricular arrhythmia and heart failure, indicating progressive RV functional decline.

Chapter 6 describes patients with pulmonary hypertension due to various forms of complex congenital heart disease and pathologic communications (shunts) between the right and left heart. Shunt interventions in these patients can be performed to optimize true pulmonary flow and decrease RV afterload. However, eligibility for interventions strongly depends on the severity of pulmonary hypertension and the ability of the pulmonary vasculature and right ventricle to adapt to the intended circulatory changes.\(^\text{20-23}\) Publications regarding shunt adjustments in congenital heart
disease patients with pulmonary hypertension are scarce and mostly limited to rather general consensus guidelines. However, pre-interventional assessment of eligibility for interventions is mandatory, as shunt procedures contain a high risk of deteriorating RV overload. In this chapter complex congenital heart disease patients with pulmonary hypertension and impaired pulmonary flow are presented. All patients had an ambiguous indication for shunt intervention. Our local multidisciplinary Grown-Ups with Congenital Heart disease team reached consensus regarding patient tailored invasive treatment strategy, adjacent to relevant guidelines. The interventions resulted in improved pulmonary hemodynamics and short term clinical functioning in all cases. It was therefore concluded that individual evaluation of disease characteristics is mandatory for tailored interventional treatment in congenital heart disease patients with pulmonary hypertension, adjacent to relevant guidelines. Both strict registration of cases and multidisciplinary and multicentre collaboration are essential in the quest for optimal therapy in this patient population.

**Part III: Right Ventricular Overload in Diseases Associated with Pulmonary Arterial Hypertension**

In chapter 7 the use of the ventricular gradient is described as a screening tool for pulmonary hypertension in patients with systemic sclerosis. Systemic sclerosis is an auto-immune connective tissue disorder and is expressed in the clinical subtypes limited and diffuse systemic sclerosis. Typically, patients with limited systemic sclerosis are prone for the development of pulmonary arterial hypertension, while patients with diffuse systemic sclerosis are at greater risk for development of interstitial lung disease and myocardial involvement which can result in respectively pulmonary hypertension group II and III. Screening for pulmonary hypertension in this population allows for early diagnosis and treatment, which may improve outcome. In addition to echocardiography, the electrocardiographic derived ventricular gradient may play an important role because it is easy and fast to obtain at a low cost. Furthermore, the ECG is an important alternative when echocardiography is inconclusive. Previous research has demonstrated that the ventricular gradient can accurately detect pulmonary hypertension. However, patients with systemic sclerosis frequently exhibit multi-organ involvement that can interfere with the electrocardiographic signal. Therefore the applicability of the ventricular gradient was assessed in 274 patients with different extent of multi-organ involvement. The study showed that an elevated ventricular gradient correlated with conventional screening parameters and corresponded with the presence of pulmonary hypertension in patients with limited systemic sclerosis, but not in patients with diffuse systemic sclerosis. A potential explanation may be that patients with diffuse SSc more frequently exhibit pulmonary and cardiac involvement which could result in obscuring of the electrical signal by electrophysiological changes not specifically related to pulmonary hypertension. Furthermore, an elevated ventricular gradient was associated with decreased survival in systemic sclerosis patients.
with pulmonary hypertension. It can therefore be concluded that the ventricular gradient has potential as a novel, easy-to-use screening tool for non-invasive pulmonary hypertension screening in patients with limited systemic sclerosis.

In chapter 8 the implications of RV overload in patients with endstage liver disease undergoing liver transplantation were assessed. RV afterload is an important determinant of prognosis in patients with endstage liver disease and it can increase through multiple causes.\(^{34,35}\) Firstly these patients frequently exhibit an increased circulating volume that leads to a mild increase in RV pre- and afterload.\(^{36,37}\) Next, endstage liver disease is associated with an increased risk for development of portopulmonary hypertension and cirrhotic heart disease that can both cause RV overload.\(^{38-40}\) According to current guidelines, patients with a mean pulmonary artery pressure less than 35 mmHg can safely undergo liver transplantation.\(^{35,41}\) However, the long-term effects of increased RV afterload and the relevance of baseline RV function on outcome after transplantation remain unknown. In the study 139 orthotopic liver transplantation recipients were included and the long-term course after liver transplantation was assessed. Preoperative RV function was within the normal range and did not correlate with the degree of RV afterload. Patients with elevated RV afterload did have higher RV dimensions. Patients with increased RV afterload had significantly more hemodynamic complications after transplantation. Moreover, survival after transplantation was significantly impaired as compared to patients with normal RV afterload. Preoperative RV parameters were, however, not predictive for outcome after liver transplantation.

**Conclusions**

The RV oriented research that has been performed in especially the last decades has contributed greatly to our understanding of the presentation and implications of RV dysfunction. This thesis contributes to the field of RV research in 3 predefined patient populations at increased risk for the development of RV overload, namely patients with congenital heart disease, left sided heart disease and diseases associated with pulmonary arterial hypertension.

RV dysfunction can be an important determinant of prognosis in patients at increased risk for the development of RV overload. This thesis demonstrates that RV dysfunction in patients before and after surgical left ventricular restoration (causing altered loading condition of the right ventricle) is associated with a worse prognosis. The presence of RV overload in liver transplantation recipients was also associated with decreased survival. Furthermore, congenital heart disease disease patients
can currently survive into the 50th decade with a right ventricle supporting the systemic circulation. However, these patients are at increased risk for the long-term development of complications caused by RV overload, such as ventricular arrhythmia and heart failure, which indicate progressive RV functional decline.

Next, different diagnostic methods for the assessment of RV overload and dysfunction are investigated in this thesis. As no unique golden standard for the quantification of RV dysfunction exists, the combination of different diagnostic methods is essential to adequately characterize RV function. This is especially relevant in populations at high risk for RV overload, with various co-morbidities that can complicate the interpretation of diagnostic results. As presented in this thesis, the combination of echocardiographic RV parameters yields additional prognostic information in heart failure patients undergoing surgical left ventricular restoration. In systemic sclerosis the electrical ventricular gradient can accurately detect RV overload and is consistent with other screening parameters in patients with limited organ involvement. However, in patients with diffuse systemic sclerosis, the ventricular gradient does not correspond to other screening parameters and the presence of RV overload. Moreover, in patients with complex congenital heart disease and pulmonary hypertension an individualized approach combining imaging and invasive diagnostic techniques is essential to deliver tailored treatment.

Moreover, this thesis shows that optimization of loading conditions can improve clinical status and RV function in patients with established RV dysfunction. RV function can be improved in LVAD patients by optimizing the synergy between the LVAD and intrinsic cardiac function. Furthermore, interventions in complex congenital heart disease patients with pulmonary hypertension aim to improve RV loading conditions and true pulmonary flow and can improve RV loading conditions and clinical functioning.

**Future Perspectives**

Although major improvements have been achieved in the understanding of RV overload and dysfunction, specific treatment options are still rather limited and morbidity and mortality associated with RV dysfunction remain high. This is especially relevant in patient populations with increased risk for the development of RV overload, such as patients with congenital heart disease, left sided heart disease and diseases associated with pulmonary arterial hypertension.
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The prevalence of complications associated with (medically or invasively treated) severe left sided heart failure will increase, as the treatment options for patients with left sided heart disease are expanding. The right ventricle can become the new weakest link in the circulation after treatment of left ventricular pathology. Similarly, improvements in treatment of congenital heart disease have resulted in an adult population with increasingly complex diseases and an increase in complications such as RV overload.

Assessment of RV function will become increasingly relevant for risk stratification and determination of treatment strategy in populations at increased risk for the development of RV overload. Currently much focus is placed on the interaction between intrinsic RV function and loading conditions. It is essential to gain further insight in factors that can predict the adaptation potential of RV function to variations in loading conditions. LVADs are very interesting in this field of study, as they permit easy adjustments in loading conditions by changing the speed of the LVAD pump. Furthermore, new imaging techniques, such as 3D echocardiography and the possibility of magnetic resonance imaging in new type ICDs, can aid in the quantification of RV function.

Early identification of highest risk patients and better understanding of the effects of early treatment could allow for more effective screening and treatment and in turn improve symptoms and survival. Future research is necessary to gain insight in the prognostic relevance of early signs of RV pressure elevation in so-called borderline pulmonary hypertension. Furthermore, future improvements in the field of RV mechanical support may have great implications for patients with RV disease.
References


