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Chapter 1

General Introduction and Outline of this Thesis
Diagnosis and Treatment of Right Ventricular Overload in High Risk Populations

Historically, the right ventricle has received less scientific attention than its left counterpart. As the subpulmonic ventricle, it was long thought not to play a significant role in the circulation. The right ventricle appeared to function as a passive conduit, connecting the venous system with the pulmonary artery.\(^1\) In particular, early studies showed that left heart output was not compromised after destruction of the right ventricular (RV) free wall in dog models with an open pericardium.\(^2\) Furthermore, patients with tricuspid atresia and RV hypoplasia could be surgically treated by redirecting blood flow from the vena cava directly to the pulmonary artery, as was first described by Fontan and Baudet in 1971.\(^3\) In the last decades, however, the insight into prevalence and implications of RV dysfunction is vastly increasing. First studies in the 1980s showed the consequences of RV impairment in the presence of RV infarction, valvular heart disease, shock and sepsis.\(^4\)\(^-\)\(^6\) The expanding population of patients with congenital heart disease has further underlined the implications of RV birth defects on hemodynamic functioning.\(^7\) Currently RV dysfunction is considered a major determinant of morbidity and mortality in populations at high risk for the development of RV overload.

**Right Ventricular Anatomy**

The way the heart is situated in the thorax, the right ventricle forms its most anterior part, located directly behind the sternum. It receives venous deoxygenated blood from the systemic circulation through the inferior and superior vena cava and subsequently the right atrium. The output generated by the right ventricle flows through the pulmonary circulation where it gets re-oxygenated and in turn enters the left part of the heart via the pulmonary veins. The left ventricle is aligned in series with the right ventricle and therefore delivers an equal flow to the systemic circulation. Anatomically the right ventricle is separated from the left ventricle by the interventricular septum. The His bundle is situated on top of the interventricular septum and divides in a left and right bundle branch, thus providing each ventricle with its own conduction system. The total heart is covered by an epicardial layer.

The right ventricle has a complex shape that appears triangular in frontal view and crescent, wrapped around the left ventricle, in cross-section.\(^8\) It consists of 3 major anatomical components, namely 1/ the inlet component, receiving blood via the tricuspid valve, 2/ the trabeculated apical component and 3/ the outlet component guiding blood towards the pulmonary valve.\(^8\)\(^,\)\(^9\) The myocardium of the right ventricle consists of a longitudinally aligned deep fiber layer and a superficial fiber layer that
runs obliquely form the basis to the apex. This fiber arrangement contributes to the complex contraction pattern of the right ventricle, which includes inward movement of the free wall towards the septum, longitudinal shortening, septal contraction and traction at the attachment points with the left ventricle.\(^9,10\) Blood supply to the RV myocardium is mainly provided by the right coronary artery. Due to the lower ventricular mass of the right ventricle as compared to the left ventricle and the lower resistance of the pulmonary circulation in comparison to the systemic circulation, RV oxygen consumption is lower than left ventricular (LV) oxygen consumption.\(^9,11\)

**Figure 1.** Right ventricular anatomy in frontal view (A) and in cross-section (B).

Right Ventricular Physiology

In contrast to the left ventricle, the RV wall is thin and highly compliant, making it especially equipped to adapt to shifts in volume loading but less to shifts in pressure loading.\(^12\) In summary, RV performance is influenced by its preload, afterload and contractility and by interdependency with the left ventricle. Preload is determined by RV filling during diastole. Afterload is the load that the right ventricle needs to overcome during systole. In healthy subjects the pulmonary vasculature is highly
distensible and has a low vascular resistance as compared to the systemic circulation. This results in low pulmonary pressures and thereby low RV afterload.\textsuperscript{12}

The relation between RV compliance, contractility and pre- and afterload is schematically demonstrated in Figure 2. This pressure-volume loop shows that the preload of the right ventricle relates to its end-diastolic volume and compliance. An increase in RV end-diastolic volume will increase preload at an equal compliance. This results in an increase in stroke volume. In the same way, the contractility of the right ventricle determines RV end-systolic volume depending on its afterload.\textsuperscript{13,15}

\textit{Figure 2. Right ventricular pressure-volume loop.}

Interventricular interdependency implies that the shape and size of one ventricle can alter the size, shape and thereby function of the other ventricle through direct mechanical interactions.\textsuperscript{10} In diastole increased distention of one ventricle can affect the compliance and geometry of the other ventricle as both ventricles are enclosed by tight pericardium.\textsuperscript{10,12} In systole, the shape, position and
contractility of the interventricular septum depend on the pressure gradient across the septum and the dimensions of the left and right ventricle.\textsuperscript{10} RV volume and pressure overload therefore predominantly cause diastolic and systolic leftward shifting of the septum, respectively.\textsuperscript{16}

### Right Ventricular Overload

RV overload can be caused by a broad spectrum of diseases. These causes can be primarily divided in conditions of volume and pressure overload. Volume overload can for instance be seen in shunt lesions from the left side of the heart to the systemic venous circulation or right atrium. These shunts cause excessive blood flow towards the right ventricle. The result is an increased end-diastolic pressure and increased RV stroke volume (Figure 2).\textsuperscript{17} Pressure overload is caused by elevated pulmonary pressures, for example through pulmonary vascular disease or a pulmonary embolism. Increases in LV diastolic pressure can also cause a retrograde increase in RV afterload. In this situation the right ventricle has to overcome a higher pressure to eject blood into the pulmonary circulation. Irrespective of the cause of increased RV afterload, in the long term it will lead to (adverse) RV remodelling; RV wall stress increases, resulting in RV hypertrophy and increased contractility.\textsuperscript{18,19} Accordingly, RV function is strongly dependent on its pre- and afterload. The right ventricle initially adapts to the altered loading conditions by way of neurohormonal activation and RV remodelling.\textsuperscript{9} RV dysfunction will develop when the RV compensatory mechanisms cannot longer compensate for the increased demands imposed by the aggravated loading conditions.\textsuperscript{20} As mentioned before, the right ventricle is in general better equipped to handle volume overload than pressure overload. An increase in RV afterload rapidly results in RV dysfunction, in contrast to the left ventricle that can handle larger shifts in afterload.\textsuperscript{21} As a consequence of the increased RV afterload, tricuspid regurgitation develops, systolic RV function decreases and RV dilation progresses at the expense of LV filling and stroke volume.\textsuperscript{16,17} The process of RV dysfunction is further enhanced by ischemia, when the increase in RV mass and work load exceeds the coronary perfusion capacity.\textsuperscript{22} Decreased renal perfusion activates the renin-angiotensin-aldosterone system, which leads to sodium and water retention.\textsuperscript{23} Tricuspid regurgitation and fluid retention further increase RV preload, resulting in a vicious circle of right atrial and ventricular dilatation and dysfunction.

### Functional Assessment of Right Ventricular Function

RV dysfunction can cause symptomatic RV failure; a clinical syndrome of impaired cardiac output that results in exercise intolerance, fatigue, fluid retention and arrhythmia.\textsuperscript{9} RV failure is a progressive and ultimately fatal disorder.\textsuperscript{17,24} Physical signs of RV failure include an increased heart rate, elevated central venous pressure, peripheral edema, ascites and weight gain as a consequence of fluid retention. On auscultation a holosystolic murmur caused by tricuspid regurgitation can be heard.
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Laboratory assessment shows an increased level of brain natriuretic peptide, which is released from the heart in response to wall stress.25

RV overload is reflected in the electrical cardiac signal. Right atrial overload results in increased duration and magnitude of the P-wave, the so-called P-pulmonale.26 RV dilatation causes stretching of the conduction system which can result in a right bundle branch block.27 Increased RV wall stress and hypertrophy cause a change in the magnitude and direction of ventricular de- and repolarization forces.28-30 These changes in electrical forces can result in discordant T waves, alterations in the ventricular gradient and right heart axis deviation.31 The ventricular gradient is a vectorial measure that represents the net electrical activity during de- and repolarization. Increased wall stress causes the ventricular gradient to change in direction and magnitude in an early disease stage, whereas the heart axis rotates to the right in long-term RV overload mainly as a result of RV hypertrophy.26-29

Non-invasive imaging of the right ventricle is challenging because of 1/ its complex 3D geometry, 2/ its retrosternal position that hampers echocardiographic imaging windows, 3/ the limited discrimination of RV endocardial margins caused by heavily trabeculated myocardium and 4/ the load dependency of measurements of RV function.9 Echocardiography can assess RV geometry and function in several acoustic windows, most importantly in the parasternal long axis view and the apical 4-chamber view. Geometrical parameters include the tricuspid annulus diameter and the RV end-diastolic diameter.32 RV systolic function can be measured using multiple parameters (Figure 3). RV fractional area change is defined as the percentage change between end-diastolic and end-systolic RV area.32 Tricuspid annular plane systolic excursion measures the longitudinal movement of the tricuspid annulus during systole.32 A relative new field of imaging is strain analysis using speckle tracking. RV strain measures the shortening of ventricular wall segments during systole as a percentage of the end-diastolic length.32 RV strain measurement does not rely on assumptions regarding RV geometry and is independent of the angle of the ultrasound beam.33

Echocardiography can furthermore be used to estimate RV afterload. The pressure gradient across the tricuspid and pulmonary valve can be measured using Doppler imaging if a sufficient regurgitation jet is visible.34 Right atrial pressure can be estimated based on the diameter and inspiratory collapse of the inferior vena cava.32 RV afterload can be calculated by summation of the maximum tricuspid or pulmonary valvular pressure gradient and right atrial pressure.
**General introduction**

Figure 3. Transthoracic echocardiographic measurements. A. Healthy situation; B. RV overload; C. RVFAC; D. TAPSE; E. RV LPSS; F. RVEDD; G. tricuspid valve annulus; H. systolic pulmonary arterial pressure.

Abbreviations: TAPSE, tricuspid annular plane systolic excursion; RV right ventricular; RVFAC, right ventricular fractional area change; RV LPSS, right ventricular longitudinal peak systolic strain; RVEDD, right ventricular end-diastolic diameter.

Magnetic resonance imaging is the best way to non-invasively visualize the right ventricle and offers the possibility to reliably calculate RV volumes and mass and to assess RV free wall motion, regardless of its complex 3D geometry. Disadvantages of magnetic resonance imaging include the
long scanning time and the incompatibility with metal parts in patients with for instance pacemakers and defibrillators.\textsuperscript{35}

RV pressures can be invasively measured during right heart catheterization, which remains the golden standard to quantify RV loading conditions. Standard right heart catheterization involves pressure measurements in the vena cava, right atrium and ventricle and the pulmonary arteries. At each measure point a blood sample is obtained to measure the level of oxygen saturation. These saturation measurements allow for calculation of cardiac output using Fick’s principle and for assessment of shunts between the left and right circulation. Furthermore an estimate of LV end-diastolic pressure can be derived with the tip of the catheter in wedge position in a peripheral pulmonary artery.\textsuperscript{36,37}

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.\textsuperscript{37} Pulmonary hypertension is classified in 5 groups, namely 1/ pulmonary arterial hypertension (PAH), 2/ pulmonary hypertension due to left sided heart disease, 3/ pulmonary hypertension due to pulmonary disease or hypoxia, 4/ chronic trombo-embolic pulmonary hypertension and 5/ pulmonary hypertension of multifactorial mechanisms. Apart from pulmonary hypertension in left sided heart disease, all other etiologies are characterized by increased pulmonary vascular resistance. This parameter is directly related to the pressure gradient across the pulmonary vasculature and inversely related to the flow through the pulmonary circulation.

\textit{Formula:}

\[
pulmonary\,\text{vascular\,resistance} = \frac{\text{mean\,pulmonary\,artery\,pressure} - \text{LV\,end-diastolic\,pressure}}{\text{cardiac\,output}}
\]

Pulmonary hypertension in left sided heart disease is associated with elevated LV end-diastolic or wedge pressure and can be divided into isolated postcapillary and combined post- and precapillary pulmonary hypertension with increased pulmonary vascular resistance.\textsuperscript{37}

Of note, aside from the assessment of RV parameters, LV functional assessment is mandatory to investigate etiology and severity in patients suspected of RV overload.
Treatment of Right Ventricular Overload

The aims of treatment in RV overload are optimization of preload, reduction of afterload and enhancement of intrinsic cardiac function. In general, management of the underlying condition is essential, as for instance treatment of left sided heart disease and pulmonary disease. In the other etiologies of pulmonary hypertension the increased pulmonary vascular resistance can be selectively targeted with calcium channel blockers, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators and / or prostacyclin agonists. The latter pharmaceuticals potentially also have a direct beneficial effect on RV function. Management of volume status encompasses diuretics and salt and water restriction. Additionally focus should be placed at maintenance of sinus rhythm and treatment of tachyarrhythmia.

Populations at High Risk for Right Ventricular Overload

Although RV overload is a rare problem in the general population, it is a major determinant of morbidity and mortality in populations at high risk for the development of RV overload. Left sided heart disease is the most frequent cause of RV overload. The prevalence of pulmonary hypertension is 60% in patients with severe LV systolic dysfunction, 70% in severe diastolic dysfunction, 65% in symptomatic aortic valve disease and virtually 100% in severe symptomatic mitral valve disease. PAH is another major cause of RV overload related morbidity and mortality. The prevalence of PAH in the general population is around 26 subjects per million. However, some diseases are specifically associated with increased risk for the development of PAH. Apart from idiopathic / hereditary PAH, the most frequent causes of PAH are congenital heart disease, connective tissue disease and endstage liver disease with prevalences of around 6%, 10% and 6%, respectively.

Right Ventricular Overload in Left Sided Heart Disease

RV dysfunction in left sided heart disease is frequently caused by biventricular pathology and elevated LV pressures. RV dysfunction is an important prognostic marker of morbidity and mortality in the general heart failure population and in patients undergoing heart failure surgery. Left ventricular surgical reconstruction (SVR) and left ventricular assist device (LVAD) implantation are especially interesting heart failure procedures with regard to RV function, as both procedures alter RV pre- and afterload.

SVR is performed in heart failure patients with a post-infarction LV aneurysm to exclude the akinetic or dyskinetic aneurysm from the LV cavity by means of a patch plasty. The aim of this procedure is to restore normal LV geometry and to improve LV function. According to the latest European Society of Cardiology guidelines, SVR in addition to coronary revascularization is recommended in patients...
with ischemic heart failure, if significant scar tissue in the left anterior descending coronary artery territory is present and if the predicted postoperative LV end-systolic volume index is smaller than 70 ml/m$^2$ (class IIbB). SVR yields a survival benefit compared to revascularization alone in this population. Furthermore, SVR improves heart failure symptoms and left ventricular ejection fraction. Previous studies have reported that this improvement in LV systolic function can result in increased RV volume load or preload. The restoration of the LV cavity through SVR can also impair LV diastolic properties, resulting in elevation of LV filling pressures and increased RV pressure load or afterload. Next, the more spherical LV geometry after SVR alters the position and function of the interventricular septum, which may also influence RV geometry and function. Preoperative RV function might therefore be an important prognostic determinant after SVR.

**Figure 4. Surgical left ventricular restoration according to the technique described by Vincent Dor.**
(Adapted from Athanasuleas et al, Heart Fail Rev, 2004)

The LVAD is one of the ultimate treatment options in patients with severe heart failure. Main indications for LVAD implantation are as bridge to heart transplantation or as long term mechanical support or destination therapy. The LVAD consists of a pump that connects the left ventricle to the aorta via an inflow and outflow cannula. The pump supports the heart by withdrawing blood from the left ventricle and delivering it directly into the aorta, thereby improving end-organ perfusion. The European Society of Cardiology recommends that an LVAD should be considered in patients, ineligible for heart transplantation, who have endstage heart failure with reduced LV ejection fraction despite optimal medical and device therapy, to reduce the risk of premature death. Currently, the 2 year survival rate after implantation is 70% and almost half of the patients have an LVAD implanted as destination therapy (DT).
Especially in LVAD-DT patients, optimal LVAD functioning and preservation of right ventricular (RV) function are major determinants of long-term survival. The LVAD pump generates cardiac output by unloading the left ventricle. The resultant decrease in LV pressures can lower pulmonary artery pressures and RV afterload and thereby beneficially influence RV function.\textsuperscript{66-68} However, excessive LV unloading can also compromise RV function through leftward deviation of the interventricular septum and increased RV preload.\textsuperscript{69,70} RV function is an established determinant of outcome after LVAD implantation, but additional focus on selection criteria for LVAD implantation and the preservation of RV function in patients on long-term mechanical support can improve preoperative decision making and outcome after LVAD implantation.

**Right Ventricular Overload in Congenital Heart Disease**

The field of congenital heart disease (CHD) is changing through improvements in medical treatment with increasingly more patients with increasingly complex congenital defects reaching adulthood.\textsuperscript{7,71,72} This rise is accompanied by an increase in the prevalence of CHD related co-morbidities such as pulmonary hypertension.\textsuperscript{7,47} Pulmonary hypertension mainly develops in patients with a persistent shunt between the systemic and pulmonary circulation. This shunt causes RV volume and pressure overload leading to increased pulmonary flow and shear stress and eventually resulting in pulmonary vascular remodelling and increased pulmonary vascular resistance.\textsuperscript{73-75}
Another particular population of CHD is formed by patients with a right ventricle that provides systemic blood flow. This situation is for instance present in patients with a transposition of the great arteries after atrial switch correction. In this procedure blood from both caval veins is redirected to the left ventricle, which is connected to the pulmonary artery, and blood from the left atrium is redirected to the right ventricle and the aorta. RV overload caused by a congenital defect is in general better tolerated than acquired pulmonary hypertension. A potential explanation is that the congenital presence of RV overload leads to preservation of the fetal RV morphology with equal LV and RV wall thickness. However, longstanding RV overload will eventually progress to RV failure.

Another important issue in the assessment and treatment of patients with congenital heart disease is the altered cardiac morphology and the lack of generally acknowledged cut-off values that make assessment of RV function especially challenging.

**Figure 6.** Atrial switch procedure (Mustard technique) for transposition of the great arteries. According to Mustard, a synthetic tube is placed to direct blood from the superior and inferior vena cava to the left atrium. Through the procedure, pulmonary venous blood drains into the right atrium posteriorly from the synthetic tube. In the Senning technique, autologous material is used to create the connection.

(Adapted from Brouwer et al, Arrhythm Electrophysi Rev, 2016)

### Right Ventricular Overload in Diseases Associated with Pulmonary Arterial Hypertension

Connective tissue disease and end-stage liver disease are associated with an increased risk for the development of PAH. Systemic sclerosis is an auto-immune connective tissue disorder characterized by small vessel disease, production of auto-antibodies and fibroblast dysfunction. Systemic sclerosis can be categorized in a limited and diffuse phenotype that differ in the amount and location of skin and organ involvement. Typically, patients with limited systemic sclerosis are prone to the development of PAH, while patients with diffuse systemic sclerosis are at greater risk for the development of interstitial lung disease, oliguric renal failure and myocardial involvement. This diversity in phenotypes relates to the different etiologies of RV overload that can be observed in patients with systemic sclerosis, namely PAH caused by obstructive proliferative vasculopathy and pulmonary hypertension caused by left sided heart disease or advanced interstitial lung...
PAH progresses especially rapidly in systemic sclerosis patients, resulting in RV pressure overload and eventually right sided heart failure with a 3-year mortality rate of around 50%. Systematic screening and early treatment of RV overload can significantly improve survival in this patient population.

RV overload can develop in patients with endstage liver disease as a consequence of increased RV preload and afterload. Patient with endstage liver disease and cirrhosis can firstly suffer from a hyperdynamic circulation. This hyperdynamic state is generated by humoral and local factors that cause vasodilatation and increased plasma volume, resulting in increased RV preload. At an equal pulmonary vascular resistance, the increased circulating volume leads to increased pulmonary pressures and thus increased RV afterload. Secondly RV afterload can increase through smooth muscle hypertrophy, remodelling and in situ thrombosis in the pulmonary vasculature. It is postulated that these pathologic changes are mediated by substances that are normally metabolized, but now bypass the liver through collaterals formed in the presence of liver cirrhosis and portal hypertension. Severe pulmonary hypertension is an acknowledged risk factor for perioperative mortality in patients undergoing liver transplantation. Mildly elevated pulmonary pressure however is frequently present in combination with increased cardiac output and preload, without elevated pulmonary vascular resistance. Currently it is unknown whether assessment of preoperative RV function can aid in the identification of patients at increased risk for worse outcome after liver transplantation.
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Aim and Outline of this Thesis

The aim of this thesis is to gain insight in the diagnosis and implications of RV volume and pressure overload in 3 major high risk populations, namely in left sided heart disease, CHD and PAH associated diseases. Part I of the thesis is designated to RV overload in LV heart failure. In chapters 2 and 3 the relation between preoperative and postoperative RV dysfunction and outcome in heart failure patients undergoing SVR is assessed. Chapter 4 comprises a prospective LVAD pump speed ramp study which assesses the effect of LVAD pump speed on RV function in this population. Part II concerns RV overload in CHD. In chapter 5 the 50 year follow-up is presented of adult survivors with a systemic right ventricle after atrial correcting for transposition of the great arteries in a tertiary center. Chapter 6 gives an overview of the current consensus on interventions in CHD patients with RV overload, illustrated with 4 case reports. In part III RV overload in diseases associated with PAH is discussed. In chapter 7 the use of the electrocardiographic ventricular gradient is described as a marker for screening and prognosis of pulmonary hypertension in patients with systemic sclerosis. In chapter 8 the implications of RV afterload and RV function on outcome in patients with endstage liver disease undergoing liver transplantation is assessed.
References


Chapter 1


General introduction