Introduction and aims

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Brief historical perspective on the right ventricle

With his statement in 1616 “thus the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them”, Sir William Harvey was the first to acknowledge that both ventricles are coupled in series and that the right ventricle (RV) has a key position in the human circulation. Despite this early recognition, for years attention in cardiovascular disease was primarily focused on the left ventricle (LV), and the RV was merely considered a bystander in most cardiovascular diseases. This has in part been attributed to experimental studies in the 1940s and 1950s, in which the need for the RV was questioned. Several decades later new experiments were conducted that contradicted prior observations, since these studies clearly demonstrated that a normal functioning RV is important for maintaining adequate blood flow. This renewed interest in the RV was followed by a large number of clinical studies in the 1980s and 1990s in which the presence of RV failure was linked to poor prognosis in all kinds of cardiovascular diseases. However, the study on the RV was still considered far lagging behind compared to that of the LV. In 2006, a special report was published on behalf of the National Heart, Lung and Blood Institute, in which awareness and more research on the RV was encouraged.

Clinical relevance of right ventricular failure

In normal conditions, the RV is coupled with a low resistant and highly compliant pulmonary vasculature. In the absence of intra-cardiac shunts, both ventricles produce the same stroke volume. However, the amount of workload of the RV in normal conditions is one fifth as compared to the LV, due to the lower vascular resistance in the pulmonary compared to the systemic circulation. Consequently, the normal pressure-volume relationship of the RV is more triangular shaped and RV output starts immediately during systole (Figure 1A).

The RV can be exposed to several stress conditions, such as ischemia and infarction, pressure or volume overload and pericardial disease. The RV is particularly vulnerable for acutely increased afterload such as pulmonary embolism, yet also longstanding pulmonary hypertension is seriously harmful for the RV. In response to increased pressure load, the characteristic RV pressure-volume relation
initially shifts to a more rectangular shape, with distinct isovolumetric contraction and relaxation phases, similar as for the LV (Figure 1B). This is accompanied by increased contractility of the RV, visualized by a leftward shift of the end-systolic elastance curve.

![Figure 1: Conceptual representation of pathophysiological changes of the pressure-loaded right ventricle.](image)

(A) Pressure-volume (PV) loops in normal hemodynamic conditions: rectangular PV-loop of the LV (red), illustrating distinct isovolumetric relaxation and contraction phases, and the triangular shaped PV-loop of the RV (blue), with absence of clear isovolumetric phases and output starting immediately during systole. (B) In the setting of increased afterload, the PV-relation of the RV shifts to a more rectangular shape, similar as for the LV. The diagonal line, representing the end-systolic elastance (Ees), shifts to the left meaning that contractility of the RV is initially enhanced. (C) With chronically increased pressure load, the eventually RV dilates leading to increased wall tension and the RV is unable to maintain its contractility, visualized by a rightward shift of the end-systolic elastance.

With longstanding pressure overload however, the RV is unable to maintain its contractility and the RV dilates, resulting in a rightward shift of the end-systolic elastance (Figure 1C). Increased afterload and RV dilatation eventually leads to increased wall stress, high metabolic demand, and oxygen-perfusion mismatch leading to myocardial ischemia. The RV is unable to maintain sufficient cardiac output leading to signs and symptoms of right heart failure and systemic congestion. If left untreated, progressive RV failure will ultimately lead to multi-organ failure and death.

RV overload also directly affects the LV via ventricular interdependence. This phenomenon occurs because the size, shape and pressure-volume relationship of one ventricle affect those of the other ventricle. This is the result of both ventricles sharing an interventricular septum and both are situated within the same pericardial sac. Approximately 30-40% of LV diastolic pressure is caused by extrinsic forces, including RV pressure and pericardial restraint. When the RV pressure rises and the RV dilates, the interventricular septum shifts leftwards and because of
pericardial restraint, the LV is compromised ("D-shaped"), as seen in Figure 2. As a consequence, LV distensibility and pre-load are reduced leading to loss of Frank-Starling recruitment and reduced cardiac output.

![Diagram of normal heart and RV overload and dilatation](image)

**Figure 2: Ventricular interdependence in right heart overload.** Volume or pressure overload of the right ventricle (RV) shifts the interventricular septum towards the left ventricle (LV), thereby changing LV geometry (’D-shape’). RV distension also leads to increased pericardial constraint that further comprise the LV, leading to decreased LV distensibility and preload, and eventually to reduced cardiac output.

**The right ventricle in left-sided heart failure with reduced or preserved ejection fraction**

The RV was mainly considered to be of relevance in specific patient populations, such as those with congenital heart disease and pulmonary arterial hypertension. These conditions are not diseases of epidemic proportions, in contrast to left-sided heart failure and coronary artery disease. However, the increasing interest for the RV was also accompanied by clinical studies in which the importance of the RV in left-sided heart failure was investigated. Ghio et al. previously demonstrated the reduced RV systolic function coupled with higher pulmonary pressures was associated with poor prognosis in patients with left-sided heart failure with reduced ejection fraction (HFrEF). The most important determinants for the development of RV dysfunction in HFrEF include myocardial ischemia and infarction, pulmonary hypertension and intrinsic myocardial disease. These and other studies reflect the growing recognition of the importance of the RV in left-sided heart failure.
Today, the presence and prognostic value of RV dysfunction is also studied in patients with left-sided heart failure with preserved ejection fraction (HFpEF). However, the mechanisms behind the development of RV dysfunction in HFpEF are less clear. Melenovsky et al. observed that RV dysfunction was present in 33% of patients with HFpEF and reduced RV function was the strongest determinant of mortality. Another community-based study reported similar observations regarding the RV in HFpEF. Both studies demonstrated that the presence of RV dysfunction was strongly associated with pulmonary hypertension, although the association with outcome was independent of pulmonary pressures. Moreover, several other factors than pulmonary hypertension, such as male sex, atrial fibrillation and coronary artery disease, were also associated with impaired RV function in HFpEF.

These recent observations regarding the prognostic value of RV dysfunction in HFpEF highlights the need for more pathophysiological insights. However, the study of the RV in HFpEF is not straightforward. While HFpEF is generally considered as a disease of the left heart, the classic signs and symptoms of left- and right-sided heart failure are not mutually exclusive. The Framingham criteria used to clinically diagnose HFpEF include typical signs and symptoms related to right-heart failure. This implies that the RV is important for the symptomatology in HFpEF. Unfortunately, signs and symptoms related to right-sided heart failure are also not unique and patients with e.g. chronic obstructive pulmonary disease may have similar symptoms without having true right-sided heart failure. Furthermore, although peripheral edema is a classic sign of chronic right-sided congestion, in the acute setting the causes of lower extremity edema are more complex and seem not entirely associated with central venous pressure and may therefore be misleading, at least in patients hospitalized for acute heart failure.

Moreover, the diagnosis of HFpEF is difficult, since HFpEF is considered a very heterogeneous disease. Next to signs and symptoms related to heart failure and in absence of a reduced LV ejection fraction, additional criteria are required. However, these additional criteria are used separately from each other and are not specific for HFpEF. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration are also elevated in patients with frequently associated comorbidities such as atrial fibrillation and renal dysfunction. In addition, NT-proBNP cannot accurately distinguish whether are not the RV is involved, because patients with
isolated pulmonary arterial hypertension may also present with elevated NT-proBNP levels and a normal LV ejection fraction. Furthermore, supportive echocardiographic criteria of HFP EF are non-specific, and left atrial enlargement is also present in atrial fibrillation and mitral valve regurgitation.

The heterogeneity of HFP EF in combination with the observation that RV dysfunction seems present in a significant number of patients with HFP EF led to the hypothesis that a distinct HFP EF sub-phenotype consists of right-heart-failure-predominant HFP EF. Currently, the clinical relevance and underlying mechanisms of the development of RV dysfunction and failure in HFP EF remain inaccurately defined. More pathophysiological insight may potentially lead to better treatment strategies. This is highly warranted for HFP EF, because in contrast to HFR EF, there are currently no specific drugs or devices identified that reduce mortality in HFP EF. Because of the heterogeneity of the disease, it has recently been suggested to design phenotype-specific therapies for HFP EF and the right heart failure-predominant HFP EF sub-phenotype might require specific treatments. Gaining insight into the development of RV dysfunction and failure in HFP EF may thus aid to: 1) unraveling the complex and heterogeneous pathophysiology of HFP EF; and 2) reveal potential effective treatment strategies by targeting the right side in HFP EF.

Aims and outline of this thesis

The main aims of this thesis are:

1) Investigate the clinical relevance of RV dysfunction in HFP EF
2) Explore underlying mechanisms of RV dysfunction in HFP EF
3) Identify potential treatment strategies targeting the RV in HFP EF

In order to explore the clinical relevance of RV dysfunction in HFP EF, a systemic review and meta-analysis on the prevalence and prognostic value of RV dysfunction in HFP EF was conducted (Chapter 2). In this study, pooled data from individual studies that investigated RV function and/or pulmonary hypertension in HFP EF was used. Conventional measures of RV systolic dysfunction and pulmonary
Chapter 1

Hypertension were obtained and were related to outcome parameters (i.e. mortality and hospitalization for heart failure). A secondary aim of Chapter 2 was to identify clinical determinants of RV dysfunction in patients with HFpEF.

From recent studies, it has been suggested that RV dysfunction is associated with pulmonary hypertension in HFpEF. Chapters 3 and 4 were set up to investigate the relation between additional pulmonary vascular disease and RV dysfunction. Chapter 3 concerned an invasive pulmonary hemodynamic study using simultaneous right heart catheterization and echocardiography at rest in patients with HFpEF. In this study we aimed to identify clinical and non-invasive functional parameters that can predict the presence of pulmonary vascular disease in HFpEF. It seemed important to identify these patients, because they may benefit from close-monitoring to prevent progressive RV failure and recurrent heart failure hospitalizations. Chapter 4 was an invasive exercise hemodynamic study performed in patients with HFpEF with and without pulmonary vascular disease, and in control subjects without heart failure. Many patients with HFpEF experience severe exercise intolerance and in this study we aimed to investigate the hemodynamic basis of exercise intolerance in HFpEF and pulmonary vascular disease.

Besides pulmonary hypertension, it has been suggested that several HFpEF-predominant comorbidities are associated with RV dysfunction. It was speculated that these comorbidities may require specific treatment strategies. In Chapter 5 we studied the importance of atrial fibrillation for the development of RV dysfunction, with a special focus on right atrial function. Via mechanisms of systemic inflammation and endothelial dysfunction, diabetes mellitus was previously linked to LV myocardial remodeling and diastolic dysfunction in HFpEF. Because these mechanisms probably occur via circulating factors, we hypothesized that diabetes mellitus had similar impact on the RV. The association between diabetes mellitus and the RV systolic and diastolic dysfunction in patients with HFpEF was further explored in Chapter 6.

Chapter 7 concerned a position paper that we have written on behalf of the Heart Failure Association of the European Society of Cardiology. In this chapter, we reviewed the latest insights regarding etiology and pathophysiology of right heart dysfunction and failure in HFpEF. In addition, we have a particular focus for
(potential) treatment strategies targeting the right heart in HFpEF. One potential tool that may aid to improved treatment in HFpEF is further discussed in detail in Chapter 8. This chapter was published as an editorial in which we discuss the use of continuous monitoring of pulmonary pressures in order to timely adjust medications and thereby reducing the number of recurrent hospitalizations in patients with heart failure, including HFpEF. Finally, in Chapter 9 the main findings of this thesis were summarized and future directions regarding the RV in HFpEF were described.

References


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