The elusive heart
Borgdorff, Reinout

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Borgdorff, R. (2014). The elusive heart: the right ventricle in chronic abnormal loading conditions. [S.l.]: [s.n.].

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
THE ELUSIVE HEART: AN INTRODUCTION

MAJ Borgdorff
‘The heart is an amazing organ. From a distance, its appearance and function may seem simple. This muscular organ just pumps blood. It receives blood from the body on one side and pumps it back to the body on the other. Yet beyond this splendid simplicity lies a complexity that is hardly matched by any other organ in the body. The heart is composed of muscle-layers, blood vessels and valves, which in itself are composed of networks of specialized cells, fibers and compartments. Then there are sub cellular structures measuring only a few micrometers, nanometers across and then there are billions of tiny molecules, which cannot be seen by even the most powerful microscopes. They are roaming solitary or swarming like shoals of herring or tightly organized like the ranks of a Roman legion. They zip across membranes in milliseconds, they tirelessly latch on and let go of each other, and they withstand enormous pressures sustaining the heart’s architecture. All these countless, widely variant components have their own unique and wonderful three-dimensional shape and rhythm, meticulously fashioned to their function, and yet they act all in harmonious choreography to produce the simple and singular pulse of life. Oh yes, the heart is an amazing organ.’
Embryology

The heart is the first organ to be formed during human development. Fifteen days into gestation, two horseshoe-shaped clusters of cells lie on the ventral surface of the embryo in an anterior-posterior relationship; the heart fields. Cells from the first heart field form an arched tube that is subsequently invaded by cells from the second heart field(1). These second heart field derived cells predominately home at the superior terminus of the tube and develop into the conal trunk and right ventricle. As the tube loops and twists, the cells from the first heart field form both atria and the left ventricle(2). A third group of cells from the neural crest joins with second heart field-derived cells to form the multiple aortic arches that predominate at early gestational stages. Intermediate structures that delineate these compartments such as the interventricular septum and the atrioventricular valves seem to consist of cells from both first-, and second heart field. At day 55, hardly 8 weeks into gestation, the heart has started beating and the layout of the mature heart (two atria receiving the venous return, functional atrioventricular valves, two separate ventricles and semilunar valves connecting the heart to the systemic and pulmonary circulations) is formed.

Congenital heart defects

This basic building plan adequately describes the normal heart, but about 1 out of 100 children is born with an abnormal heart: they have a congenital heart defect (CHD)(3). The group of congenital heart defects comprises a wide spectrum of abnormalities ranging from lesions with hardly any consequences for normal physiology, which do not require any treatment and may go unnoticed throughout life to lesions with major consequences for physiology that, left untreated, are not compatible with life. Examples include mild narrowing of valves and small defects in septa for the former category and complete abnormal architecture with abnormal or absent connections and basically one functional ventricle for the latter. Congenital heart defects have long been a leading cause death in children. However, in recent decades enormous progress has been made in the management of congenital heart defects(4). Whereas only a few decades ago a high percentage of children with a CHD would die at a very young age, currently most of the patients survive through childhood, into adolescence and adulthood(5). They form a new and quickly expanding group of patients with unique characteristics and challenges(6): their heart
and vessels are repaired, but rarely completely normal. Consequently, there are oftentimes chronic changes in the physiology of their heart and circulation. The cardiac ventricles may face longstanding abnormal loading conditions, such as an increased volume load requiring the ventricle to pump more blood per minute than normal, or increased pressure load, in which a normal volume of blood must be pumped against an abnormally high resistance. In other patients the ventricles are challenged by a combination of volume- and pressure load.

**The right ventricle in chronic abnormal loading conditions**

Follow-up studies have shown that whether the left or right ventricle is abnormally loaded plays a crucial role in determining the outcome of these patients. Patients with a chronically loaded right ventricle are much more likely to develop early heart failure(7). That means that already at young age, they are more likely to experience symptoms because of insufficient pump function of the right heart (RV failure). The right ventricle thus, appears to be particularly vulnerable to chronic abnormal loading. More than in the left ventricle, abnormal loading conditions (especially pressure load) on the RV are thought to impede function, which causes symptoms like fatigue, exercise intolerance and edema and may ultimately threaten survival(8).

An archetype-disease of the overloaded RV is pulmonary hypertension (PH). PH is characterized by excessive remodeling of the pulmonary vasculature, resulting in increased pulmonary vascular resistance and RV pressure load, which leads to RV failure and premature death(9). Even in the setting of maximal treatment, the prognosis of PH-patients is very poor, with a 5-year survival of about 50%(10-13). Interestingly, it is the severity of RV dysfunction rather than the severity of the pulmonary vascular disease that appears to determine prognosis in these patients(14,15).

However, the importance of the RV is not limited to the fields of congenital heart defects and pulmonary hypertension: in recent years RV function has emerged as a pivotal determinant of outcome, also in different forms of left sided heart disease(16-18).

Collectively, these progressive insights have sparked increasing interest in the right ventricle over the last few decades. In 1982, my birth year, 1,471 scientific papers on right ventricular failure were published; in 1992, 2,765; in 2002, 4,994;
and in 2012 nearly 10,000! (trumping for instance ‘myocardial infarction’, which was at 7,933 papers in 2012) (source: US National Library of Medicine, National Institutes of Health at www.pubmed.gov, using queries ‘right ventricular failure’ and ‘myocardial infarction’). The shift of attention towards the right ventricle is truly remarkable: currently regarded as a central factor in a broad range of cardiovascular diseases, 50 years ago it was the subject of debates whether or not the RV had any hemodynamic significance at all(19-21).

The elusive heart

However, despite the expansion of scientific literature on right ventricular failure, it remains largely unknown how chronic abnormal loading conditions physiologically lead to RV failure, and which biological mechanisms govern the adaptive and maladaptive processes associated with the changed physiology (9,22). To further complicate this field of research, the more became known about the RV, the more it became apparent that the RV differed markedly from the LV and thus LV derived knowledge could not necessarily be applied in RV diseases. Indeed, major anatomical, functional and embryological differences exist between the RV and LV. Most importantly, the RV is morphologically and functionally adapted for the generation of low pressure perfusion of the pulmonary vascular bed(23). It is thin-walled, compliant, has a complex triangular-crescent shape and a peristaltic contraction pattern. The coronary perfusion is different than for the LV, there is a different oxygen/energy demand and the coupling between the ventricle and the vascular bed is different(9,24).

Intriguingly, the RV is derived from different embryological precursor cells than the left ventricle(25). However, it is largely unknown to what extent RV cardiomyocytes differ from LV cardiomyocytes and whether the embryological difference translates in a distinct response to chronic abnormal loading conditions(26).

In summary, there is a paucity of knowledge at all levels about the normal and pathological function of the RV(22); the right ventricle is the elusive heart. As a consequence, there are currently no clinically established treatments for RV failure.
Treating RV failure

However, today one could suggest three possible routes towards the treatment of RV failure, and these are all three well worth pursuing. Firstly, treatment strategies that have proven invaluable for left ventricular failure(27,28) (e.g. beta adrenergic blockade, inhibition of the renin-angiotensin-aldosterone system) could be of benefit in right ventricular failure(15). Although —as pointed are before— there are important embryological, functional and morphological differences between the LV and RV, and the etiology of left and right ventricular failure are very different (ischemic heart disease vs. chronic abnormal loading), it might be that there are common pathways and adverse changes that can effectively blocked in RV failure as much as in LV failure.

A second route towards the identification of successful RV treatment relates to drugs used to treat pulmonary hypertension. These drugs directly target the pulmonary vascular disease (e.g. phosphodiesterase type 5A(PDE5A)-inhibitors, endothelin antagonists), but have been suggested to have also direct beneficial effects on the RV(29,30). Treatment of RV failure with PDE5A-inhibitor Sildenafil for instance, might be attractive as it would kill two birds with one stone, simultaneously reducing pulmonary vascular resistance and sustaining RV function. However, also some authors do warn for adverse effects on the RV of effective PAH-targeted drugs (30).

The third route is the most challenging and requires identification of the (mal) adaptive mechanisms involved in RV failure. Such mechanisms may provide new therapeutic targets of which the value can be asserted in preclinical proof-of-concept studies.

The studies presented in this thesis represent steps on all three routes.

Animal models of RV failure

Unfortunately, answering the here studied research questions required animal experiments. This puts both the researcher and society as a whole in the dilemma of weighing the ethical and emotional burden of using animals to a scientific end against the importance of developing treatments for a disease that causes significant suffering in the lives of (young) patients and their families. While animals should never be used for research when alternative methods exist, animal models of RV failure are of paramount importance in the current stage of RV research for myriad reasons. Firstly, they allow for highly controlled and
detailed studying of the pathophysiology and pathobiology of the RV subjected to abnormal loading conditions and its responses to therapeutic interventions. The severity of pressure load or volume load can be precisely titrated and the RV response can be measured at any chosen moment thereafter. This avoids the heterogeneity that complicates the interpretation of findings in clinical studies, in which the mechanism, severity and duration of abnormal loading vary from patient to patient leaving ample room for debate where to place the observed changes in the spectrum from adaptation to failure. This becomes especially apparent in studies of therapeutic interventions. Animal studies allow for specific timing in starting or withdrawing treatment, which is important because the effect of therapeutic intervention may to a large extent depend on its timeliness. On one hand the intervention may be too late, when the harm is already done, on the other hand the intervention may be too early, having no (or even adverse) effects in early stages of disease, while being beneficial in more advanced stages of the disease. In clinical studies, the stage of disease is determined by using secondary parameters such as echocardiographic measurements or the presence of (subjective) symptoms. In animal studies the pathophysiology of RV overload can be studied from day to day and therapeutic intervention can be commenced at any given moment; elucidating its effects in a time-, and severity specific manner.

Secondly, in animal models assessment of RV function by pressure-volume analysis is feasible. Pressure-volume analysis is the gold-standard of assessing ventricular function, but requires an invasive procedure to catheterize the RV, which limits its applicability in the clinical setting. Echocardiography is a practical and easy alternative (both in clinical and animal studies) but provides only limited information on RV function, most importantly because echo-derived function parameters are highly load dependent and the complex RV anatomy precludes accurate measurement of RV volumes. Cardiac magnetic resonance imaging does allow RV volume measurements but is time consuming and lacks pressure data. Pressure-volume analysis provides simultaneous pressure and volume data in real-time, of which load-independent parameters of RV contractility, compliance, muscle energetics and other important quantitative measures of function can be derived. Especially diastolic function can hardly be assessed by any other technique than pressure-volume analysis, which may explain why the role of diastolic function in RV failure has received little attention so far.
We therefore used pressure-volume analysis for functional RV assessment and evaluation of treatment effects in all the studies in rat models.

The third reason why animal models are a necessary evil in RV research, is the possibility to collect tissue samples to study biomolecular and histopathological changes. In clinical studies, sources of tissue samples are limited to surgery specimens and material from autopsies. Obviously, these represent a very narrow segment of the spectrum of RV disease and may not adequately reflect the pathobiological changes that determine disease progression in early stages of the disease, particularly when the patient may be amenable to treatment. Finally, animal models are also a safe platform to assess the putative beneficial and adverse effects of therapeutic interventions without putting patients at risk.

Historically, many models of RV failure (31),(32) came from the field of PH research. Although much of the current knowledge about the pressure loaded RV is obtained in these models, they have limitations that require the (additional) development of other models. Direct effects of the agents used to induce PH (monocrotaline, SUGEN, hypoxia) on the RV limits their use to study the pathobiology of RVF. Additionally, in PH models, direct effects of drugs on the RV are difficult to distinguish from indirect effects caused by reduction of pressure load (e.g. due to pulmonary vasodilatation). The pulmonary artery banding (PAB) model circumvents these limitations and some reports suggest that PAB may be a valid model of RV failure (33, 34). However, extensive functional and pathobiological characterization of a PAB model displaying RV failure is lacking in literature.

Compared to the pressure loaded RV, the volume loaded RV has received very little attention so far, also in terms of animal models, despite its clinical significance (35,36).

In this thesis, we aimed to expand the current knowledge of right ventricular failure due to chronic abnormal loading conditions, using preclinical models, by describing in detail the physiological and biological consequences of different types of abnormal loading and by studying the effects of therapeutic agents with a putative beneficial effect on the RV.
Specifically, we aimed to:

1. **Characterize the clinical, physiological and biological RV response in rodent models of chronic pressure load, volume load and combined pressure-volume load.**

   To this end, we tested whether the adaptive RV response depends on the ‘type’ of loading. Do different loading conditions elicit a common or distinct adaptive response?

   In **chapter 2**, we compared RV hemodynamics, voluntary exercise and hypertrophy in rat models of pressure overload due to pulmonary artery banding (PAB), pressure overload due to experimental PH, combined pressure- and volume overload and isolated volume load.

   A similar comparison was made in the studies described in **chapter 3**, where we tested whether the RV response to pressure load is different than the response to volume load, in terms of ventricular function (measure by cardiac MRI), voluntary exercise tolerance and activation of hypertrophy pathways.

2. **Identify biological processes that play a role in right ventricular failure due to fixed chronic RV pressure load.**

   To this end, we characterized advanced right ventricular failure in a model of severe pressure load (PAB) (**chapter 4**). To identify physiological and biological processes involved with the RV response to pressure load and the transition from subclinical to clinical RV failure, we compared healthy rats to rats with ‘clinical’ RV failure and rats with ‘subclinical’ RV failure using echocardiography, pressure-volume analysis, histological techniques and transcriptome-wide expression profiling.

3. **Study the effects phosphodiesterase type 5A-inhibiting therapy on fixed chronic RV pressure load and chronic RV volume load.**

   Does PDE5A-inhibition have a beneficial effect on the RV, apart from its vasodilatory effects on the pulmonary vasculature? If so, is this effect specific for the pressure loaded RV or does it also benefit the (hypertrophied) volume overloaded RV? And how important is the timing of the start of treatment? To
answer these questions, we studied the effects of phosphodiesterase 5-blocker Sildenafil in models of abnormal loading. We assessed preventive effects of PDE5-inhibition by starting Sildenafil treatment from day 1 in both volume- and pressure load (chapter 5). We followed-up the preventive study in pressure load by a therapeutic study (chapter 6), where Sildenafil treatment was not started until RV dysfunction had developed.

4). Study the effects of renin-angiotensin-aldosterone-system inhibiting therapy on fixed chronic RV pressure load.

Does a cornerstone of left ventricular failure treatment also work in the RV? In chapter 7, we studied RAAS-inhibiting therapy by angiotensine II-receptor blocker Losartan and mineralo-corticoid-receptor blocker Eplerenone. Based on its effects in the left ventricle we hypothesized that this intervention would prevent pressure load-induced RV dysfunction, particularly disturbances of diastolic function.

In chapter 8, we integrated our findings in a review of the current literature on animal models of right ventricular failure due to chronic abnormal loading conditions.

Finally in chapter 9, specifically the results presented in this thesis are placed in a broader perspective and directions for future research are indicated.
Srivastava D. Making or breaking the heart: from lineage determination to morphogenesis. *Cell* 2006;126:1037-1048.


the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:e391-479.


