Heart failure secondary to chronic pulmonary arterial hypertension: cardiac imaging and electrophysiologic characteristics

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Chapter 1

Introduction
Introduction

List of abbreviations:

- α-MHC: alpha-myosin heavy chain
- β-MHC: beta-myosin heavy chain
- BNP: brain-type natriuretic peptide
- CTEPH: chronic thromboembolic pulmonary hypertension
- LV: left ventricle
- PAH: pulmonary arterial hypertension
- RV: right ventricle
- VF: ventricular fibrillation
- VT: ventricular tachycardia
The normal right ventricle

1. Anatomy

In the normal heart, the right ventricle (RV) is the most anteriorly situated cardiac chamber and lies immediately behind the sternum. The RV is a thin-walled chamber of a complex geometry, very much different from that of the ellipsoid shaped concentric left ventricle (LV): crescent shaped in cross section due to the concave free wall opposite to the convex interventricular septum, approximating a pyramid with a triangular base longitudinally (Table 1). It comprises an inflow tract (tricuspid annulus) and outflow tract (RVOT), separated by the *crista terminalis*. Additionally, the (RV) can also be divided into anterior, lateral, and inferior walls, as well as basal, mid, and apical sections.

Compared to the LV, the RV has a lower volume-to-surface area ratio, and this makes it a highly compliant chamber designed to work under low pressure conditions and pump the blood against low pulmonary vascular resistance. Accordingly, macroscopically, ultrastructurally, and biochemically, the RV differs drastically from the LV. The normal RV seldom exceeds 2–3 mm wall thickness at end-diastole, compared with 8–11 mm for the LV (Table 1). The biochemical composition of the RV and LV differ, with the RV having a higher proportion of the α-myosin heavy chain (α-MHC) isoform that results in more rapid but less energy efficient contraction. In the normal adult human RV, the α-MHC isotype makes up approximately 23 to 34% of total MHC, and β-MHC the remainder.
Table 1. Comparison of Normal RV and LV Structure and Function

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RV</th>
<th>LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Inflow region, trabeculated myocardium, infundibulum</td>
<td>Inflow region and myocardium, no infundibulum</td>
</tr>
<tr>
<td>Shape</td>
<td>From the side: triangular (^1) cross section: crescentic</td>
<td>Elliptic (^1)</td>
</tr>
<tr>
<td>End-diastolic volume, mL/m(^2)</td>
<td>75±13 (49–101) (^8)</td>
<td>66±12 (44–89) (^8)</td>
</tr>
<tr>
<td>Mass, g/m(^2)</td>
<td>26±5 (17–34) (^8)</td>
<td>87±12 (64–109) (^8)</td>
</tr>
<tr>
<td>Thickness of ventricular wall, mm</td>
<td>2 to 5 (^9)</td>
<td>7 to 11 (^8)</td>
</tr>
<tr>
<td>Ventricular pressures (systolic)/(diastolic), mmHg</td>
<td>(15–30)/(1–7) (^2)</td>
<td>(90–140)/(5–12) (^2)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>61±7 (47–76) (^8)</td>
<td>67±5 (57–78) (^8)</td>
</tr>
<tr>
<td>Ventricular elastance, mmHg/mL</td>
<td>1.30±0.84 (^10)</td>
<td>5.48±1.23 (^11)</td>
</tr>
<tr>
<td>Exercise reserve</td>
<td>↑RVEF ≥5% (^1)</td>
<td>↑LVEF ≥5% (^12)</td>
</tr>
</tbody>
</table>

Data are mean±SEM(range)

2. Electromechanical aspects of RV contraction

In most individuals without cardiovascular disease, RV is activated either simultaneously with LV or slightly earlier starting from the anterior paraseptal region and ending in the RV outflow area\(^13\)\(^15\). The repolarization sequence is believed to be unaffected by the activation sequence\(^14\), with the longest monophasic action potentials in or near the earliest activated area, and the shortest ones in or near the latest activated area\(^16\). Of note, average RV activation recovery interval, a measure of action potential duration, is \(~32\) ms shorter than in LV\(^14\). Altogether, RV completes electrical activation virtually simultaneously with LV and ends repolarization slightly earlier than LV\(^13\)\(^14\)\(^16\).
RV contraction is sequential and resembles, in general, the electrical activation sequence. It starts with the contraction of the inlet and trabeculated myocardium and ends with the contraction of the infundibulum (approximately 25 to 50 ms apart)\(^1\). Furthermore, contraction of the infundibulum is of longer duration than contraction of the inflow region\(^1\). The RV contracts by 3 separate mechanisms: (1) inward movement of the free wall, which produces a bellows effect; (2) contraction of the longitudinal fibers, which shortens the long axis and draws the tricuspid annulus toward the apex; and (3) traction on the free wall at the points of attachment secondary to LV contraction\(^2\). Shortening of the RV is greater longitudinally than radially\(^1^7\). In contrast to the LV, twisting and rotational movements do not contribute significantly to RV contraction. Moreover, because of the lower volume-to-surface area ratio of the RV, a smaller inward motion is required to eject the same stroke volume\(^2\). Maximal systolic longitudinal strain values are highest at the apex and base, with a pronounced decrease in the medial segments, while maximal systolic circumferential strain has the highest values at the apex\(^4\). Moreover, peak systolic longitudinal and circumferential shortening occurs earlier at the apex than at the mid-ventricle and base\(^4\). Importantly, such electrical activation-relaxation sequence, closely coupled with the contraction sequence, allows the heart to function optimally via mechanisms of systolic and diastolic interventricular interaction by synchronizing RV and LV mechanics\(^{18-20}\). For example, experimental animal studies showed that approximately 20% to 40% of RV systolic pressure and volume outflow results from LV\(^1^8\).

### 3. RV hemodynamics and myocardial perfusion

Under normal conditions, the RV is coupled with a low impedance system, i.e., the highly distensible pulmonary vasculature. Compared with the systemic circulation, pulmonary circulation has a much lower vascular resistance, greater pulmonary artery distensibility, and a lower peripheral pulse wave reflection coefficient\(^1^2\). Right-sided pressures are significantly lower than corresponding left-sided pressures (Table 1)\(^2\). RV pressure tracings show an early peaking and a rapidly declining pressure in contrast to the
rounded contour of LV pressure tracing. RV isovolumic contraction time is shorter because RV systolic pressure rapidly exceeds the low pulmonary artery diastolic pressure.

The blood supply of the RV varies according to the dominance of the coronary system. In a right-dominant system, which is found in ~80% of the population, the right coronary artery supplies most of the RV. The lateral wall of the RV is supplied by the marginal branches of the RV, whereas the posterior wall and the inferoseptal region are supplied by the posterior descending artery. The anterior wall of the RV and the anteroseptal region are supplied by branches of the left anterior descending artery. The infundibulum derives its supply from the conal artery, which has a separate ostial origin in 30% of cases. The separate ostium explains the preservation of infundibular contraction in the presence of proximal right coronary occlusion. In the absence of severe RV hypertrophy or pressure overload, proximal right coronary artery flow occurs during both systole and diastole. However, beyond the RV marginal branches, diastolic coronary blood flow predominates.

4. Cardiodynamics
RV systolic function is a reflection of contractility, afterload, and preload. RV performance is also influenced by heart rhythm, synchrony of ventricular contraction, RV force interval relationship, and interventricular interdependence. RV afterload represents the load that the RV has to overcome during ejection. Compared with the LV, the RV demonstrates increased sensitivity to afterload change. RV preload represents the load present before contraction. Within physiological limits, an increase in RV preload improves myocardial contraction on the basis of the Frank-Starling mechanism. Beyond the physiological range, excessive RV volume loading can compress the LV and impair global ventricular function through the mechanism of ventricular interdependence. Compared with LV filling, RV filling normally starts earlier and finishes later.
Adaptive response of RV to chronically increased pressure

In general, the RV adapts better to volume overload than to chronic pressure overload\(^2\). For example, chronic increases in pulmonary blood flow can be well tolerated by the RV in patients with atrial septal defect and tricuspid regurgitation\(^2\). In contrast to volume-overload states, moderate to severe acquired pulmonary arterial hypertension (PAH), leading to chronic RV pressure overload, often results in RV dilatation and failure in the adult\(^2\). In the RV, an increase in end-systolic pressure results in a corresponding increase in end-systolic volume and a decrease in ejection fraction\(^2\). If nothing else changed, an increase in pulmonary artery pressure would result in a decrease in RV ejection fraction and stroke volume, and a corresponding decrease in cardiac output. Thus, for the RV to maintain cardiac output when confronted with an increase in afterload or pressure, RV performance must increase to generate the required increase in stroke work\(^3\), through either an increase in contractile state or the Frank-Starling mechanism.

From the Laplace relationship it follows that, in a thin-walled sphere, an increase in intraluminal pressure results in an increase in wall stress, unless the thickness of the chamber wall is augmented or the internal radius of the chamber is reduced. Since an increase in wall stress not only increases myocardial oxygen demand, but also impedes myocardial perfusion, an important adaptation of the RV to the high pressure in PAH is to increase wall thickness by accumulating muscle mass (hypertrophy) and to assume a more rounded shape. The increase in ventricular mass induced by an increase in afterload is predominantly the result of protein synthesis and an increase in cell size through the addition of sarcomeres. Protein synthesis in the cardiomyocytes is directly induced by stretch and enhanced by autocrine, paracrine, and neurohormonal influences\(^2,27,31,32\). An increase in afterload is sensed by integrins\(^3\) and stretch-activated ion channels\(^3\) in cardiac cells (myocytes, fibroblasts, endothelial cells), and leads to increased protein expression\(^27,34\). Pressure-induced growth (and proliferation) of cardiomyocytes needs to be paralleled by increase in the extracellular matrix, predominantly collagen with relatively small amounts of fibronectin, laminin, and elastin, and synthesis and growth of the supporting vasculature. Under physiologic circumstances, signaling by vascular
endothelial growth factor, Angiopoietin 1, and other growth factors provides a tight match between angiogenesis and myocyte growth.

**Maladaptive structural remodeling during development of PAH-associated RV heart failure**

It is generally believed that sustained pressure overload per se is enough to induce maladaptive hypertrophy and cardiac failure. However, little is known how the development of PAH-associated RV heart failure is modified by neurohormonal activation, oxidative and nitrosative stress, immune activation, myocardial ischemia, cardiomyocyte apoptosis, electrophysiological remodeling, and altered interventricular interaction.

In heart failure secondary to chronic PAH, the RV is characterized by increased end-diastolic and end-systolic volumes, and changes from a normal ventricular conformation tetrahedron to a crescentic trapezoid, and varying degrees of RV hypertrophy\(^{27, 28, 32}\). With hypertrophy, the RV becomes more concentric and the interventricular septum flattens\(^{27, 29, 31, 32}\). RV chamber remodeling and (dys)function are interrelated, and one alteration may produce the other. Contractile dysfunction can result from a remodeled ventricle because of RV ischemia\(^{35}\), the increased energetic load of heightened wall stress\(^{36}\) and/or a switch from the α-MHC to the β-MHC isoform. For example, the reduction in α-MHC content (down to ± 5%) that is encountered in PAH-associated RV heart failure\(^{7}\) can have important functional consequences. β-MHC has lower adenosine triphosphatase activity than α-MHC; in an experimental study, the disappearance of the latter resulted in a significant decrease in systolic function\(^{37}\). Yet, RV endomyocardial biopsy specimens from patients with PAH showed increased levels of fibrosis\(^{7}\), confirming earlier findings in rats after pulmonary artery banding\(^{38}\) and monocrotaline-treated rats\(^{39}\). Other factors in chronic PAH appear to be involved in progression from adaptive RV hypertrophy to RV heart failure. For example, pressure overload is the primary determinant of (mal)adaptations in β-adrenoreceptor density\(^{40}\), angiotensin type 1 receptor density\(^{41}\), atrial natriuretic peptide expression\(^{7}\), and altered calcium handling\(^{42}\).
Besides that, the rate of cardiomyocyte apoptosis was shown to be elevated in rats after pulmonary artery banding\textsuperscript{13}.

Ventricular interdependence plays an important role in progression from heart failure secondary to chronic PAH\textsuperscript{27, 28, 32}. The mechanical aspects of right and left ventricular interaction have been studied in detail by Dong et al.\textsuperscript{44} in animal experiments and by applying a mathematical model\textsuperscript{45}. It was clearly shown that this interaction is due to the common septum shared by the ventricles, further enhanced by the limited and relatively noncompliant space within the pericardial sac. The mechanical model also showed that RV pressure overload due to chronic PAH led to diastolic unloading of both the LV free wall and the septum. Accordingly, LV in acquired chronic RV pressure overload is underfilled\textsuperscript{32,36,46,47}. Importantly, peak of LV diastolic filling rate is directly related to RV ejection fraction\textsuperscript{48}. Although LV diastolic dysfunction due to direct and series interventricular interaction, particularly in the early phase of diastole, is most common\textsuperscript{28,32, 48-50}, LV systolic dysfunction may also occur in patients with heart failure secondary to chronic PAH\textsuperscript{48,50-52} and contribute to heart failure progression in patients with chronic PAH\textsuperscript{27, 32}. Not surprisingly, gene expression patterns\textsuperscript{53}, altered neuromediators concentration\textsuperscript{54}, and β-adrenoreceptor density reduction\textsuperscript{55} observed in LV of experimental animals with RV failure due to chronic PAH were similar to changes found in RV.

(\textit{Mal})adaptive electrophysiological remodeling and arrhythmias during development of PAH-associated RV heart failure

Experimental studies have indicated that RV heart failure secondary to chronic pressure overload is associated with action potential prolongation in RV myocytes\textsuperscript{56,57}, similar to changes in LV during the development of LV failure. Changes in repolarization in RV heart failure are caused by cardiac ion channel remodeling, e.g., downregulation of inwardly rectifying potassium current (\(I_{K1}\)), transient outward potassium current (\(I_{to}\)), and the slow component of the delayed rectifier potassium current (\(I_{Ks}\)). At the stage of compensatory RV hypertrophy, AP prolongation may be caused mainly by an increase in
inward calcium current \((I_{\text{Ca}})\) density\(^{56}\). Life-threatening ventricular tachyarrhythmias (ventricular tachycardia/fibrillation, VT/VF) are frequently observed in patients with left ventricular (LV) heart failure\(^{58}\). Accordingly, VT/VF incidence and electrophysiological and structural remodeling of LV in LV failure have been extensively studied. In contrast, little is known about the occurrence of VT/VF in RV heart failure secondary to PAH. In a number of studies, the reported incidence of VT/VF was low in PAH and subsequent RV heart failure\(^{59,60}\). On the other hand, VT/VF may occur in patients with congenital heart defects who were exposed to corrective cardiac surgery\(^{27}\). However, these tachyarrhythmias are often linked to the surgical scars\(^{61}\), rather than to the presence of RV overload/failure\(^{61}\). Yet, atrial tachyarrhythmias are the most common arrhythmias encountered in patients with RV heart failure secondary to chronic PAH\(^{27,59}\).

**RV heart failure due to chronic pulmonary arterial hypertension**

RV heart failure is the main determinant of poor survival of untreated patients with idiopathic PAH\(^{27, 31, 32}\), chronic thromboembolic pulmonary arterial hypertension (CTEPH)\(^{29, 62, 63}\), and other types of chronic PAH\(^{27, 64}\). Clinical experience suggests that some patients with PAH develop heart failure earlier than others despite a similar degree of pulmonary pressure\(^{27, 32}\). This leads to a variable natural history with some patients living a surprisingly long time and others dying more rapidly. Therefore, one of the important questions related to chronic RV pressure overload is identification of the factors which determine why subjects may differ substantially in their tendency to develop RV failure.

1. **Definitions and clinical features**

RV heart failure secondary to chronic PAH is a complex clinical syndrome that mainly results from the compromised ability of the RV to fill or to eject blood against chronically elevated pulmonary vascular resistance at abnormal central venous filling pressure\(^{27,28,32}\). This definition of RV failure provides a practical means of identifying RV failure clinically: RV failure is not present if there is adequate cardiac output and central
venous pressure is normal. The essential clinical manifestations of heart failure are (1) fluid retention, which may lead to peripheral edema, ascites, and anasarca; (2) decreased systolic reserve or low cardiac output, which may lead to exercise intolerance and fatigue; and (3) atrial arrhythmias. However, no single sign, symptom, or laboratory test can perfectly identify all episodes of RV heart failure. Nevertheless, decompensated RV heart failure is not present if jugular venous pressure is normal, regardless of any measured index of RV contractile function. Absence of pulmonary congestion with elevated central venous pressure is often considered to be the most specific finding of isolated RV failure; however, severe RV heart failure may result in elevated left ventricular end-diastolic pressure due to interventricular septal shift, so at least in theory pulmonary venous pressure may be able to rise to the point of causing pulmonary congestion.

2. Diagnostic tools for assessment of RV function

Methods proposed for assessing RV function include echocardiography, magnetic resonance imaging (MRI), intermittent hemodynamic monitoring, implantable hemodynamic monitors, nuclear medicine, and natriuretic peptide levels.

1. Echocardiography

The majority of the proposed methods of echocardiographic assessment of RV function are based on volumetric approximations of the RV. Such approaches have inherent limitations, firstly, because volume-related measures such as ejection fraction (EF) are load dependent, and secondly, because of the complex geometry of the RV. The issue of RV geometry is usually overcome using geometry-independent parameters such as tricuspid annular velocity. Tricuspid annulus velocity assessed by Doppler has been shown to correlate closely with radionuclide ventriculography assessed RV-EF, with Pulse Tissue Doppler-derived systolic annular velocity of <11.5 cm/s having a sensitivity of 90% and a specificity of 85% for predicting RV-EF of <45%. Tricuspid annulus plane systolic
excursion (TAPSE) is a simple and easily obtained measurement with reasonable correlation with radionuclide RV-EF and MRI-derived volumes. The development of 3D echocardiography promises reliable assessment of volumetric parameters even of such a complex chamber as the RV. However, both the short-axis summation method and, recently, the longitudinal axial plane method have also been shown to be accurate for the assessment of RV volume. Other promising tools for assessment of RV function are myocardial strain and/or strain rate and RV fractional area change measurements.

II. Magnetic resonance imaging
MRI is becoming the method of choice for early detection of RV dysfunction. In addition to producing more accurate and consistent determinations of RV end-diastolic and RV end-systolic dimensions than echocardiography, MRI is capable of measuring ventricular volumes and mass by computer processing of multiple cross-sectional areas. These measurements can then be used to calculate RV ejection fraction, cardiac output, and RV hypertrophy. RV stroke volume can be determined via volumetric flow in the pulmonary artery, and RV output can be calculated from the product of RV stroke volume and heart rate. Indices of RV function determined by serial MRIs correlate well with changes in functional capacity in patients being treated for chronic PAH.

III. Biomarkers of RV heart failure
Another approach to assess RV function in PAH is to monitor circulating levels of biomarkers such as BNP and troponin. The natriuretic peptides appear to play an important role in blunting the development of maladaptive cardiac hypertrophy. Pulmonary hypertension increases RV mRNA and circulating levels of both atrial natriuretic peptide (ANP) and BNP. Furthermore, circulating BNP levels correlate directly with pulmonary artery pressure, pulmonary vascular resistance, and right atrial pressure, and inversely with cardiac index, six-minute walking distance, and peak oxygen uptake. These findings suggest that plasma BNP can serve as a biomarker of RV overload and as a useful tool to monitor RV function in patients with chronic PAH.
Cardiac troponin, a sensitive indicator of myocardial ischemia in coronary artery disease, is another biomarker that holds promise for assessing RV function in chronic PAH. Small increases in plasma troponin levels are commonly seen in clinical situations where myocardial oxygen demand exceeds supply without acute obstruction to coronary blood flow. A rising RV pressure in PAH patients with progressive disease increases RV wall tension and oxygen demand. At the same time, reduced systemic blood pressure combined with a falling cardiac output compromises RV coronary perfusion. Under these conditions, the imbalance of oxygen supply and demand renders the RV ischemic, promoting troponin release.

3. Main therapeutic strategies for heart failure due to chronic PAH

I. RV afterload reduction

The mainstay of treatment is relief from pressure overload by reducing pulmonary arterial pressure. Patients with PAH-associated RV heart failure may benefit from prostanoid therapy, phosphodiesterase inhibitors, or endothelin receptor antagonists. All three therapies have led to a significant, but modest improvement in exercise capacity in patients with PAH. Yet, prostacyclin derivatives are potent pulmonary vasodilators, and chronic administration improves pulmonary vascular remodeling, but these agents also cause an acute increase in cardiac output that can be attributed at least partially to improvements in cardiac contractility. Pulmonary endarterectomy may be lifesaving in patients with CTEPH. Although afterload reduction cannot be achieved in all cases, increased RV wall thickness and reversal of a fetal gene expression program have not yet been investigated as potential targeted treatments.

II. RV and LV preload optimization

Diuretics are indicated when peripheral edema, hepatic congestion, or ascites become uncomfortable for patients with advanced PAH, but their use must be balanced against the need to maintain adequate RV preload. Patients with advanced RV failure may require higher filling pressures to maintain cardiac output and often will need to tolerate some
degree of volume overload. Judicious diuresis may improve RV function by returning the RV to a more favorable position on its Frank-Starling curve. In addition, adequate diuresis may dramatically improve symptoms of discomfort in the legs and abdomen swelling even without altering the severity of PAH. On the other hand, overzealous diuresis can reduce cardiac output and systemic blood pressure by excessively lowering intravascular volume. Some patients may become refractory to diuretics due to decreased cardiac output; under these circumstances, sodium and fluid restriction become important. Potassium sparing diuretics, such as spironolactone, may be useful in treating patients with chronic ascites.

In advanced disease, atrial septostomy has been used successfully to unload the failing RV. This technique creates an alternative pathway, permitting a portion of the RV preload to reach the left heart without transversing the pulmonary circulation. The resultant right-to-left shunt reduces RV work, increases LV diastolic filling but at the cost of greater arterial hypoxemia due to venous blood reaching the left atrium. Hypoxia due to right-to-left shunting across the septostomy is essentially irreversible and does not respond to supplemental oxygen. Thus, this procedure is typically used as a bridge to a more definitive procedure such as heart-lung transplantation.

III. RV contractility increase
Ideally, the strategy that aims at improving RV function should not only address reduction in afterload but also increase in contractility. However, the role of positive inotropic agents in RV failure associated with PAH is limited due to a fixed myocardial oxygen supply and a reduction of functional myocardial tissue from myocardial fibrosis and apoptosis. In end-stage RV failure, dobutamine and milrinone have been used to augment RV function as rescue therapies. Digoxin therapy for RV failure has been studied in pulmonary hypertension and chronic pulmonary disease. In severe chronic PAH, Rich and colleagues showed that digoxin, given acutely, may improve cardiac output by ~10%. Long-term studies are needed, however, to better define its role in PAH.
IV. Other therapies
Among other therapeutical options for PAH-associated RV failure, maintenance of sinus rhythm, anticoagulation, supplemental oxygen and ventilation, lung transplantation, and RV assist device implantation are of importance\textsuperscript{27,29}.

Conclusion
RV heart failure due to chronic PAH is a progressive disorder that involves both RV and LV. Neurohormonal activation, cytokine activation, altered gene expression, and ventricular remodeling may contribute to the progressive nature of the syndrome. Ongoing research will lead to a better understanding of the mechanical, electrophysiological, molecular, genetic, and neurohormonal bases of the syndrome, which will help us tailor the management of RV heart failure.
Aims and outline of the present thesis

The outcome of patients with various types of chronic PAH (for example, patients with idiopathic PAH and CTEPH) is predominantly determined by the response of the RV to the increased afterload. However, the specific mechanisms underlying the development of RV heart failure secondary to chronic PAH are not fully clear. For example, very little is known about the structural and functional evolution of RV and LV (dys)function in chronic PAH. Secondly, the underlying electrophysiological mechanisms that result in the reported low incidence of life-threatening ventricular tachyarrhythmias in patients with chronic PAH-associated RV failure are not fully clarified. Thirdly, it is unknown to what extent cardiac electrophysiological remodeling in patients with chronic PAH contributes to loss of interventricular contraction synchronicity. Finally, while surgical reduction of RV afterload by pulmonary endarterectomy is the treatment of choice for RV heart failure in patients with CTEPH, this treatment is not always effective. Thus, the identification of those patients who can benefit from pulmonary endarterectomy is of importance.

Therefore, the aims of the present thesis were:

- To characterize the sequence of changes in cardiac structure and function during development of RV heart failure secondary to chronic PAH
- To assess the incidence of tachyarrhythmias in patients with chronic PAH and relate possible changes in incidence to electrophysiological properties of RV and LV in RV heart failure secondary to chronic PAH
- To investigate the relationship between changes in electrophysiological properties of RV and LV, and interventricular dyssynchrony in patients with chronic PAH
- To study whether diastolic interventricular resynchronization improves hemodynamic in patients with RV dysfunction due to chronic PAH
- To develop novel echocardiographic predictors of outcome in patients with chronic PAH treated operatively
To address these aims, we studied patients with RV dysfunction due to CTEPH and a rat model of RV heart failure secondary to chronic PAH.

Since the results of experimental animal studies can be extrapolated to human only with limitations, it is important to choose a relevant animal model for investigation of pathophysiology and effectiveness of treatments in PAH. We discussed this issue in Chapter 2. To study RV heart failure following chronic PAH, we have chosen a well-established rat model of RV heart failure, i.e., monocrotaline injection. In order to investigate structural evolution of RV in chronic PAH, we characterized the temporal relation between the onset of PAH and development of RV heart failure in Chapter 3. In particular, RV dimensions, free-wall thickness, contractility, and systolic pulmonary arterial pressure were assessed by serial echocardiography.

In patients with chronic PAH, RV systolic peak shortening and, accordingly, diastolic relaxation is delayed with respect to LV. This RV-to-LV interventricular diastolic delay is associated with RV contractile dysfunction, altered LV diastolic filling, reduced stroke volume, and functional limitation. We hypothesized that the loss of interventricular contraction synchronicity in patients with chronic PAH is related to RV activation delay and action potential prolongation. Having tested this hypothesis in Chapter 4, we investigated whether RV-to-LV interventricular resynchronization of onset of early diastolic relaxation by atrioventricular sequential pacing improves hemodynamics in patients with RV dysfunction secondary to CTEPH. This acute proof-of-concept study is described in Chapter 5.

Since both RV and LV dysfunction occur in patients with heart failure secondary to chronic PAH, we hypothesized that structural and electrophysiological remodeling occur in both RV and LV. However, despite the occurrence of such remodeling during RV heart failure, the incidence of life-threatening ventricular tachyarrhythmias in patients with chronic PAH is low. Therefore, in Chapter 6, we studied whether electrophysiological properties of the heart during RV heart failure secondary to chronic
PAH can protect from development of ventricular tachyarrhythmias. Moreover, because LV dysfunction may contribute to symptoms of heart failure in patients with chronic PAH, in Chapter 7, we tested our hypothesis that during RV heart failure secondary to chronic PAH underfilled LV undergoes atrophic remodeling. Furthermore, we studied whether the electrophysiological remodeling in LV during RV heart failure may be explained by LV cardiomyocytes atrophy.

A particular feature in the pulmonary systolic flow velocity profile, the so-called pulmonary flow systolic notch (midsystolic deceleration in pulmonary flow, as assessed using Doppler echocardiography), may distinguish proximally located obstructions in the pulmonary arterial vasculature (surgically accessible) from distal obstructions (inaccessible). This notch occurs significantly later in systole in case of distal location. Accordingly, in Chapters 8 we tested the hypothesis that a late notch, assessed preoperatively by Doppler echocardiography, in patients with CTEPH is associated with in-hospital mortality and unfavorable mid-term hemodynamic PEA outcome.
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