The Right Heart

Sean P. Gaine
Robert Naeije
Andrew J. Peacock
Editors

Second Edition

Springer

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To Francine Schrijen, who taught me to catheterise the right heart, Jack Reeves, who inspired my interest in right ventricular function.

Robert Naeije

To my family as well as to my mentors, colleagues, and patients who have inspired and supported me along my right heart odyssey.

Sean P. Gaine

To my wife Jila and children Leila, Johnnie, and Vita who have always supported my interests in the pulmonary circulation and the right heart even though their interests lay elsewhere.

Andrew J. Peacock

Foreword

Scientific interest in the heart, and particularly the differences between the two sides of the heart, dates back over 2000 years to its earliest depiction by Hippocrates and Galen as a two-sided structure. The description of the pulmonary circulation, accompanied by more accurate speculation regarding its function, however, was only first made over a millennium later by Ibn al-Nafis in 1242. Subsequently, Vesalius performed detailed anatomical studies of the heart and lungs in the mid-sixteenth century, followed by William Harvey's first accurate description of the circulatory system in 1628.

More recent scientific study of the cardiopulmonary system came with the pioneering work by Andre Cournand and his colleagues at Bellevue Hospital in New York City in the mid-twentieth century using the novel technique of catheterisation of the right side of the heart. Their early work included detailed measurements of cardiac function in normal and disease states, particularly conditions that affect both the heart and lungs, such as acute and chronic lung diseases.

As the field of cardiology evolved from primarily observational to interventional, the bulk of cardiovascular scientific study was focused on arteriosclerotic, hypertensive, and valvular heart diseases. Nevertheless, a group of physician-scientists including Al Fishman, Bob Grover, and Jack Reeves made important contributions to our understanding of the cardiopulmonary unit in physiologic conditions such as high altitude and pathologic conditions such as pulmonary hypertension. The development of noninvasive technologies to study the structure and function of the heart and the integrated cardiopulmonary unit, including echocardiography and magnetic resonance imaging, has led to a fuller understanding of right heart function, including important concepts like ventricular interdependence. Indeed, the editors and contributors to this book performed much of this scientific work; their chapters provide the reader with a comprehensive, state-of-the art foundation necessary for both contemporary clinical care and future investigation. For example, the development of specific therapies for pulmonary vascular diseases—pharmacologic, surgical, and interventional—provide the opportunity to study how these approaches affect right heart function and may lead to novel treatments for pulmonary vascular diseases, such as measures directly targeting the diseased right heart.

The global impact of pulmonary vascular disease today remains predominant by age-old conditions such as chronic lung disease, left-sided heart failure, thromboembolic and connective tissue diseases. However, more recently

described conditions that affect the pulmonary circulation, such as infectious etiologies like the HIV, hepatitis C, and COVID-19 viruses, are major global health challenges and remain poorly understood. Their emergence underscores the importance of multidisciplinary efforts to further our understanding of the right heart and pulmonary circulation. That the contributors to this volume exemplify this multidisciplinary interest and approach sets the stage for an exciting new era of scientific progress in this field.

New York, NY, USA Lewis J. Rubin

Preface

The first edition of *The Right Heart* was published in 2014. We believe it was the first book to look exclusively at the normal anatomy and physiology of the right heart as well as the impact of disease on structure and function. It was hoped at the time that the book would take a step towards reversing the historical neglect of the 'lesser circulation' by both pulmonary physicians and cardiologists. The book was very well received with over 22,000 downloads. The growing understanding of the crucial role of the right heart as a fundamental integral component of the cardiopulmonary system has led to significant advances in our understanding since that first edition.

In this second edition, leading right heart experts from around the world have come together to explore the most up-to-date information we have gained over the past decade. The book is divided into sections on physiology, pathology and pathobiology, imaging, as well as sections on the causes of right heart dysfunction and its treatment. Previously, it was accepted that direct treatment of the pulmonary vascular abnormalities was the only way to improve right heart dysfunction by reducing RV afterload, but we realise now that direct treatment of the RV is also possible and indeed desirable.

We do hope that this book will be received with the same enthusiasm as the first edition. The 'lesser circulation' continues to grow in importance to an even wider audience beyond the pulmonologist and cardiologist to include specialists as diverse as the intensivist, radiologist, haematologist, and indeed those involved in transplantation and the development of stents and ventricular assist devices.

In 1989, Jack Reeves invited us to further explore the right heart by remarking that 'One must inquire how increasing pulmonary vascular resistance results in impaired right ventricular function'[1]. We hope after reading this edition that you will agree his invitation has been enthusiastically accepted and that real progress in our understanding of the right heart is now being made.

Dublin, Ireland — Sean P. Gaine
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[1] Reeves JT, Groves BM, Turkevich D, Morrisson DA, Trapp JA. Right ventricular function in pulmonary hypertension. In: Weir EK, Reeves JT, editors. Pulmonary vascular physiology and physiopathology. New York: Marcel Dekker; 1989. p. 325–51. Chap. 10.

Contents

Part I

Physiology, Pathology and Pathobiology

Function of the Right Ventricle

1

Jeroen N. Wessels, Frances S. de Man, and Anton Vonk Noordegraaf

From Early to Recent Ideas on RV Function

Ideas about right ventricular (RV) function have changed tremendously since the second century when Galen described the RV as merely a conduit, through which part of the blood moves to the lungs for nourishment. The remainder of the blood was thought to go through invisible pores of the septum to the left ventricle for the formation of the vital spirit [1]. It took about ten centuries before Galen's view was opposed. In the thirteenth century, Ibn Nafis disputed the existence of septum pores and stated for the first time in known history that all the blood had to go through the lungs to get from the right to the left ventricle [1, 2]. Ibn Nafis' idea about RV function was also different from Galen's view as he believed that it was responsible for thinning of the blood, making it fit for mixing with air in the lungs [2]. The origin of the idea that the right ventricle is responsible for transmission of blood through the lungs and not for their nourishment has been accredited mostly to William Harvey who described this idea in 1628 in his de Motu Cordis, about three centuries later than Ibn Nafis [3, 4]. Even though Ibn Nafis and Harvey both emphasized the role the right ventricle plays in the pulmonary circulation, centuries passed before the true importance of RV function for both the pulmonary and systemic circulation would be established. The road to this understanding started in the 1940s during which more detailed studies on RV function were performed. Several open-pericardial, open-thorax dog experiments showed that cauterization of the right ventricle did not lead to changes in systemic venous or pulmonary artery pressures [5–7]. Based on these studies it was, still then, concluded that an actively functioning RV was not essential for the maintenance of a normal pressure gradient in the pulmonary and systemic arterial tree. However, several studies conducted between 1950 and 1980 that used experimental models excluding the RV from the circulation concluded that the RV was unquestionably necessary for the maintenance of blood flow and life [8–10]. But because the models used in these studies were far from physiological, the idea of the necessity of the right ventricle for the maintenance of circulation did not gain much support. It took until 1982 to recognize the role of the RV, when it was shown that RV myocardial infarction, this time using an animal model with an intact pericardium, did lead to a reduction in cardiac output [11]. Since then, multiple studies have shown RV function to be of functional and/or prognostic significance in exercising healthy subjects and in disease states [12–15]. Thus at present, we know that the right ventricle is not just a passive conduit for systemic

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venous return: the RV plays an important role in maintaining cardiac output in both health and disease.

Physiology of RV Contraction and Relaxation

Myocyte Contraction

In both the left and right ventricles, the structural unit of a cardiomyocyte that is responsible for diastolic muscle properties and cardiac contraction is the sarcomere [16]. The sarcomeric thick (myosin) and thin (actin) filamentous proteins (see Fig. 1.1) determine the contractile properties. The third filament, titin, is responsible for the passive properties of the sarcomere. The myosin filament is composed of a body and cross-bridges. The cross-bridges consist of an "arm and head" and extend outward from the body [17]. The actin filament is made of actin and tropomyosin which form the backbone of the filament. Attached to tropomyosin is the troponin complex (troponin I, T, and C). In a relaxed state, the troponin complex is attached to tropomyosin in a manner that prevents the binding of myosin heads with actin. Cardiomyocyte contraction is initiated by the arrival of the action potential. During the action potential, calcium channels in the cell membrane open, allowing calcium to enter the cell [18]. This event triggers the release of calcium from the sarcoplasmic reticulum, which causes the main increase in the cytosolic calcium concentration (calcium-induced calcium release). The increase in free calcium concentration allows binding of calcium to the myofilamental protein troponin C, thereby changing the confirmation of the troponin complex. The result is exposure of the myosin-binding sites of the actin filament, creating the opportunity for a reaction

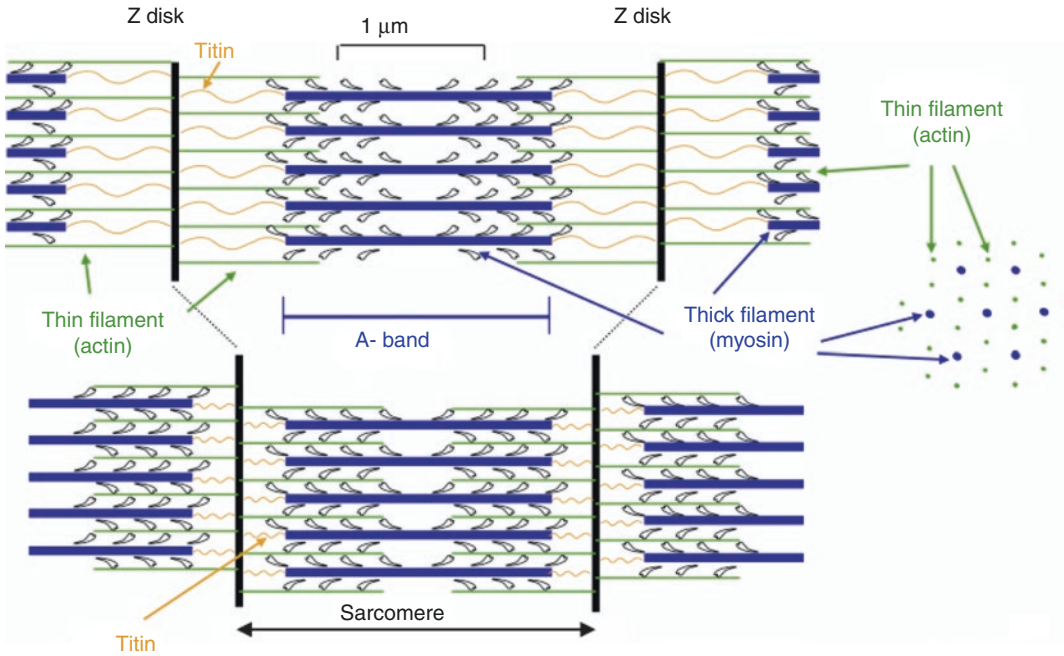

Fig. 1.1 The structural unit of a cardiomyocyte that is responsible for contraction, the sarcomere, is presented at two different muscle lengths. Each sarcomere is bounded at the end by Z-discs. Two types of filaments are shown: (1) the thick filament (blue), with the myosin heads extending from the backbone and connected to the Z-disc by a titin molecule (drawn here is one molecule instead of six), and (2) the thin filament (green), directly attached to the Z-disc. Note that both filaments overlap each other, the extension of which is dependent on muscle length. (Reprinted from Westerhof et al. [17]. With permission from Springer Science)

between actin and myosin heads resulting in sliding of actin along myosin and consequently shortening of the muscle [17, 19].

Myocyte Relaxation

After muscle shortening, calcium ions are pumped out of the cytosol back into the sarcoplasmic reticulum and to the extracellular fluid allowing the sarcomere to relax and lengthen up to its initial diastolic state [17, 18]. The sarcomeric protein that is responsible for the stiffness of the relaxed, diastolic muscle is titin (see Fig. 1.1) [20]. It is the largest protein in the human body and it extends from the Z-disc to the center of the myosin filament. It has several "springlike" regions which determine the stiffness of the protein. Alteration of phosphorylation of these regions or alternative splicing can increase or decrease titin compliance [21]. Myocardial passive tension is also influenced by extracellular collagen, especially at longer sarcomere length. However, titin remains an important contributor to total passive tension, even at large sarcomere lengths [20].

RV Contraction, Ejection, and RV Pressure Curve

That contraction of one single cardiomyocyte leads to shortening of the muscle cell is clear. A more complicated story is how the combined shortening of all the individual RV cardiomyocytes results in the ejection of blood into the pulmonary artery (PA). This is due to the complex geometry and contraction sequence of the RV. The RV is composed of two different anatomical parts, that is, the body (sinus) and the outflow tract (conus or infundibulum). The sinus contains more than 80% of total RV volume [22] and has a different fiber orientation compared to the conus. Also, the timing of contraction during the cardiac cycle is different between these two compartments [22–27]. RV contraction occurs sequentially starting at the apex of the ventricle moving in a peristalsis-like pattern towards the conus [25]. In early systole, the conus even expands before it starts to contract about 20–50 ms later than the body of the ventricle [22, 24, 26]. During early diastole, the conus' tonus partially continues and relaxation may not be seen until atrial contraction [22, 24, 26].

The net result of RV contraction is a chamber volume reduction with propulsion of blood into the pulmonary artery. This is mediated by several mechanisms. The largest contribution to RV volume decrease is shortening of the ventricle in the longitudinal direction, that is, from base to apex [28]. Another mechanism of volume reduction is movement of the RV free wall to the septum (transverse shortening) [4, 29, 30]. Several investigators have mentioned another mechanism of ejection, that is, ejection of blood due to blood momentum [31–33]. Blood momentum refers to the event of continued movement of blood mass under the late-systolic negative pressure gradient (PA > RV pressure) [8, 33]. This mechanism was originally suggested based on LV ejection hemodynamics [33], but similar observations were made on RV ejection hemodynamics. RV ejection, starting when the RV pressure exceeds PA pressure leading to pulmonary valve opening (see Fig. 1.2), continues even when myocardial muscle relaxes and ventricular pressure decreases to values lower than PA pressure. Indeed, RV ejection continues in the presence of declining RV pressure and a negative pressure gradient between the RV and PA [30, 31, 34, 35]. Both observations support the theory of blood momentum. The fact that continued ejection can occur in the course of a declining RV pressure is likely the effect of mass: moving mass continues moving even when a counteracting force exists. Importantly, the disparity between end systole (end of active myocardial shortening) and end ejection makes it necessary to assume equal use of terminology concerning the two events to avoid confusion. However, in pressure-volume analysis end systole is defined as end ejection (see description on pressure-volume analysis below).

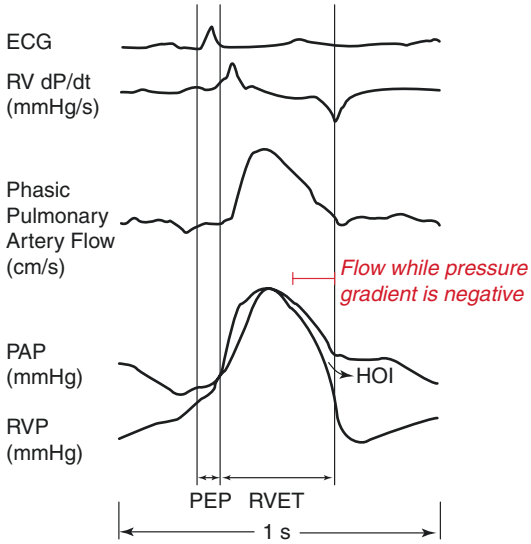

Fig. 1.2 Simultaneously recorded electrocardiogram (ECG), right ventricular (RV) d*P*/d*t*, pulmonary artery (PA) flow, PA and RV pressure. Note the short duration of the pre-ejection time (PEP) and the negative pressure gradient visible during late ejection. *HOI* hangout interval, *RVET* RV ejection time, *PAP* pulmonary artery pressure, *RVP* right ventricular pressure. (Reprinted from Dell'Italia and Walsh [35]. With permission from Elsevier)

Influence of LV Contraction on RV Ejection

The RV is connected in series with the LV; this is called *series* ventricular interaction [36]. As a result, RV stroke volume will greatly determine LV filling and subsequently LV stroke volume. Consequently, factors that influence RV output will also affect LV output. Diseases that affect RV function are described in detail in subsequent chapters in this book.

On top of the indirect *series* interaction, a *direct* ventricular interaction occurs as both ventricles share the interventricular septum, have intertwined muscle bundles, and are enclosed by one single pericardium [8, 36]. Because the pericardium encloses the septum-sharing ventricles and is highly resistant to acute distention, the compliance of one ventricle is influenced by the volume and pressure of the other ventricle [37–39]. Also during systole, ventricular interaction can be observed as LV contraction influences pressure development in the RV [36, 40]. Approximately 20–40% of the RV systolic pressure development may result from LV contraction [41].

Although ventricular interactions are present in healthy subjects, negative consequences of ventricular interaction manifest only in disease states. For example, in pulmonary arterial hypertension, LV diastolic filling is impaired by both a reduced RV stroke volume resulting from an increased pulmonary vascular resistance (*series* ventricular interaction) and leftward ventricular septum bowing resulting from RV pressure and volume overload (*direct* ventricular interaction) [42].

Description of RV Function

The cardiovascular system has the essential task to provide the tissues in our body with sufficient nutrients and oxygen. Therefore, it is important to maintain cardiac output at an adequate level. Since the left and right ventricles are connected in series, cardiac output is more or less similar for both. Often used methods to determine RV cardiac output are thermodilution or the direct Fick method during a right-heart catheterization [43]. Cardiac output is determined by stroke volume and heart rate. Cardiac magnetic resonance imaging (MRI) is a noninvasive method to assess RV stroke volume. With MRI, aortic and pulmonary flows can be measured. Stroke volume can also be determined by taking the difference between end-systolic and end-diastolic volume. It holds for all methods that both LV and RV measurements can be used to determine stroke volume, since it should be the same for both ventricles. Please note that when valvular insufficiency or a shunt is present, the use of ventricular volumes is not accurate [44]. Despite the fact that stroke volume is the net result of RV contraction, it only gives a limited amount of information about RV function per se. Stroke volume is first of all determined by RV filling (preload). Stroke volume is further determined by RV myocardial function (ventricular contractility) and by the load that opposes RV ejection (arterial system, afterload). Therefore, to understand RV myocardial function,

load-independent measures are needed as provided by ventricular pressure-volume analysis.

The Ventricular Pressure-Volume Loop

The first person to describe the cardiac cycle by means of a pressure-volume graph was Otto Frank in 1898 [17, 45]. He described pressure changes during isovolumic (non-ejecting) contractions at various filling volumes and showed maximal pressure increases with increasing diastolic volume. Later, in 1914, Starling described ejection against a constant ejection pressure and found increased stroke volumes with increased filling. The combination of the two findings is what we nowadays call the Frank-Starling mechanism, which will be explained in detail in the section "Regulation of RV Function" below.

A pressure-volume loop describes the changes in ventricular pressure and volume observed during the cardiac cycle (see Fig. 1.3a for a schematic presentation). The cardiac cycle can be divided into four different phases: (1) the filling phase, (2) isovolumic contraction phase, (3) ejection phase, and (4) isovolumic relaxation phase. During the filling phase, RV volume increases considerably while RV pressure only slightly changes [46]. After the onset of contraction, RV pressure increases rapidly. The pulmonary valve opens when RV pressure exceeds PA pressure, thereby ending the isovolumic contraction phase. Normally, this RV isovolumic contraction phase is of short duration due to the low PA pressures (see also Fig. 1.2) [47]. In the ejection phase RV pressure peaks early to subsequently rapid decline during late ejection [48]. During late ejection, a negative pressure gradient between the RV and PA can be observed; this is referred to as the hangout interval (see Fig. 1.2) [35]. The isovolumic relaxation phase starts at pulmonary valve closure and pressure declines back to its initial value.

The information that can be derived from a single pressure-volume loop includes stroke

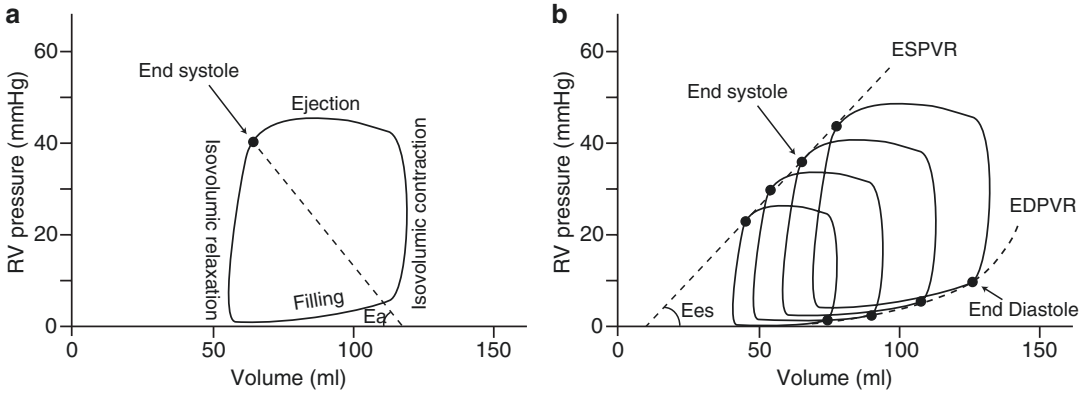

Fig. 1.3 (**a**) Schematic presentation of a pressure-volume (P-V) loop of a single beat. Diastole (or the filling phase) starts after tricuspid valve opening (lower left corner P-V loop). At this moment, the volume in the ventricle is at its minimum, corresponding to end-systolic volume (ESV). During the filling phase, volume increases up to maximum filling, that is, end-diastolic volume (EDV). Contraction leads to an increase in pressure (isovolumic contraction) until the pulmonary valve opens. This is the start of ejection. After valve closure, isovolumic relaxation occurs with a rapid decrease in pressure until the intracardiac valve opens again and the ventricle reenters its filling phase. Right ventricular ejection fraction (RVEF) can be calculated from a single pressure-volume loop by dividing stroke volume and end-diastolic volume, and then multiplying by 100%. Effective arterial elastance (E_a) is a measure of RV afterload and calculated as the slope of the dotted line from the end-systolic P-V point to the *x*-intercept at EDV. (**b**) Schematic representation of multiple pressure-volume loops obtained during gradual preload reduction. Note that the end-diastolic pressure-volume points can be connected by a nonlinear line, the end-diastolic pressure volume relation (EDPVR). Also shown is the linear end-systolic pressure volume relation (ESPVR) and its slope E_{es} (end-systolic elastance)

volume, end-diastolic volume, end-systolic volume, and ejection fraction (calculated from end-diastolic volume and stroke volume, see Fig. 1.3a). The information that these parameters give about RV myocardial properties is limited. However, if multiple loops under alteration of loading conditions (preferable preload reduction by vena cava occlusion [17]) are collected, information on both systolic and diastolic properties of the ventricle can be obtained.

Systolic Properties: The End-Systolic Pressure-Volume Relation

Figure 1.3b gives a graphical representation of multiple pressure-volume loops obtained during preload reduction [49]. Although multiple pressure-volume loops can also be acquired by changing afterload, the preferable method is preload reduction, since changes in afterload are more likely to affect the systolic and/or diastolic properties one wishes to measure [50]. When multiple pressure-volume loops are obtained during preload reduction, for example by partial vena cava occlusion using a balloon catheter, both the end-systolic and end-diastolic pressure-volume points can be connected by a line (see Fig. 1.3b). The line connecting the end-systolic pressure-volume points is referred to as the end-systolic pressure-volume relation (ESPVR). This relation is reasonably linear over a physiological range in both the LV and the RV [34, 51, 52]. Therefore, in practice, linearity is assumed for the ESPVR. The slope of the ESPVR is called end-systolic elastance (E_{es}) and due to the assumption of linearity it can be described by the following formula: $E_{es} = P_{es}/(V_{es} - V_0)$, where P_{es} is end-systolic pressure, V_{es} is end-systolic volume, and V_0 is the so called intercept volume of the ESPVR. E_{es} is used as a measure of myocardial contractility for several reasons. First of all, positive and negative inotropic agents such as catecholamines and acute B-blockade, respectively, increase or decrease E_{es} [46, 51–56]. In addition, E_{es} is assumed independent of pre- or afterload, and therefore considered load independent [34, 56].

In theory, elastance is a measure of stiffness in terms of pressure and volume and the idea that ventricular properties could be described by elastance came from Suga's work on the isolated heart, where the time-varying elastance concept was proposed in the late 1960s [57]. The time-varying ventricular elastance implies that the heart changes its stiffness during the cardiac cycle, with maximal elastance occurring near or at end systole. More extensive information on the theory of time-varying elastance can be found elsewhere [17, 45].

Considerations for the Application of RV ESPVR and E_{es}

For the assessment of changes in contractile state one should consider that the measured ventricular properties, both systolic and diastolic (see below), are influenced by the amount of muscle mass, myocardial properties, and ventricular configuration [45, 50]. Therefore, a shift of the ESPVR in an acute setting (where muscle mass and ventricular configuration are constant) reflects a change in myocardial contractility. However, in a clinical setting muscle mass or ventricular configuration may change over time and an observed shift in the ESPVR can therefore not only be attributed to a change in myocardial contractility [50].

The Cardiopulmonary System

The systolic properties of the right ventricle have to be seen in light of its load [58]. The pulmonary circulation is a low-pressure, high-compliance system in contrast with the systemic circulation. Because the afterload for the right ventricle is low, there is no need for a high E_{es}. However, during exercise, or in disease states in which the

afterload increases, the E_{es} has to increase as well [59, 60]. An appropriate measure to describe the afterload is called effective arterial elastance (E_a), which is a measure of total resistance [61]. It can be determined by the ratio of end-systolic pressure to stroke volume (see Fig. 1.3b). In healthy individuals, the transfer of energy from the right ventricle to the pulmonary artery is optimal. In other words, RV contractility is adequately matched to the afterload. This concept is called coupling and is represented by the ratio of E_{es}/E_a. Both E_{es} and E_a describe the function of a subsystem (right ventricle and pulmonary circulation, respectively), independently of each other. The function of the cardiopulmonary system as a whole results from the interaction of these subsystems. Stroke volume, for example, is determined not only by RV function, but also by afterload. Other often used parameters that result from functional interaction include cardiac output, RV ejection fraction, and pulmonary artery pressure [60].

Diastolic Properties: The End-Diastolic Pressure-Volume Relation

In contrast with the rather linear end-systolic pressure-volume relation, the diastolic pressure-volume relation is nonlinear (see Fig. 1.3b) [45, 50]. The end-diastolic pressure-volume relation (EDPVR) shows that at low volumes pressure increases only minimally for a given increase in volume. At higher volumes the pressure rise for an increase in volume is progressively larger, which gives the EDPVR its characteristic nonlinear curve [50]. The sarcomeric structures responsible for the steeper rise in pressure at larger filling volumes are the titin molecules, while outside the sarcomere the extracellular matrix (collagen) resists the further stretching of the myocyte [50, 62]. Diastolic elastance can be measured like systolic elastance with multiple pressure-volume loops under quick alteration of preload and reflects the passive properties of the ventricle (see Fig. 1.3b) [50]. However, because of the nonlinearity of the EDPVR, nonlinear regression analysis is mandatory to obtain a curve fit and a diastolic stiffness constant [50, 63]. RV diastolic stiffness can be described by the slope of the EDPVR at end-diastolic volume. This measure is called end-diastolic elastance (E_{ed}) [64].

Single-Beat Analysis of E_{es} and E_{ed}

Because the measurement of systolic and diastolic elastances as described above requires simultaneous measurement of RV pressure and volume including an intervention on ventricular loading, this measurement is not easy to apply in a clinical setting and may even be contraindicated in some patients. To overcome these problems, more applicable methods have been developed that do not require multiple pressure-volume loops. These so-called single-beat analyses are available for both the left and right ventricles and for both the systolic [53, 65, 66] and diastolic elastance [63]. Results of the single-beat method to calculate the coupling of E_{es}/E_a are comparable to the multiple-beat method [67].

Regulation of RV Function

The regulation of RV function can best be illustrated by its response to changes in volume and afterload. The RV ventricular response to filling (diastolic) volume is described by the Frank-Starling mechanism and is based on the alteration of the sensitivity of the myofilaments to calcium, as will be described below [18]. The response of the right ventricle to changes in afterload is mediated by neurohormonal mechanisms. Cardiac output can further be altered by changes in heart rate. For mechanisms of subacute and chronic alterations in contractility and diastolic function we refer to the chapters on disease states with altered ventricular loading by volume and/or afterload.

Volume Response: The Frank-Starling Mechanism

The Frank-Starling mechanism refers to the observation that with increasing ventricular end-diastolic volume, stroke volume simultaneously increases. Changes in end-diastolic volume are usually mediated by changes in venous return. Consequently, stroke volume is regulated by venous return in most conditions [19]. At a molecular level the Frank-Starling mechanism refers to the observation that with greater sarcomere length at the start of contraction, a greater force is generated. This is caused by an altered myofilamental sensitivity to calcium by stretching. The proposed mechanism for this altered myofilamental sensitivity has long been the theory of "lattice spacing" [68]. This theory is based on a decrease in spacing between the filaments upon stretching. Consequently, the binding of myosin heads to actin is more likely to occur, thereby increasing force per amount of calcium available. Recently, another explanation has been put forward [68]. It was observed that the stretching of sarcomeres favorably alters the orientation of the myosin heads, making it easier to bind with the actin filament. According to these new findings, the Frank-Starling mechanism may be largely explained by favorable alteration in myosin head orientation, and to a lesser extent by lattice spacing.

Afterload Response: Sympathetic Activation

When the afterload of the right ventricle is acutely increased, stroke volume will decrease if no compensatory mechanisms existed. However, compensatory mechanisms do exist and stroke volume can be maintained to a certain extent under altered loading conditions. One mechanism to maintain stroke volume is by the Frank-Starling mechanism as described above. This occurs when the RV's end-diastolic volume increases as a result of the increased afterload. Another mechanism to maintain stroke volume in an acute setting is through an increase in contractility, facilitated by sympathetic nervous system activation. Sympathetic activation of the heart occurs through B-adrenergic receptors that are localized on cardiomyocytes. Stimulation of B-adrenergic receptors leads to an increase in contractility (inotropy) through increased availability of free intracellular calcium. Sympathetic activation also slightly reduces myofilamental calcium sensitivity. However, the increase in intracellular calcium availability outweighs this reduction [18]. Secondly, sympathetic activation leads to faster relaxation (lusitropy) as a result of a faster reuptake of calcium ions by the sarcoplasmic reticulum and consequently a faster release of calcium from the myofilaments.

A secondary, slower mechanism that increases contractile force has been described by Gleb von Anrep [69]. The so-called Anrep effect refers to the observation that after the initial response, cardiomyocytes further increase their contractile force slowly over the following minutes [69]. The Anrep effect results from autocrine/paracrine mechanisms involving stretch-induced release of angiotensin II and endothelin. More detailed information on the Anrep phenomenon can be found elsewhere [69, 70].

Conclusions

RV function is important in both healthy individuals and disease states. The right ventricle has a complex geometry consisting of two different anatomical parts and RV contraction occurs in a peristaltic-like pattern. In the healthy right ventricle, ejection continues after maximal shortening and in the presence of a negative pressure gradient. Despite the complex hemodynamics, RV systolic and diastolic function can be described by a time-varying elastance. RV output is highly sensitive to changes in filling, which is mediated through the Frank-Starling mechanism, and increases in afterload. An accurate description of RV function incorporates so-called load-independent measurements.

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Right Ventricular Pathobiology

2

Vineet Agrawal, Evan Brittain, and Anna R. Hemnes

Introduction

Right ventricular (RV) function is a strong, independent prognostic indicator of outcomes in a number of disease states including valvular heart disease, ischemic and nonischemic cardiomyopathy, pulmonary embolism, and pulmonary arterial hypertension (PAH), among others [1–4]. Despite the recognized importance of RV function in these diseases, the underlying pathobiology of RV failure is poorly understood [5]. Global RV function is primarily determined by three dynamic factors: preload, afterload, and myocardial contractility. The primary inputs of RV afterload are pulsatile reflections from the main pulmonary arteries (PA) and early bifurcations, impedance of the proximal PAs, and arteriolar resistance (pulmonary vascular resistance, PVR). RV contractility is a reflection of loading conditions, adrenergic state, heart rate, medications, metabolic status, and ventricular interdependence. How these three facets of RV function alter or are altered by molecular changes in the RV myocardium are in their infancy of mechanistic understanding, but undoubtedly powerfully affect outcomes in situations of RV stress and may be independent targets of therapy. This chapter focuses on the pathobiology of right-heart failure in chronic pulmonary hypertension and highlights areas of recent advances in our molecular understanding of RV function and dysfunction.

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RV Functional Decline and Recovery Are Highly Variable

RV failure is a heterogeneous clinical problem. Some patients develop severe RV failure at a given elevation in PA pressure and PVR whereas others maintain long-term preservation of RV function given the same hemodynamic profile. For example, many patients with congenital heart defects who develop Eisenmenger physiology maintain normal RV function for decades despite systemic PA pressures [6]. Relatively good outcomes in Eisenmenger patients are postulated to be related to the development of compensatory RV hypertrophy or persistence of the fetal gene program, but ultimately these mechanisms are not well understood. In many diseases, the RV exhibits a remarkable capacity for functional recovery after insult, for example after RV myocardial infarction or pulmonary thromboendarterectomy [7]. A molecular understanding of

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the mechanisms mediating RV decline and recovery will improve our understanding of RV failure and aid in the development of RV-targeted therapy.

RV Failure Is in Part Independent of Pulmonary Hemodynamics

In diseases primarily affecting the pulmonary vasculature such as chronic thromboembolic pulmonary hypertension (CTEPH) and PAH, outcomes more closely mirror RV function and reverse remodeling than improvement in pulmonary hemodynamics [5]. There is increasing recognition that elevated RV afterload is not the sole determinant of RV failure and that RV function often declines despite significant improvement in pulmonary hemodynamics in response to medical therapy. Van de Veerdonk et al. showed that decline in RV function despite a clinically significant decline in PVR was associated with significantly worse survival in patients with PAH [8]. Additional evidence includes the good outcomes of patients with pulmonic valve stenosis and Eisenmenger's syndrome who develop adaptive RVH and the lack of RV failure in experimental models of RV pressure overload using pulmonary artery banding [6, 9]. These findings suggest that the development of RV failure depends not just on elevated afterload from pulmonary vascular resistance and large vessel stiffness but also on additional pathogenic mechanisms. Because RV functional decline is in part independent of pulmonary vascular disease, therapies directed at RV function may lead to improved outcomes. The lack of currently available RV-specific therapies stems from an incomplete understanding of the molecular mechanisms of RV failure.

Pathology of RV Failure

Despite well-characterized pulmonary vascular pathology, the pathology of RV failure has not been well studied. In addition to gross increase in mass, RV myocyte hypertrophy is well described in the context of PAH [5]. Changes in capillary density or size, role of fibrosis, and differences across the clinically variable causes of RV failure are little described in humans. Several causes of acute RV failure, such as pulmonary embolism and RV infarction, are associated with RV myocardial necrosis [10], but this is not described in chronic causes of RV failure such as PAH. Little comparative information is available about RV pathology in the WHO groups of pulmonary hypertension, but data from humans suggesting that diseases such as scleroderma-associated PAH has disproportionate RV failure [11–13] may point to different patterns of RV pathology in this disease.

On a gross level, it is clear that RV hypertrophy is a key feature of the strained and failing RV. At the time of birth and switch from fetal to adult circulation patterns, the RV undergoes a profound shift from being a high-pressure, high-resistance pump to a low-pressure, high-flow conduit for blood to enter the pulmonary circulation. Mechanical changes including high oxygen tension in the lungs and closure of the patent ductus arteriosus facilitate this switch, but the molecular changes of the RV at this time are unknown. What is clear is that the RV in the adult is a thin-walled structure with a morphology that is described elsewhere in this edition. In situations of acquired increased PVR, the RV increases in size, i.e., hypertrophies, to transition from a flow conduit to a pressure pump. This switch is thought to be required to maintain cardiac output in the face of increased load stress and thus adaptive. However, over time, the RV often fails and thus transitions to maladaptive hypertrophy. In congenital heart disease lesions that include persistent elevations in pulmonary pressure after birth, the RV often retains the capacity to generate high pressures through persistent adaptive hypertrophy. This may underlie the well-described improved survival in congenital heart disease-associated PAH compared with idiopathic PAH in which the elevated pulmonary vascular resistance occurs in the adult circulation [14]. Molecular triggers of this switch from compensated hypertrophy to failing RV are presently unknown and active areas of research.

Molecular Mechanisms of RV Failure

Several molecular mechanisms have been identified to contribute to RV failure in animal models and humans including myocardial ischemia, neurohormonal activation, metabolic dysregulation and mitochondrial dysfunction, sex hormone signaling, and maladaptive myocyte hypertrophy. Ultimately, many of these processes potentiate one another leading to a cycle of worsening myocardial failure (Fig. 2.1). Chronic myocardial ischemia leads to mitochondrial dysfunction and abnormal energy substrate utilization that then fails to provide adequate ATP for efficient myocardial contraction. Ischemia is worsened by the development of maladaptive RVH and a compensatory increase in contractility is compromised by β(beta)-receptor downregulation from chronic neurohormonal stimulation. Much progress has been made in our understanding of these processes in recent years with most available data coming from experimental models of PAH and human cardiac imaging.

Ischemia and Angiogenesis

RV failure has been associated with both macro- and microvascular ischemia. We will touch on macrovascular ischemia first. Patients with PH develop increased myocardial wall stress due to increased RV pressure and dilation resulting in an increased myocardial oxygen demand [15]. A decrease in systemic blood pressure resulting from poor cardiac output combined with an increase in RV pressure augments a decrease in coronary perfusion pressure resulting in ischemia, often manifesting as chest pain in patients with PAH both at rest and with exercise [16]. Right ventricular myocardial ischemia has been documented in PAH using myocardial scintigraphy and correlates directly with increases in RV diastolic pressure [17]. Detailed study of coronary flow patterns in PAH demonstrates a decrease in systolic flow in the right coronary artery compared to healthy controls and a decrease in total flow with increasing RV mass, indicating an imbalance between myocardial supply and demand [18]. Additional factors may contribute to supply/demand mismatch in PAH such as coronary compression from increased wall tension and hypoxemia due to impaired gas exchange.

In addition, there is growing evidence of microvascular dysfunction in the RV as well [19]. Initially noted, capillary loss and failure of new capillary growth in proportion to myocyte hypertrophy were demonstrated to differentiate angioproliferative models of experimental PAH from RV pressure-overload models. In an experimental

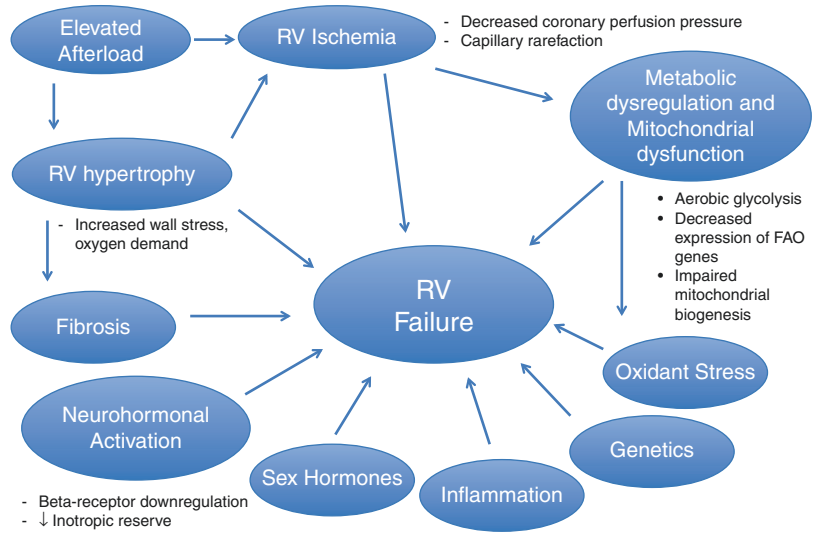

Fig. 2.1 Molecular mechanisms of RV failure. Alone or in combination, the various mechanisms pictured have been implicated in the development of RV failure. Several molecular mechanisms of RV failure such as RV ischemia and hypertrophy occur primarily as a result of elevated RV afterload. However, others such as metabolic dysregulation and mitochondrial dysfunction may be inherent features of PAH

model of PAH using the vascular endothelial growth factor (VEGF) receptor blocker (SuHx), RV failure was associated with decreased RV capillary density accompanied by a reduction in VEGF mRNA and protein transcription [9]. Capillary density and VEGF expression were unchanged in a model of early, adaptive hypertrophy using pulmonary artery banding, providing further evidence that RV failure is not governed solely by elevated afterload and highlighting the potentially critical role of decreased oxygen delivery in the failing right heart. Reductions in both VEGF and capillary density were shown in the monocrotaline model of PAH and genetically engineered reductions in VEGF have been shown to reduce capillary volume in the mouse myocardium. Capillary density is also decreased in RV myocardium from humans with PAH who died of RV failure [20]. These data suggest that VEGF production in PAH may be insufficient to induce adequate angiogenesis relative to cardiac hypertrophy, resulting in RV ischemia. While capillary rarefaction is present in RV failure, it is unknown if reversal of this condition improves RV function. One particular mechanism underlying rarefaction may be miR-126 which is decreased in failing human RVs and mouse models of RV failure, while increased expression of miR-126 was associated with improved vascular density and RV function [21]. Moreover, the relevance to human disease has been called into question by studies using stereology to define RV vascularity in which the failing human PAH RV had an increase in total vascular length [22]. Further study is needed to understand the role of vascular volume in the failing RV.

There is an emerging literature supporting dysregulated angiogenesis, not simply insufficient capillary volume, in the failing RV. There are many regulators of angiogenesis that are relevant to the RV [23] including genetic and epigenetic modulators [24, 25], transcription and growth factors, and immune cells that have been extensively reviewed elsewhere [26]. Perhaps best studied is VEG-F as described above. It is important to note that many studies use VEG-F inhibition in combination with hypoxia (SuHx) to study RV failure and thus there may be, not surprisingly, alterations in angiogenesis genes in this model compared to controls [27]. In addition, it is presently unknown if restoration of normal angiogenesis is beneficial to the RV. In general, animal studies have focused on models of pulmonary vascular disease where independent effects on the RV cannot be discerned [23].

Neurohormonal Activation in RV Failure

Neurohormonal activation is likely both a cause and a consequence of RV failure. Elevated RV afterload results in an increase in norepinephrine to increase inotropy and renal vein hypertension decreases renal perfusion resulting in renin-angiotensin-aldosterone systemic (RAAS) activation. As in left-heart failure, the initial compensatory mechanisms of sympathetic system and RAAS activation ultimately become detrimental in patients with right-heart failure. After prolonged stimulation, this results in downregulation of β(beta)-receptors impairing RV inotropic reserve and worsening RV failure. There is abundant evidence of neurohormonal activation in patients with RV failure: increased heart rate with reduced heart rate variability [28], increased plasma norepinephrine levels [29], decreased β_1-receptor density in the RV in PAH, and increased muscle sympathetic nerve activity [30]. In addition, hyponatremia, an indirect marker of RAAS activation, is associated with reduced survival and RV failure in PAH [31]. Within the RV, there are data that this system is relevant to RV failure. Boehm et al. demonstrated that increase in the pulmonary artery banding model increased mineralocorticoid receptor expression in the RV, though there was no improvement in RV function with eplerenone administration [32]. Focusing on angiotensin II, Friedberg and colleagues did demonstrate that losartan reduces RV hypertrophy and fibrosis in the pulmonary artery banding model, suggesting the relevance of this pathway to RV load stress responses [33].

The role of the sympathetic and parasympathetic nervous system has also been queried in the failing RV and has been recently described in

detail [34]. There are limited data on therapeutic interventions to blunt neurohormonal activation in RV failure. In the case of β-blockers, clinical dogma has held that patients with RV failure are heart rate dependent and β-blockers would impair both chronotropic and inotropic reserve [35]. However, evidence from preclinical models of RV failure suggests a potential benefit from β-blockers [36–38]. In the SuHx and monocrotaline PAH models, carvedilol, a $\beta_{1,2}$- and $\alpha(\text{alpha})_1$-blocker with potentially beneficial pleiotropic effects, was found to improve RV function and increase exercise capacity compared to vehicle-treated animals. These effects were associated with an increase in protein kinase G, decreased myocardial fibrosis, and increased RV capillary density [38]. Similarly, the β_1-receptor blocker bisoprolol improved RV function in experimental PAH [23]. Early-phase clinical trials have been published with somewhat conflicting data on the effects of β-blockade in human PAH [39, 40], but they have generally not been adopted in clinical practice as therapy for RV failure. Elevated pulmonary aldosterone expression is present in PAH and correlates directly with endothelin-1 secretion [41]. Treatment with aldosterone antagonists in the SuHx and monocrotaline PAH models reduces pulmonary pressure and PVR without significant systemic side effects [42]; however there are no definitive trials of mineralocorticoid receptor antagonists in RV failure, only demonstrations of their safety [43]. Interestingly, recent data has suggested that impaired parasympathetic nervous system activity is present in PAH-associated RV failure and that drugs to increase activity may be beneficial [44]. Human trials are, however, presently lacking on these interventions.

Right Ventricular Metabolism and Mitochondrial Function

In patients with PH, chronically increased pulmonary pressure and pulmonary vascular resistance result in a stimulus for compensatory RV hypertrophy (RVH), thereby increasing myocardial metabolic demand. Decreased coronary perfusion pressure and capillary rarefaction limit oxygen supply, leading to RV ischemia and oxygen supply/demand mismatch. Evidence from both experimental models and human PAH suggests that the ability of the myocardium to maintain energy substrate flexibility in the setting of RVH and ischemia is an important determinant of RV failure. In the normal adult heart, fatty acid oxidation accounts for the majority of energy supply and metabolic flexibility exists to use glucose as an additional fuel source. Recent evidence suggests that RVH and RV failure is associated with increased utilization of glycolysis for ATP production, even in the setting of abundant oxygen when oxidative metabolism would otherwise be used [45, 46]. This process, well described in cancer cells, is hypothesized to be advantageous because these cells are less reliant on oxygen for energy production and can therefore proliferate in regions of relative hypoxia [47]. Direct measurement of increased RV glycolysis has been demonstrated in the monocrotaline PAH model [48]. Increased glycolysis (and decreased glucose oxidation) in this model is shown to be due to increased pyruvate dehydrogenase kinase (PDK) activity, which inhibits conversion of pyruvate (the product of glycolysis) to acetyl CoA, the substrate for Krebs cycle initiation. Failure to produce additional ATP from glucose oxidation results in decreased oxygen consumption and impaired RV function. Increased RV glucose uptake in human PAH has been shown in several studies using ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) [49–51]. Although this suggests an increase in glycolysis given the findings in experimental PAH, it is difficult to draw definitive conclusions because FDG uptake does not directly measure glycolysis but simply glucose uptake. Combination of FDG with other PET tracers measuring oxidative metabolism may help determine the relative activity of glycolysis and fatty acid oxidation in the human RV.

Glucose oxidation and fatty acid oxidation are reciprocating processes in the mitochondria—as one increases the other decreases and vice versa through Randle cycle [52]. This feedback facilitates metabolic flexibility, which is particularly

critical for myocardial function in times of nutritional restriction. This cycle has been exploited for therapeutic purposes in experimental PAH in which the PDK inhibitor dichloroacetate and fatty acid oxidation inhibitors trimetazidine and ranolazine have improved RV function [53, 54]. However, recent data from our group and others has shown that impaired fatty acid oxidation may underlie RV failure in PAH [55–58]. Our group first demonstrated that in both human PAH RVs and in a rodent model of BMPR2 mutation with RV failure, there is lipid deposition consistent with lipotoxicity. This lipid accumulation is due to both increased lipid import into cardiomyocytes and impaired mitochondrial fatty acid oxidation, and the net result is increased cytoplasmic triglyceride and ceramide causing lipotoxicity [56, 57]. Others have demonstrated similar findings in the SuHx rodent model [58]. Importantly, lipid deposition is not a unique feature of end-stage RV failure and is demonstrable in humans with early RV strain [55]. Whether lipid deposition is reversible is an unanswered question. There is some preliminary data from a pilot study of metformin, which enhances fatty acid oxidation in addition to increasing glucose sensitivity, that this drug may reduce RV lipid content in humans with PAH [59], but more data is needed. Other approaches to modulating fatty acid oxidation such as PPARγ have shown promise in preclinical studies [27, 60, 61] and may be appropriate for further study in humans.

Mitochondrial dysfunction is present in both adaptive and maladaptive RVH and forms the basis for the abnormal energy metabolism observed in RV failure described above. RV failure in the monocrotaline model of PAH is associated with decreased expression of genes required for fatty acid oxidation and mitochondrial biogenesis as well as reduction in mitochondria number per gram of tissue and oxidative capacity [62]. Similar mitochondrial dysfunction was not observed in a pulmonary artery banding model suggesting that mitochondrial metabolic remodeling may be an inherent feature of RV failure in PAH and not simply a consequence of elevated RV afterload. The observation of mitochondrial hyperpolarization in RV tissue from humans with PH further indicates the presence of mitochondrial dysfunction in RVH [63]. Dysfunction in mitochondria including number, size, and master regulators of biogenesis has been extensively studied and published in PAH and well described elsewhere [23].

There are early trials of metabolic interventions in the failing RV in PAH targeting RV metabolism. The pilot study of metformin was discussed above. Dichloroacetate, an inhibitor of PDK, has been studied in a clinical trial where its effect was primarily in the pulmonary vasculature and appeared to be modulated by sirtuin-3 and uncoupled protein 2 gene variants [64]. Clinical trials of ranolazine, which inhibits fatty acid oxidation, are presently listed in clinicaltrials.gov but have not been published yet. In summary, while it is well accepted that there is metabolic dysfunction in the RV in PAH, many questions remain about how, when, and if intervention on these abnormalities will improve RV function.

Sex Hormones

Although PAH has been known for decades to be female predominant [65, 66], it has recently come to light that males with PAH tend to have worse outcomes than women with PAH [67, 68]. This observation has led to studies of the effects of sex hormones on the RV, as poorer RV function has been identified in males with PAH [68–70]. Not surprisingly, cardiomyocytes express receptors for sex hormones and are capable of sex hormone production and metabolism [71, 72]. Findings of sex hormones in the plasma of patients with PAH have been recently reviewed [23] and there is a growing literature on the molecular underpinnings of these observations. Estrogen (E2) has been recently identified to have RV-protective effects. Using hormone depletion and repletion experiments, Frump et al. showed that E2 reduces RV hypertrophy, improves function, and, on a molecular level, reduces pro-apoptotic signaling, oxidative stress, and mitochondrial dysfunction using rodent models [73–75]. There has been limited research

on testosterone in the RV, where it appears to cause increased fibrosis and excess mortality in the pulmonary artery banding model [76]. There are ongoing trials of modulation of estrogen signaling using tamoxifen (clinicaltrials.gov NCT03528902) and anastrozole (clinicaltrials.gov NCT03229499) and the effects of these interventions on RV function will be closely assessed. A pilot study of anastrozole suggested potential safety for the RV [77].

Other Causes of RV Failure

Additional contributing mechanisms for RV failure may include inflammation, oxidant stress, and fibrosis though the relative importance of these processes is not well understood. Myocardial fibrosis is present on cardiac MRI (CMR) in patients with RV failure as well as histology in experimental models of PAH. Fibrosis on CMR correlates with pulmonary hemodynamics and independently predicts clinical worsening in PAH [78]. Whether fibrosis is a consequence of chronic myocardial mechanical strain or myocardial ischemia [46] or an independent pathologic process as a result of endothelial cell dysfunction is not known [79, 80]. Recent work has called into question the hypothesis that all fibrosis is maladaptive as there may be a role for collagen in strengthening the myocardium in an adaptive effort to preserve function in the context of increased load stress [81]. Evidence of RV fibrosis and its molecular origins have been reviewed elsewhere [81].

Genetics of RV Failure

BMPR2

A major hindrance to the study of right-heart failure has been the limitations of currently available animal models. Monocrotaline, SuHx, and pulmonary artery banding all have heterogeneous effects on RV size and function and are of questionable relevance to human diseases. Transgenic models would facilitate a more detailed molecular dissection of the signaling pathways key to the development of RV failure. Archer et al. have used the fawn-hooded rat to identify the key metabolic derangements in RV failure [82]. Our group has described worse survival in patients with heritable PAH compared with idiopathic PAH that may be due to impaired RV compensation in heritable PAH [83]. Heritable PAH is most commonly associated with mutations in the bone morphogenic protein receptor type 2 (BMPR2), for which there are transgenic rodent models [84, 85]. As above, we have found evidence of reduced fatty acid oxidation intermediaries associated with lipid deposition in humans with heritable PAH and in transgenic mice with similar mutation that is universally expressed [55–57]. Moreover, hypertrophic responses in this strain appear to be impaired [86]. The use of transgenic models to study RV failure will facilitate a deeper molecular understanding of the mechanisms that drive the development of this syndrome with particular relevance to humans and potentially point to new, effective therapeutic targets.

RV Failure in Non-group 1 PH

Despite the growing recognition of the importance of RV failure in non-group 1 PH, little is known about the molecular mechanisms underlying RV failure in the absence of PAH. Clinical and translational studies, however, suggest that PAH-related RV failure may share pathophysiologic overlap with PAH-related RV failure, specifically with respect to metabolic dysregulation [23, 87–89]. In the subset of patients with PH due to left-heart disease, patients with concomitant obesity or metabolic syndrome are at the greatest risk for adverse structural RV remodeling and development of RV failure [89, 90]. Supporting the connection between obesity, metabolic syndrome, and RV failure, recent translational studies have also identified that obesity is associated with activation of a unique transcriptional program in myocardial biopsies from patients with heart failure and RV dysfunction, and isolated RV cardiomyocytes from obese patients with heart failure show impaired contractility

compared to nonobese patients with heart failure [91]. However, the precise molecular pathways that lead to RV failure from obesity and metabolic syndrome in non-PAH-related conditions are less well understood because relatively few preclinical models have systematically investigated RV function [92–94]. In two models utilizing rodents prone to obesity and insulin resistance in the presence of high-fat diet, RV dysfunction was an early manifestation of heart failure [93, 94], somewhat similar to phenotypes that have been identified in humans [87]. One study identified the natriuretic peptide clearance receptor (NPRC), a gene highly upregulated in the setting of obesity and associated with insulin resistance [95], as the most upregulated gene in the diseased RV [94]. The second study identified both cardiac and extracardiac dysregulation of metabolism by sirtuin-3, an intracellular regulator of mitochondrial function and AMP kinase, as a primary driver of RV dysfunction [93]. Broad metabolic dysregulation and mitochondrial dysfunction have also been reported in multiple studies of diabetic cardiomyopathy-related RV failure (reviewed in [96]).

Future Directions

Preclinical studies of metabolic modulation have shown promise for the treatment of RV failure and pilot clinical trials of metabolic therapy for RV failure in human PAH are underway (metformin and exercise clinicaltrials.gov NCT03617458). If successful, metabolic modulators may represent the first RV-specific heart failure therapies. Whether these therapies will be efficacious in RV failure of other etiologies is unknown. A parallel focus on RV function in addition to pulmonary vascular disease is critical given the strong prognostic power of RV function in PAH. Future clinical trials of pulmonary vasodilator therapies should also include RV-specific functional outcomes [97]. Additional clinical studies are needed to determine the optimal medical management for acute RV failure, including a direct comparison of different inotropic agents.

The current noninvasive evaluation of RV function with echocardiography and CMR is largely descriptive and does not allow for early detection of impending RV failure. Molecular imaging tools that provide a more mechanistic understanding of RV pathophysiology should be expanded and potentially extended into clinical practice. PET imaging with metabolic tracers such as FDG, ^{11}C acetate, and others can provide detailed information about mitochondrial function and metabolic remodeling in the RV. PET may ultimately provide superior biomarkers and clinical trial endpoints of therapeutic efficacy compared to conventional metrics. Finally, given the impact of metabolic dysregulation on RV function, broad metabolite profiling may provide novel insights into the metabolic etiology of both acute and chronic RV failure. Because they are downstream of transcription, translation, and posttranslational modifications, metabolites reflect early alteration in the body's response to disease. A metabolomics approach has previously been used to detect early metabolic changes after myocardial infarction and identify markers of cardiopulmonary fitness [98, 99] and may bear fruit in the study of RV failure.

References

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