Sean P. Gaine
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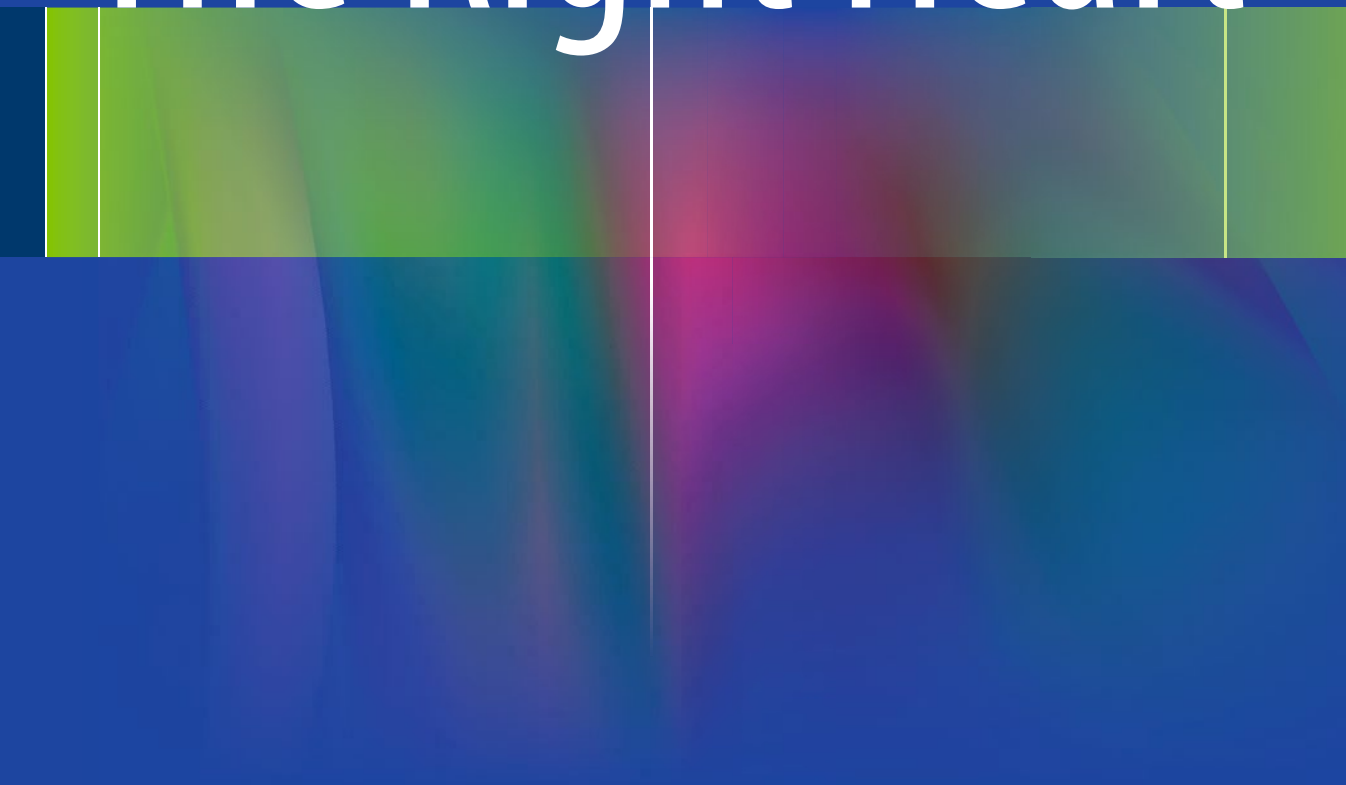
Editors

The Right Heart



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To my wife Jila and my children Leila, Johnnie and Vita, who have had to endure my enthusiasm for pulmonary circulation and the right heart over a number of years despite the fact that their own enthusiasms lie in different areas. Somehow they continue to retain their sense of humour.

Andrew John Peacock

From Dublin to Baltimore and back; to my mentors for their inspiration, colleagues at home and abroad for their support, my family for their understanding and our patients who make it all worthwhile.

Sean Gaine

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

Robert Naeije

Foreword

While Middle Age anatomists first recognized the unique anatomic features that distinguish the two sides of the heart, it is only in the last century that scientists have had the tools to explore the structural and functional characteristics that differentiate the systemic and pulmonary circulations. Technologies to investigate cardiac function in the clinical setting, from cardiac catheterization to echocardiography and magnetic resonance and radionuclide imaging, have not only revolutionized diagnosis and treatment of diseases primarily affecting the left heart, but also have more recently been applied to gain a fuller understanding of right heart structure and function in normal and disease states. Following the path of the early pioneers of cardiopulmonary physiology such as Andre Cournand, Dickinson Richards and their colleagues at Bellevue Hospital in New York in the late 1940s and 1950s, a global coterie of physiologists, molecular biologists, pharmacologists, and specialists in respiratory medicine, cardiology, imaging and other disciplines has emerged with the objective of gaining a deeper understanding of the central role played by right heart adaptation and compensation in normal and disease pulmonary circulatory states. This renewed interest in the right heart is timely and welcome, as clinical advances in treatment of pulmonary vascular diseases over the past several years have primarily targeted the vasculature, with little attention paid to targeting the failing right heart as well. The importance of this work, and the progress that has been achieved over just the past decade, are nowhere made more clearly evident than in this monograph expressly dedicated to the right heart.

Future advances in the treatment of pulmonary vascular disease will depend not only on the application of molecular biologic tools to identify novel mechanisms responsible for altered pulmonary vascular proliferation and develop drugs that target these pathogenic pathways, but on the recognition of the right heart as an important therapeutic target in its own right. The heart may be an innocent bystander in the early pathogenesis of pulmonary vascular disease, but it is the capacity of the right heart to deal with the increased afterload that ultimately dictates the outcome for patients with pulmonary hypertension. By compiling this comprehensive state-of-the-art text on the subject, the editors have provided an indispensible reference and guide for future work to those interested in the integrated cardiopulmonary circuit.

La Jolla, CA
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Lewis J. Rubin, MD

Preface

> One must inquire how increasing pulmonary vascular resistance results in impaired right ventricular function[1]

The right heart has, in the past, been neglected by both pulmonary physicians and cardiologists. Pulmonary physicians saw it as part of the heart and therefore not of interest to them, whereas cardiologists viewed it as merely a conduit of blood to the lungs and therefore not of great interest to them either. It is now realised that the right heart is a fundamental integral component of the cardiopulmonary system and that its function can be deranged when there are abnormalities of the heart itself – whether left or right – and when there is an abnormality of the pulmonary circulation. We now realise that the right heart, which normally has a load of only 15 % of the left, has a fundamental role in cardiopulmonary performance in normals, in those with left heart disease, in those with intrinsic right heart disease whether congenital or acquired and in those with pulmonary hypertension.

In this book, a distinguished group of international authors have brought together all the knowledge about the right heart that we have gained over the last few years. The book starts with an examination of the structure, function and imaging of the normal right heart both at rest and also under the stress of exercise or high altitude. It continues with a detailed examination of the pathophysiology and pathobiology of right heart dysfunction, both in experimental models and human disease, including congenital heart disease. Finally we deal with right heart dysfunction caused by pulmonary hypertension.

Most right heart dysfunction is a consequence of increased afterload due to the increased impedance caused by pulmonary hypertension, whether due to abnormalities in the arterial wall (pulmonary arterial hypertension) or obstruction caused by acute or chronic thromboembolism. However, there is an increasing realisation that even in these conditions, where the principle pathology is in the pulmonary circulation, there may be changes in RV biology which are amenable to specific treatment. In the treatment section, we have concentrated on direct treatment of the right ventricle rather than treatment of the pulmonary vasculature which has been dealt with in other texts.

[1] Source: Reeves JT, Groves BM, Turkevich D, Morrisson DA, Trapp JA. Chapter 10. 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.

To this end, we have looked at cardiac transplantation, arrhythmic cardiomyopathy and the treatment of acute right heart failure.

We hope this book will appeal to respiratory physicians, cardiologists and intensivists, all of whom must now surely share our belief that the right heart is a fundamental cog in integrated cardiopulmonary performance.

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The Normal and Abnormal Right Heart: Introduction to a Clinical Classification

1

Mandeep R. Mehra, Myung H. Park,
Michael J. Landzberg, and Aaron B. Waxman

Abstract

Often misunderstood, the right heart has been generally underappreciated in phenotypic expression of cardiopulmonary disorders. Success with left heart failure has led to a more vivid illumination of the importance of right heart dysfunction in determining clinical outcomes. Isolated right heart failure can be seen in pathology such as right ventricular infarction, but it typically occurs in the setting of an anatomico-physiological dislocation from its principal structures (the right ventricle) and adjoining circuits (systemic venous system, pulmonary circulation and the left heart). In this introductory chapter, we shall review the normal structure of the right ventricle, define the distinction between right ventricular and right heart failure, discuss an international definition for this unique clinical syndrome and propose a clinically relevant classification to facilitate a universal conversation.

Often misunderstood, the right heart has been generally underappreciated in phenotypic expression of cardiopulmonary disorders. Success with left heart failure has led to a more vivid illumination of the importance of right heart dysfunction in determining clinical outcomes. Isolated right heart failure can be seen in pathology such as right ventricular infarction, but it typically occurs in the setting of an anatomico-physiological dislocation from its principal structures (the right ventricle) and adjoining circuits (systemic venous system, pulmonary circulation and the left heart). In this introductory chapter, we shall review the normal structure of the right ventricle, define the

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distinction between right ventricular and right heart failure, discuss an international definition for this unique clinical syndrome and propose a clinically relevant classification to facilitate a universal conversation.

The Normal Right Heart System

In order to understand and appreciate the normal right, one must first define its elements. The *International Right Heart Failure Foundation* collaborative working group definition provides clarity in this regard [1]. This group defines the *right heart circulatory system* elements as those that fundamentally participate in the handling of deoxygenated blood from the systemic veins up to the pulmonary capillaries. Thus, the right heart system can be subdivided into systemic and pulmonary circuits. While the pulmonary circuit includes the main pulmonary artery (post pulmonic valve), secondary and tertiary branches of the pulmonary arteries, the systemic circuit includes the systemic veins, right atrium, coronary sinus (and cardiac venous drainage), tricuspid valve, right ventricular free wall, right ventricular outflow tract and pulmonic valve. The pulmonary and systemic capillary beds are shared equally between the right and the left sided circulatory systems.

The structure that garners most attention within the right heart is the right ventricle (RV) and while it anatomically shares contiguity with the remainder of the heart, its embryological origins, genetic make-up, post birth remodeling changes and interactive characteristics are unique and distinct. The RV and outflow tracts are developed from the anterior heart field with its own unique genetic pathways and cellular physiology while the remaining three chambers develop from the primary heart field [2]. Shaped like a crescent, the RV characteristically contracts using a "bellows" peristaltic motion, facilitated predominantly by longitudinal fibers in contradistinction to the left ventricle where the participation of longitudinal and circumferential fibers allows for a more cylindrical contractile motion. This difference works well, in health for the RV, since it functions against a low impendence pulmonary circuit. Thus, the RV is 1/6th in comparison to left ventricular mass and 1/4th in generating stroke work [3]. Three distinct compartments characterize the RV chamber components –the inlet, the coarsely trabeculated myocardium (with its moderator band), and the outlet (infundibulum or conus) tightly linked to the left ventricle through the pulmonary circulation, the interventricular septum and the myocardium inside the pericardium. The RV wall has circumferential myofibers in the subepicardium that encircle the sub-pulmonic infundibulum. At the apex, spirally arranged superficial myofibers invaginate to form longitudinally aligned subendocardial deep myofibers oriented toward the base [4].

Although the structure and shape as well as inherent elastic properties of the normal RV are similar to the left ventricle (LV), a distinct trapezoidal pressure-volume relationship exists compared to the LV's more rectangular one [5]. In health, the RV is coupled to the pulmonary vascular circulation's low hydraulic impedance and failure implies a disturbance in this tightly coupled physiology.

The RV differs from the LV in its genetic and neurohormonal make-up. Early in life, the wall thickness and force generated by the RV and LV are equal. In the first year after birth, the RV involutes and increases its compliance. Since pulmonary hypertension that exists early in life as a consequence of congenital heart disease syndromes does not allow the RV to involute, it may well be the reason why a distinctly favorable profile of prognosis is observed in these settings in contradistinction to pulmonary hypertension developing late in life after regression of RV muscle mass [6]. The cellular neurohormonal basis of RV adaptation is also distinct from the LV. With increasing pulmonary pressures, the RV expresses endothelin-1 and phosphodiesterase-5 mRNA and protein, two unique neurohormonal profiles not observed in the LV in response to increased strain [7].

The RV is uniquely protected against ischemia [8]. Due to the low preload and afterload, its oxygen requirements are lesser and during stress, the

RV is able to achieve adequate increases in oxygen extraction. The lower intramyocardial pressures allow coronary blood flow in both diastole and systole, and branches from the right and the left coronary artery dually supply the free wall. A transcoronary gradient from the left to right also favors collateral development, another protection against ischemia.

The Abnormal Right Heart System

The International Right Heart Failure Foundation working group defines ***right heart failure as a disturbance in any component that comprises the right heart circulatory system*** [1]. It is important to emphasize that this definition is overarching and beyond just the monocentric view of the RV chamber and its perturbations. Thus, ***Right Heart Failure is defined as a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to sub-optimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures – at rest or with exercise*** [1].

This definition broadly includes sub-clinical and clinical manifestations of anatomico-physiological-functional disturbances in the right-sided circulatory system, thereby also allowing inclusion of a variety of etiologies not restricted to the RV. Importantly, abnormalities uncovered during exercise alone that manifest as right heart dysfunction are embraced by this definition. This definition is designed to include most lesions that include the RV or could occur before the RV (pre-tricuspid). There will certainly be exceptions to this definition but it is hoped that this will include most common entities and presentations of right heart failure.

An anatomic lesion in the right heart system leads to a dynamic alteration in preload stress, afterload, and contractility insufficiency. Preload stress is a function of the overall return of intravascular volume from the vena cava and the manifest tricuspid valve (TV) gradient. The contributors to right heart afterload include the usually negligible resistance at the level of the pulmonary valve, pulsatile flow reflected back from the main pulmonary arteries and their bifurcations and the impedance of the proximal PAs and arterioles, typically referred to as pulmonary vascular resistance (PVR) [8]. Although PVR is most often used as a surrogate for right heart afterload, it may be inaccurate since it does not account for reflectance pressures. Furthermore, in those situations where there is more proximal disease in the pulmonary vessels such as with chronic thromboembolic pulmonary hypertension (CTEPH), the PVR may underestimate the afterload. Contractile insufficiency of the RV represents the result of dynamic changes in preload stress and afterload but is equally dependent on cellular metabolism, heart rate, adrenergic influences and ventricular interdependence.

In a manner similar to the LV, volume overload is better tolerated than pressure overload by the RV. As an example, chronic tricuspid regurgitation or high flow states such as a large atrial septal defect with left to right shunting can be tolerated for years before right heart dysfunction becomes clinically overt. In an unconditioned RV as with a massive acute pulmonary embolus, small changes in pulmonary pressures lead to large effects on circulatory outputs and systemic pressures. The septum plays a critical role in preserving RV function through its participation in ventricular interdependence. When the RV becomes volume overloaded and dilated, the septum bows to the left, compromises LV filling and may therefore compromise left sided output. Upto 1/3rd of right-sided stroke work is due to septal contraction and even if the free wall is severely dysfunctional, increasing systemic pressures and LV contractility can enhance right heart function by improving coronary perfusion and recruiting septal work.

Right heart failure is associated with poor outcomes across diverse diagnoses including congenital heart disease, left heart failure, acute and chronic pulmonary embolism, valve disease, post-cardiac transplantation, post-LVAD implantation, and post-valve surgery [7]. In pulmonary arterial hypertension, the trajectory of an adverse prognosis is intricately linked to the behavior of the right heart. As RV failure worsens, the PA

pressures tend to drop and so become uncoupled from a prognostic standpoint. Similarly, in states of adequate RV adaptation to the rising pulmonary pressures, a coupled RV to the PA is associated with a better prognosis [9]. As RHF becomes manifest, one can first uncover symptoms only during exercise or with advancing stages, congestion and edema, abdominal pain from organ enlargement, altered appetite due to gastrointestinal congestion and hepatorenal failure become evident.

Yet, the right heart demonstrates considerable plasticity. The RV has a remarkable ability to improve its function, restore adaptation and even normalize its structure once the inciting insult can be overcome. The most vivid examples of RV plasticity are noted with amelioration of CTEPH with pulmonary thromboendarterectomy or after lung transplantation [10, 11]. In these situations, RV recovery is not generally noted immediately after surgery but rather within 2 months. This is contrary to the LV where, reverse remodeling in response to removal of the inciting lesion can take upwards of a year to be fully manifest. Another important issue relates to correction of preload stress for RV recovery to occur. In situations where right heart afterload is decreased with a left ventricular assist device (LVAD), RV failure often persists (although it may also worsen). This is due to the altered RV geometry by the suction forces from the LVAD that distort the septal motion and insertion points of the tricuspid leaflets. Importantly, preload to the RV is increased by the enhanced cardiac output [12]. It is therefore conceivable that for adequate right heart failure recovery to occur, we need to restore the physiology of not only afterload but also preload stress.

Right Heart Failure: Towards a Uniform Classification

Whether one seeks to approach the right heart for enhanced understanding through research or for a clinical therapeutic intervention, a structured and uniform language to describe the aberrations will be important. The International Right Heart Failure Foundation has proposed a set of principles to develop such a nomenclature [1]. In this proposal, it is recommended that the classification follow a structured etiology, anatomy, physiology and functional disturbance description. Thus, it is important to describe the basis of the etiology (congenital or acquired; infectious, hematological, inflammatory, autoimmune etc.), the precise anatomic defects (primary locations and secondary lesions), the altered physiology in the three distinct areas of preload stress, afterload and contractile insufficiency and finally the more clinically relevant functional abnormality by describing subjective changes (patient reported symptoms, quality of life, activity profiles), objective changes (cardiopulmonary exercise testing, 6 min walk test), limitations (obesity, orthopedic) and end organ effects (hepatorenal syndromes, protein losing enteropathy).

In summary, the right heart circulatory system should not be confused with just the RV; a universal definition of RHF can be applied broadly to include aberrations at rest or those that are subclinical, manifested only with extreme stress. A uniform structured classification system will allow for an enhanced understanding of the disease state, allow development of more accurate descriptions and help us in more focused targets for therapy.

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Part I

Physiology, Pathology and Pathobiology

Function of the Right Ventricle

2

Pia Trip, Nicolaas Westerhof,
and Anton Vonk Noordegraaf

Abstract

The role that the right ventricle (RV) plays in the body circulation is only recently acknowledged. Especially in disease states, RV function may be of great importance. As such, knowledge on RV function in both health and disease is essential for clinicians. The present chapter provides current knowledge available on RV function, starting with a brief description of ideas on RV function that have passed from the second century up to now. This will be followed by a portrayal of the physiology of cardiomyocyte and RV contraction and relaxation. Furthermore, the most used and up till now most applicable method to describe RV myocardial systolic and diastolic function in terms of their stiffness ("elastances") using the systolic and diastolic pressure-volume relationships will be explained in detail. Finally, factors that are known to regulate function will be discussed.

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From Early to Recent Ideas on RV Function

The idea of the function of the right ventricle (RV) has changed tremendously since the second century when Galen described the RV as merely a conduit through which part of the blood is moving to the lungs for nourishment. The remainder of the blood was thought to go through invisible pores of the septum to the left ventricle (LV) 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

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blood had to go through the lungs to get from the RV to the LV [1, 2]. Ibn Nafis's idea about the function of the RV was also different from Galen's view as he believed that RV function was for the thinning of the blood, making it fit for mixing with air in the lungs [2]. The origin of the idea that the RV functions for the 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 RV 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 in which more detailed studies on the function of the RV were performed. Several open-pericardial open thorax dog experiments showed that cauterization of the RV 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 RV 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, using an animal model with now an intact pericardium, did lead to a reduction in cardiac output [11]. Since then, multiple studies have revealed 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 RV is not just a passive conduit for systemic venous return: the RV plays an important role in maintaining cardiac output in both health and disease.

Physiology of RV Contraction & Relaxation

Myocyte Contraction

In both the left and right ventricle, 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) filamental proteins (see Fig. 2.1) determine the contractile properties. The myosin filament is composed of a body and cross-bridges. The cross-bridges providing an 'arm and head' extending outward from the body [17]. The actin filament is made of actin and tropomyosin that forms the backbone of the filament and 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 between actin and the 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. 2.1) [17].

RV Contraction, Ejection and the 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 cardiomyoctes 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 RV body (sinus) and outflow tract (conus or infundibulum). The sinus contains more than 80 % of total RV volume [20] and has a different fiber orientation compared to the conus, which is discussed in greater detail in Chap. 1. Not only fiber orientation is different between the body and outflow tract. Also the timing of contraction during the cardiac cycle is different between these two compartments [20–25]. RV contraction occurs sequentially starting from the apex of the

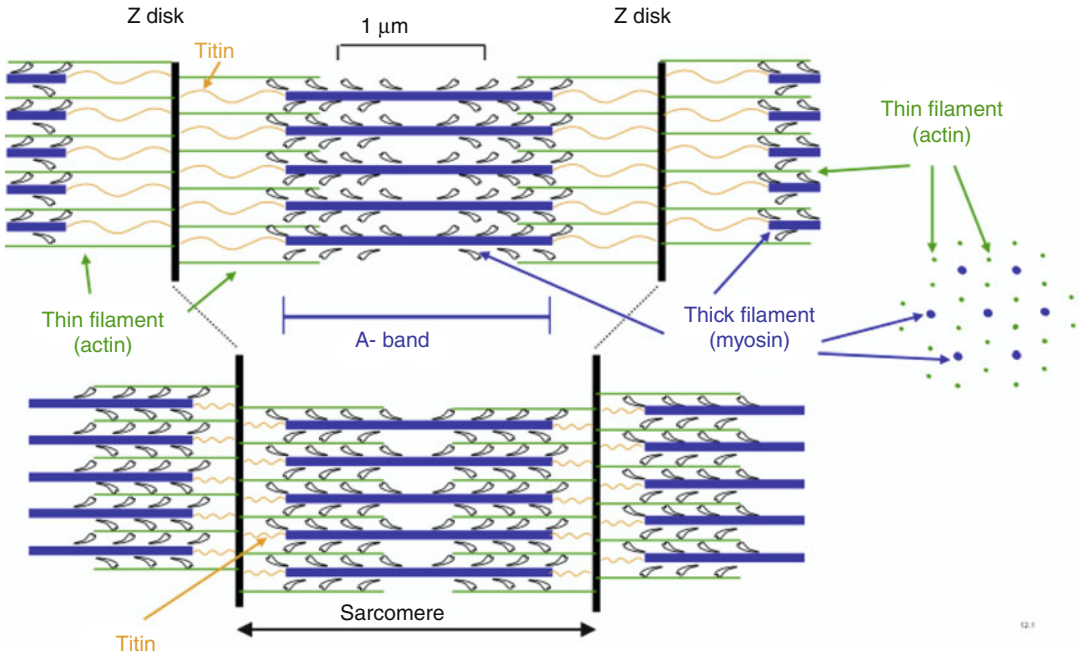

Fig. 2.1 The structural unit of a cardiomyocyte that is responsible for contraction, the sarcomere, is presented at two different muscle lengths. Each sarcomere is bounded at the end by Z-discs. Two type of filaments are shown: (1) the thick filament (*blue*), with the myosin heads extending from the 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 extend of which is dependent on muscle length (Reprinted from Westerhof et al. [17]. With permission from Springer Science)

ventricle moving in a peristalsis-like pattern towards the conus [23]. In early systole, the conus even expands before it starts to contract about 20–50 ms later than the body of the ventricle [20, 22, 24]. During early diastole, the conus's tonus partially remains and relaxation may not be seen until atrial contraction [20, 22, 24].

The net result of RV contraction is a chamber volume reduction with the propulsion of blood into the pulmonary artery. RV chamber volume reduction is mediated by three mechanisms. The largest contribution to RV volume decrease is shortening of the ventricle in the longitudinal direction, that is from base to apex [26]. Other mechanisms of volume reduction are movement of the RV free wall to the septum (transverse shortening) and bulging of the septal wall into the RV cavity [27, 28]. Several investigators have mentioned another mechanism of ejection, that is ejection of blood due to blood momentum [29–31]. Blood momentum refers to the event of continued movement of blood mass under the late-systolic negative pressure gradient (PA > RV pressure) [8, 31]. The idea of this mechanism was originally based on LV ejection hemodynamics [31], 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. 2.2), continues even when myocardial muscle relax 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 [28, 29, 32, 33]. 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).

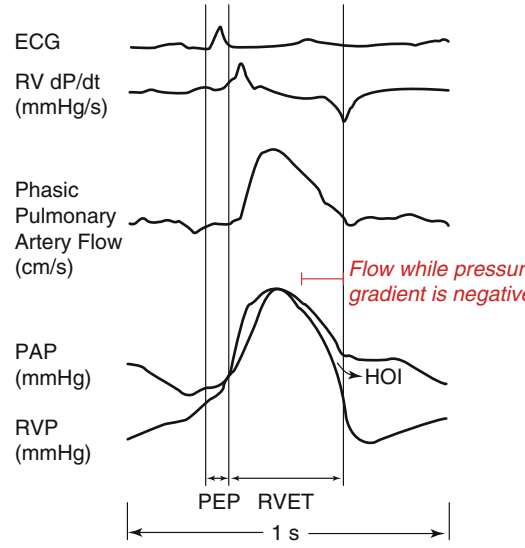

Fig. 2.2 Simultaneously recorded electrocardiogram (*ECG*), right ventricular (RV) dP/dt, pulmonary artery (PA) flow, PA and RV pressure. Note the short duration of the pre-ejection time (*PEP*) and the negative pressure gradient visible during late ejection. *HOI* hangout interval, *RVET* RV ejection time, (*PAP*) pulmonary artery pressure (*RVP*) right ventricular pressure (Reprinted from Dell'Italia and Walsh [33]. 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 [34]. 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, 34]. 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 [35–37]. Also during systole, ventricular interaction can be observed as LV contraction influences pressure development in the RV [34, 38].

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 by leftward ventricular septum bowing resulting from RV pressure and volume overload (*direct* ventricular interaction) [39].

Description of RV Function

The result of RV ejection is stroke volume. RV stroke volume can be easily measured during right heart catheterization. When cardiac output is measured by for example thermodilution, stroke volume can be calculated by dividing cardiac output by 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. Also, when ventricular end-systolic and end-diastolic volumes are known stroke volume can be calculated by taking the difference between the two volumes. It holds for all methods that both LV and RV measurements can be used to determine stroke volume, since stroke volumes of both ventricles should be the same. Notable, when mitral or tricuspid regurgitation is present the use of ventricular volumes is not accurate [40]. Despite of 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, 41]. He described pressure changes during isovolumic (non-ejecting) contractions at various filling volumes and showed that 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, and that will be explained in detail in the section on regulation on RV function below.

A pressure-volume loop describes the changes in ventricular pressure and volume observed during the cardiac cycle (see Fig. 2.3a 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. Unlike the rectangular shape of the LV pressure-volume loop, in a healthy person with normal PA pressures the RV pressure-volume loop is more triangular in shape. During the filling phase, RV volume increases considerably while RV pressure only slightly changes [42]. 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. 2.2) [43]. In the ejection phase RV pressure peaks early to subsequently rapidly decline during late ejection [44]. 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. 2.2) [33]. 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 volume, end-diastolic volume, end-systolic volume, and ejection fraction (calculated from end-diastolic volume and stroke volume, see Fig. 2.3a). The information that these parameters give about RV myocardial properties is limited. However, if multiple loops under alteration of loading conditions (preferable preload reduction

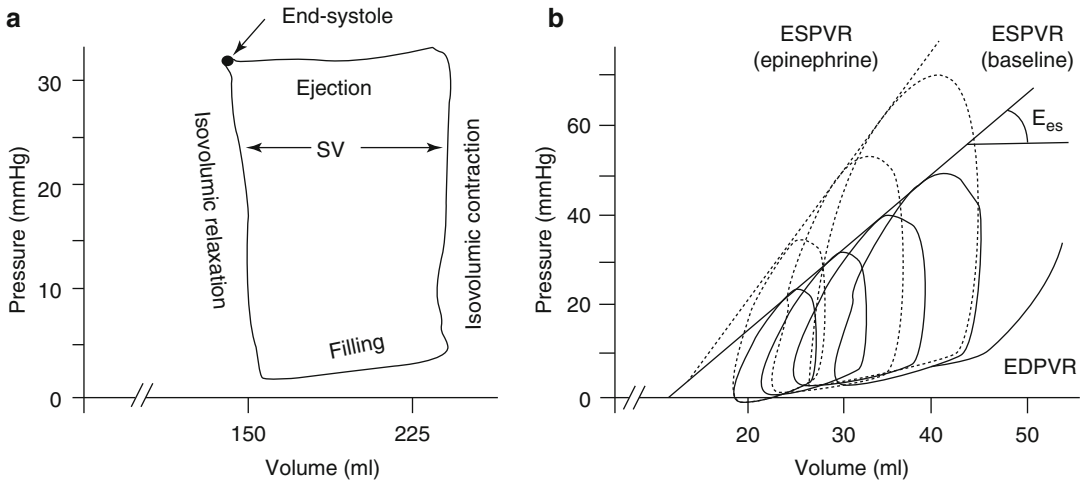

Fig. 2.3 (**a**) Schematic presentation of a pressure-volume (P-V) loop of a single beat. Diastole (or the filling phase) starts after tricuspid (or mitral) valve opening (lower left corner P-V loop). At this moment, the volume in the ventricle is at its minimum, corresponding to end-systolic volume (ESV). During the filling phase, volume increases up to maximum filling, that is end-diastolic volume (EDV). Starting of contraction leads to an increase in pressure (isovolumic contraction) until the pulmonary (or aortic) 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, then multiplying by 100 %. (**b**) Multiple pressure-volume loops obtained during gradual preload reduction in an isolated right ventricle in two conditions: (1) baseline (*solid lines*) and (2) after inotropic intervention with epinephrine (*broken lines*). 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) (Modified from Maughan et al. [42]. With permission from Wolters Kluwer Health)

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 2.3b gives a graphical representation of multiple pressure-volume loops obtained during preload reduction [45]. 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 [46]. 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. 2.3b). 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 [32, 47, 48]. 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 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 increases and decreases E_{es} respectively [42, 47–52]. In addition, E_{es} is assumed independent of pre- or afterload, and therefore considered load-independent [32, 52].

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 [53]. The time-varying ventricular elastance implies that the heart changes its stiffness during the cardiac cycle, maximal elastance occurring near or at end-systole. More extensive information on the theory of time-varying elastance can be found elsewhere [17, 41].

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, the myocardial properties, and ventricular configuration [41, 46]. Therefore, a shift of the ESPVR in an acute setting (where muscle mass and ventricular configuration is 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 [46].

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. 2.3b) [41, 46]. 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 [46]. 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 [46]. 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. 2.3b) [46]. However, because of the nonlinearity of the EDPVR nonlinear regression analysis is mandatory to obtain a curve fit and a diastolic stiffness constant [46, 54].

Single-Beat Analysis of E_{es} and E_d

Because the measurement of systolic and diastolic elastances as described above requires simultaneously measured pressures and volumes including an intervention on ventricular loading, this measurement is not easy to apply in a clinical setting and may even be contraindicated in some diseased patients. To overcome these problems, more applicable methods have been developed that do not require multiple pressure-volume loops. These so-called single-beat analysis are available for both the left and right ventricle and for both the systolic [49, 55, 56] and diastolic elastance [54].

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 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 RV to changes in afterload is mediated by neurohormonal mechanisms. Cardiac output can further be maintained or increased by changes in heart rate. For mechanisms of subacute and chronic alterations in contractility 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 volumes, stroke volume simultaneously