Sean P. Gaine
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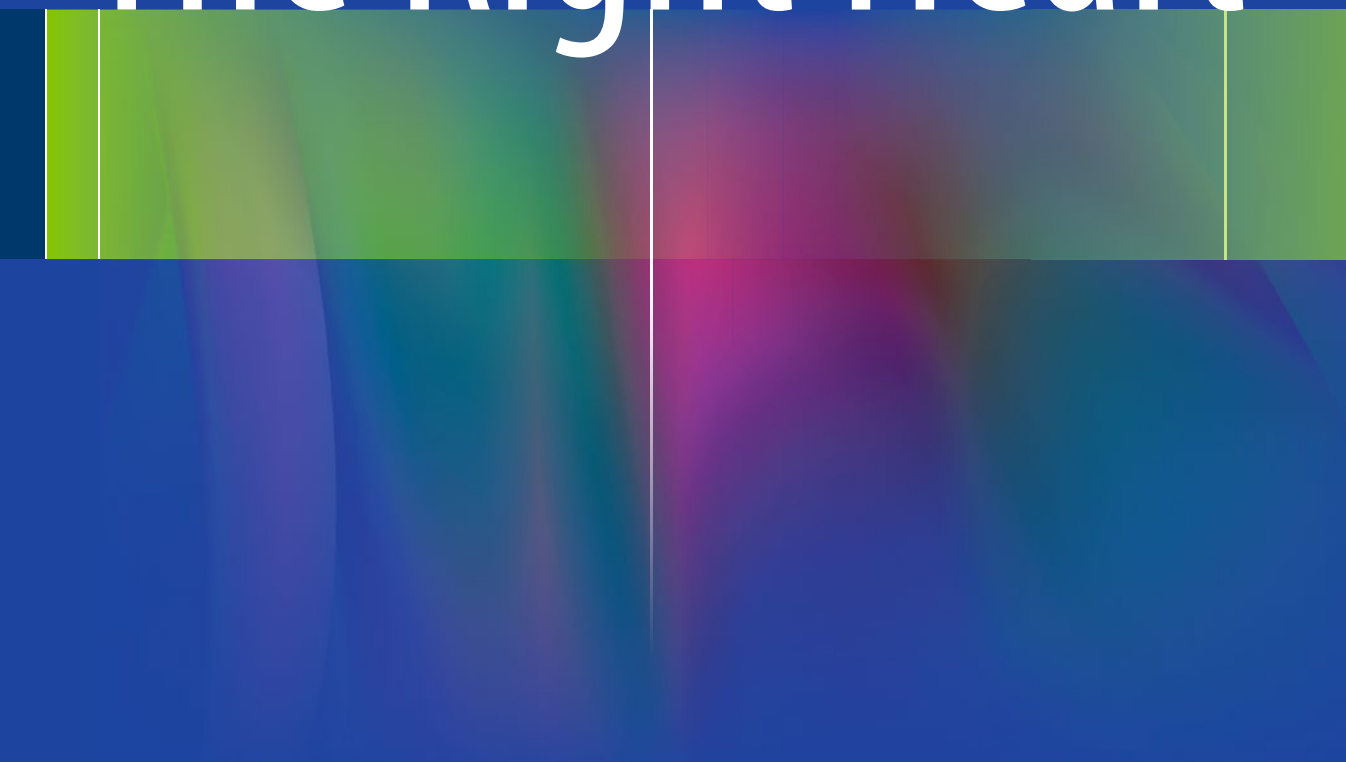
Andrew John Peacock
Editors

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

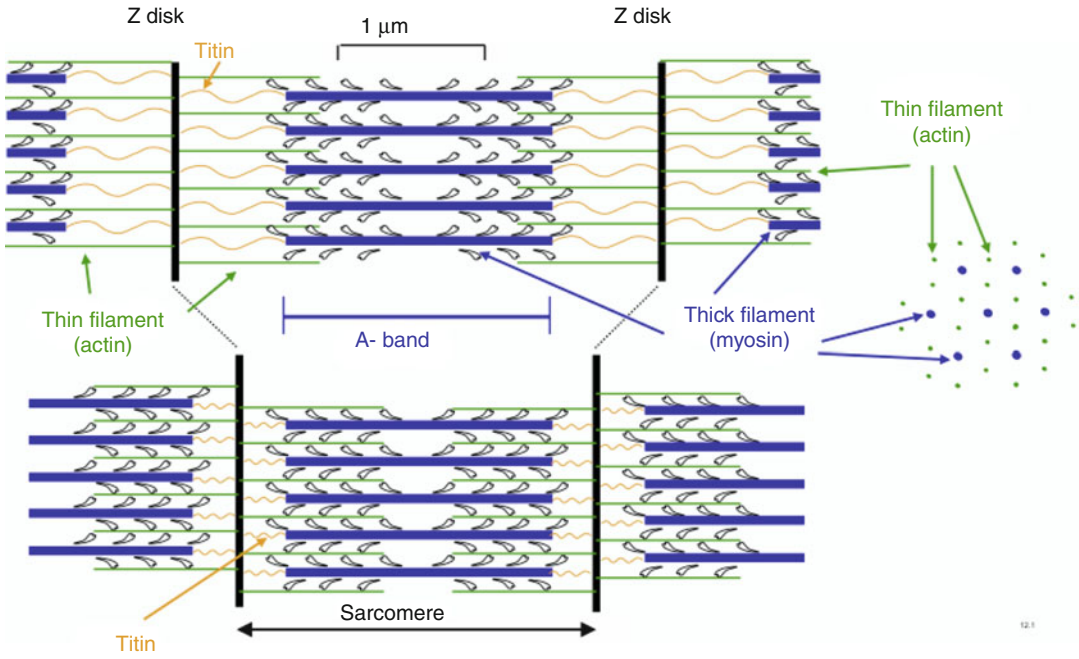

Fig. 2.1 The structural unit of a cardiomyocyte that is responsible for contraction, the sarcomere, is presented at two different muscle lengths. Each sarcomere is bounded at the end by Z-discs. Two type of filaments are shown: (1) the thick filament (*blue*), with the myosin heads extending from the 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).

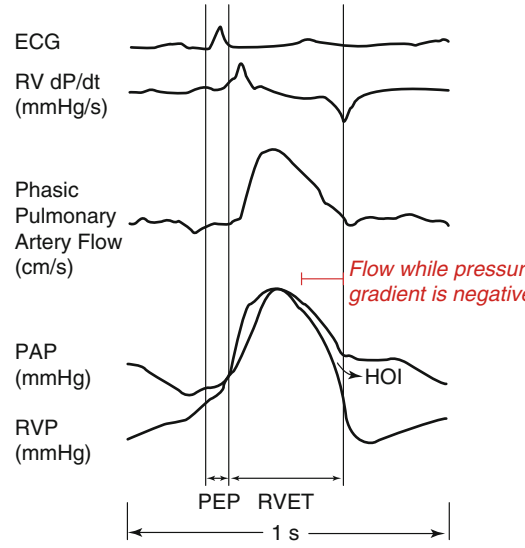

Fig. 2.2 Simultaneously recorded electrocardiogram (*ECG*), right ventricular (RV) dP/dt, pulmonary artery (PA) flow, PA and RV pressure. Note the short duration of the pre-ejection time (*PEP*) and the negative pressure gradient visible during late ejection. *HOI* hangout interval, *RVET* RV ejection 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

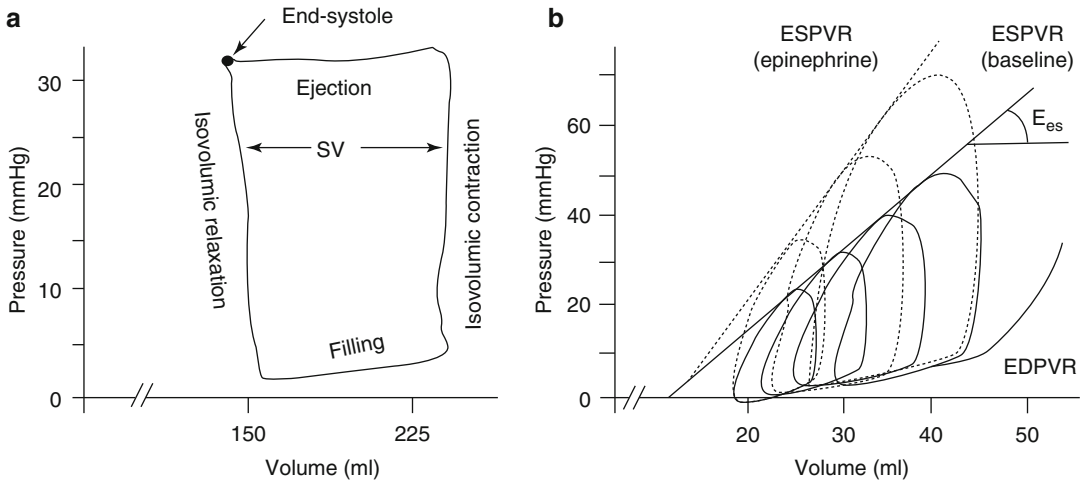

Fig. 2.3 (**a**) Schematic presentation of a pressure-volume (P-V) loop of a single beat. Diastole (or the filling phase) starts after tricuspid (or mitral) valve opening (lower left corner P-V loop). At this moment, the volume in the ventricle is at its minimum, corresponding to end-systolic volume (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

increases. This means that when venous return changes, stroke volume changes at the same time. 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, greater force of contraction is produced. The greater force at greater sarcomere lengths 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' [57]. This theory denotes to 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 [57] when it was observed that stretching of sarcomeres favorably alters the orientational ordering of the myosin heads, thereby 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 RV 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 extend 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 is through an increase in contractility which is facilitated in an acute setting 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.

An additional mechanism that increases contractile force has been described by Gleb von Anrep [58]. The so-called "Anrep effect" refers to the observation that in response to an increase in afterload the cardiomyocyte increases its contractile force not only rapidly in response to an increase in stretch (Frank-Starling mechanism), but also increases its contractile force more slowly over the following minutes (Anrep phenomenon) [58]. The Anrep phenomenon 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 [58, 59].

Conclusions

RV function is important in both healthy subjects and disease states. The RV has a complex geometry consisting of two different anatomical parts and RV contraction occurs in a peristaltic-like pattern. In the healthy RV, ejection continues after maximal shortening and in the presence of a negative pressure gradient. Despite of 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.

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3 The Impact of Long-Term Endurance Sports on the Right Ventricle: Evidence for Exercise-Induced Arrhythmogenic RV Cardiomyopathy

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Abstract

As discussed in Chapter 7 of this book, the right ventricle (RV) undergoes a disproportionate increase in load during exercise. This leads to acute changes like dilatation and temporary dysfunction, and may be associated with minor cell damage as evidenced by cardiac enzyme elevations that are very commonly observed after endurance competition. In general, these changes seem to recover within a few days. This chapter reflects on the thesis that the RV can develop chronic sports injury, based on our hypothesis that was originally put forward in 2003. We speculate that repetitive acute injury may culminate in a chronic overload syndrome of the RV, which is very reminiscent of what is observed in patients with familial arrhythmogenic RV cardiomyopathy (ARVC), despite the absence of underlying demonstrable genetic abnormalities. The syndrome of 'exercise-induced ARVC' may easily be overlooked. It may even become more prevalent now that modern sports tries to push the limits of human performance in a much more 'professionalised' way and on a much larger scale. The aim of this chapter is to describe the pathophysiological findings of 'exercise-induced ARVC' and its relation with desmosomal ARVC.

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Introduction

When considering cardiac performance during exercise, and the heart's chronic adaptation to it, the main focus has always been on the left ventricle (LV). However, as discussed in Chap. 6 of this book, the right ventricle (RV) undergoes a disproportionate increase in load during exercise. This leads to acute changes like dilatation and temporary dysfunction, and may be associated with minor cell damage as evidenced by cardiac enzyme elevations that are very commonly observed after endurance competition. These changes recover over the next days. In this chapter, we speculate that repetitive injury however may culminate in a chronic overload syndrome of the RV, which is very reminiscent of what is observed in patients with familial arrhythmogenic RV cardiomyopathy (ARVC), despite the absence of underlying demonstrable genetic abnormalities.

Ventricular arrhythmias in athletes are rare, but by nature they may be life-threatening. Physical activity is associated by a 2.5 times increased risk for sudden death [1]. The classical concept is that arrhythmic events are due to underlying (structural or electrical) heart disease, on which physical activity acts as a trigger for initiation of arrhythmias. A multitude of underlying cardiovascular conditions have been shown to predispose an athlete to exercise-related sudden death. ARVC is an important part of that [1, 2] We presented a second, additional, hypothesis in 2003, postulating that intense endurance activities may also lead to the chronic underlying proarrhythmic RV alteration [3]. The syndrome of 'exercise-induced arrhythmogenic RV cardiomyopathy' may have been overlooked before and/or becomes more prevalent now that modern sports tries to push the limits of human performance in a much more 'professionalised' way and on a much larger scale. The aim of this chapter is to describe the pathophysiological findings that support the hypothesis of 'exercise-induced ARVC', and to discuss its relation with desmosomal ARVC.

Ventricular Arrhythmias in Athletes: Most Often a Right Ventricular Origin

Sudden death in athletes is usually the result of ventricular tachy-arrhythmias. The most common underlying cardiovascular abnormalities that have been identified in younger athletes (<35 year) are hypertrophic cardiomyopathy, coronary anomalies, arrhythmogenic right ventricular cardiomyopathy (ARVC), myocarditis and channelopathies, while silent coronary artery disease is the main cause in athletes over 35 years [1, 2, 4]. Given this distribution of underlying disease, we were puzzled by findings in 46 high-level endurance athletes (performing $\geq 3 \times 2$ h of sports per week for more than 5 years; 80 % competitive; 80 % cyclists) that were referred to us for evaluation in the context of aspecific symptoms like palpitations and dizziness, but that after work-up could be attributed to ventricular arrhythmias [3]. The great majority of those ventricular arrhythmias (86 %) had a RV origin (i.e. with left bundle branch block morphology in the right precordial leads), which would not be expected based on the mentioned underlying pathologies, which statistically would have a much higher probability of inducing arrhythmias of left ventricular (LV) origin. Nevertheless, the arrhythmic outcome, although clinically mild at presentation, proved to have an ominous course: after a medium follow-up of 4.7 years, 18 out of 46 had a major rhythm disorder, of which 9 were (aborted) sudden death (all cyclists; a mean of 3 years after presentation). Only an electrophysiological study inducing re-entrant arrhythmias was predictive for later arrhythmic events outcome (RR 3.4; $P = 0.02$). That pointed to an underlying structural substrate. Although the athletes presented with RV arrhythmias, overt structural findings of ARVC were less frequently present than seen in familial forms. Only 1/46 had a familial history. Nevertheless many of them showed other electrical signs of right ventricular changes like deep negative T-waves in the right precordial leads up to or even beyond V3, or the presence of late potentials on the signal averaged

ECG (each about 40 %) [3]. Combining major and minor criteria of the (original) ARVC diagnostic framework, 59 % had manifest ARVC and an additional 30 % had probable ARVC [5]. It is of interest that others have also noted that asymptomatic athletes, and especially endurance athletes, develop changes on the signal averaged ECG, intermediate to those of controls and those of athletes with ventricular arrhythmias [6]. We therefore started to wonder in how far structural adaptation of the athlete's RV, especially under extreme endurance load, had developed into RV degeneration and arrhythmogenicity [3].

Many studies have shown that in athletes performing a marathon, triathlon or other ultra-endurance event, there are increases in B-type natriuretic peptide (BNP; in 54–100 %), and cardiac enzymes like CK-MB, troponin-T and troponin-I (in 40–57 %) [7–14]. The rise in cardiac enzymes is somewhat less in subjects performing habitual exercise [7], but cannot be denied even when experienced athletes perform high-intensity endurance events. On the other hand, echocardiographic studies have shown that the LV at the end of such an event usually has dimensions comparable to those before the event, with preserved, or minimally altered, global and regional function [7, 8, 14–21], Given the minimal alterations in LV measures, no correlation was noted between the enzyme rise and the degree of LV dilatation/hypokinesia [22, 23]. In contrast, RV dilatation and global hypokinesia are noted in at least one third of the athletes [7, 8, 14–16, 18, 20]. In a recent study on 40 athletes studied after different endurance events (from marathon to ultra-endurance triathlon, 3–11 h in race duration), we reported an overall reduction in end-diastolic and end-systolic LV volumes immediately after the race, in sharp contrast to dilation of the RV (in both phases) [23]. Moreover, RV ejection fraction decreased immediately after the event (LV EF was unchanged), recovering to normal after 1 week. Intriguingly, the degree of transient RV dysfunction was significantly related to the duration of the endurance event. Moreover, BNP and cardiac troponin-I increases correlated with reductions in RVEF ($r=0.52$, $P=0.001$ and $r=0.49$, $P=0.002$, respectively), but not LVEF (Fig. 3.1) [23]. These findings support our 2003 hypothesis that endurance events lead to RV insults (reflected in enzyme rise and slight dysfunction), recovering after a single bout, but that repetitive 'hits' in the long-term may result in RV dysfunction and arrhythmias (Fig. 3.2). There may be a limit to what is healthy for the RV….

We have performed detailed quantitative RV angiographic evaluation in 22 high-level endurance athletes presenting with ventricular arrhythmias, and compared those with age and sex matched comparable athletes ($n=15$) and non-athletes ($n=10$) [25]. Twenty-seven per cent of the athletes with arrhythmias had definite Task Force criteria for ARVC, although only 2/22 had a familial history. Four different software algorithms were used to measure RV and LV volumes and EF from biplane RV angiography. All athletes had normal LV function. Athletes with arrhythmias had a modestly but significantly lower RV ejection fraction than athletes without arrhythmias and controls (49.1 % vs. 63.7 % vs. 67 %; $p<0.001$) [25]. This decrease is clearly less pronounced than what is known from familial series of ARVC, but again points to underlying structural changes in the RV that may be associated with the observed arrhythmogenicity. Of note, many of these angiographies, when evaluated qualitatively by an experienced evaluator, were labelled as 'normal for athlete's heart', indicating the importance of quantitative evaluation as stated also in the revised ARVC Task Force criteria [26].

What Defines Susceptibility to Exercise-Induced RV Arrhythmogenicity?

As mentioned, 80 % of the athletes whom we have evaluated with this syndrome were high-level (often competitive) cyclists or triathlon athletes [3, 25]. Cyclists perform the most protracted exercise, more hours per day and more days per year than most other athletes. They frequently sustain heart rates around 80 % of maximum for

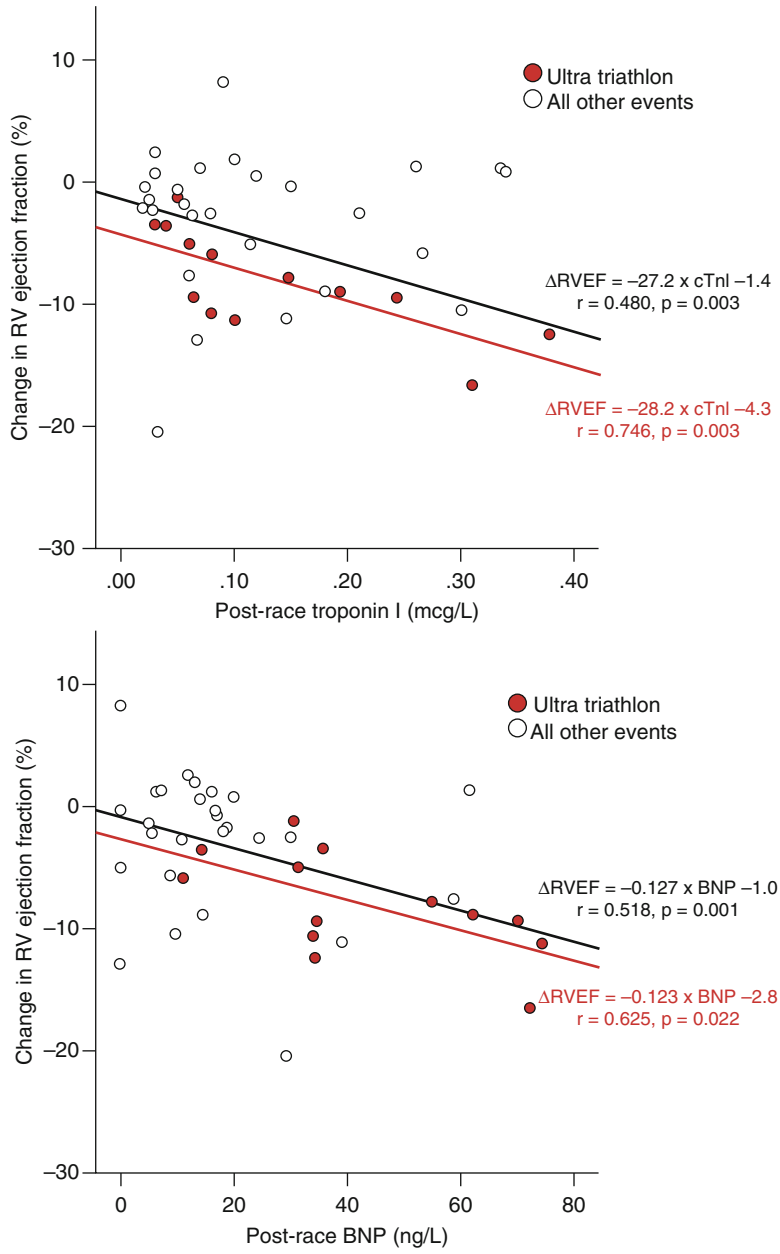

Fig. 3.1 Correlation between reductions in right ventricular function and biomarkers. The release of cardiac troponin and B-type natriuretic peptide have been repeatedly observed following ultra-endurance exercise but have not correlated with changes in left ventricular function. We hypothesized that, given that the RV was the predominant source of exercise injury, changes in RV function might explain the increases in markers of myocardial injury and strain. Indeed, we demonstrated a moderate correlation between change in RV ejection fraction and increases in biomarkers

prolonged periods. Their protracted aerobic exercise is regularly interrupted by intense anaerobic dashes, which is more uncommon in other endurance athletes: long-distance runners are notably scarce in our series, although this sport is very popular in our region. Therefore, the RV effects seem to be linked to high-intensity endurance activities, particularly those that are of long-duration and combine endurance and power. We have observed the same presentation in rowers, triathletes and swimmers. We suspect that other sports with a similar physiological load, e.g. cross-country skiing, may also be associated with an increase in RV arrhythmias but this sporting demographic is not part of our experience.

However, not all such athletes develop RV dysfunction at the end of an event, and the incidence of long-term (acquired) RV cardiomyopathy is

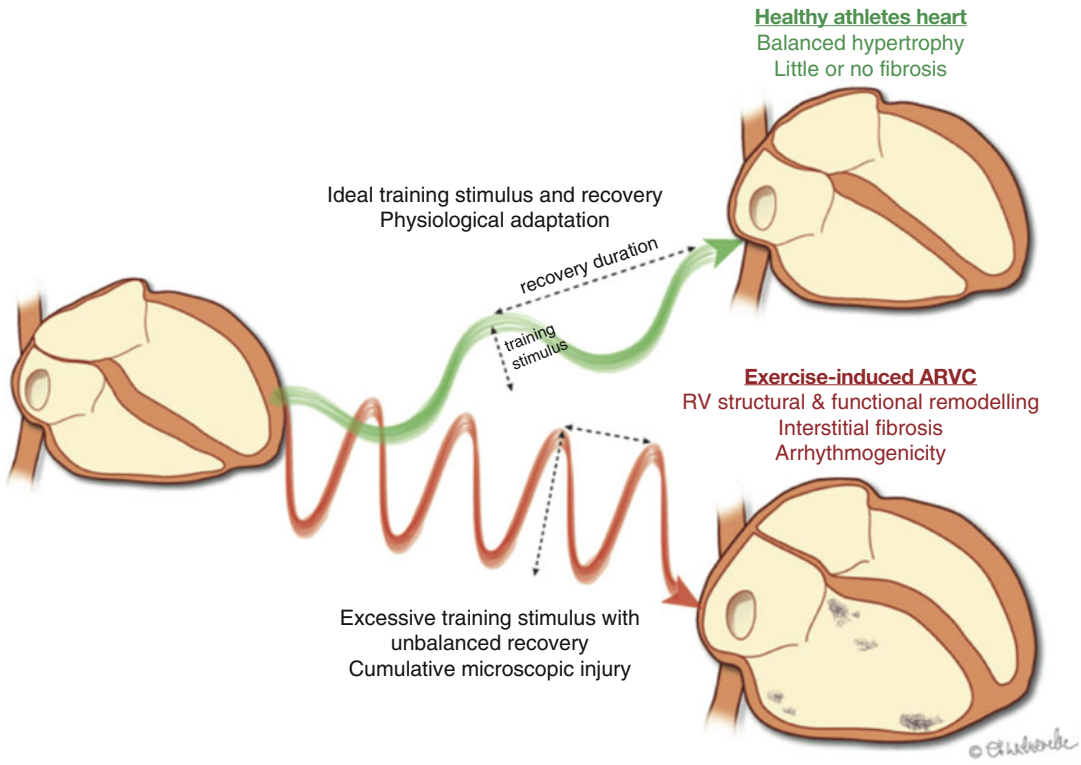

Fig. 3.2 Healthy training vs. overtraining of the heart. Healthy training with balanced exercise and recovery results in physiological remodelling in which enhanced cardiac structure and function enable greater cardiac performance during exercise. On the other hand, we propose that excessive exercise (training which is too intense and/or recovery that is too short) may cause cardiac injury and proarrhythmic remodelling which predominantly affects the right ventricle (Reprinted from Heidbuchel et al. [24]. With permission from BMJ Publishing Group Ltd.)

seemingly small. No formal estimates exist due to the lack of centralised registries. There is both uncertainty about the numerator (complete registry of cases?) and denominator (population of intense endurance athletes at risk?). Rough estimates based on the referral pattern for our tertiary care centre and the number of registered competitive and high-level recreational cyclists in our country, show that the yearly incidence for developing the phenotype may be around 1/1,000 overall, but it may be 1/100 in international top-level athletes in the mentioned disciplines. Its relatively low prevalence is further highlighted by a normal survival curve in 119 former athletes participating to the Tour of Switzerland between 1975 and 1995: the observed survival was the same as that of a matched Swiss male population [27]. Similarly, studies of Tour de France cyclists have suggested that endurance exercise may be associated with better than average survival [28, 29]; although these studies used crude epidemiological techniques which are subject to considerable "healthy cohort" bias [30]. However, even if health outcomes are excellent for the majority of athletes, some arrhythmias are clearly more prevalent and the question remains as to which individual facilitating factors may play a role in the development of arrhythmias such as in exercise-induced ARVC [31].

Illicit Drug Use?

The first suspect is always performance-enhancing drugs. Illicit drug use may be common in high-level endurance athletes although no reliable data exist on its prevalence. However, for most modern performance-enhancing drugs,

no direct cardiopathic effect has been described [32]. Moreover, if they were the direct cause, it is unclear why they would selectively have impact on the RV. Amphetamines for instance are known to cause LV micro-infarcts and scarring, with secondary arrhythmias that often originate in the LV. Therefore, we do not consider illicit drugs as the direct cause. Their use may however be involved indirectly, i.e. by allowing longer and more strenuous endurance activity more frequently, facilitating development of the phenotype. As interesting circumstantial evidence for this premise, Abergel et al. studied 286 Tour de France cyclists using echocardiography [33]. One hundred forty eight cyclists participated in the 1995 race, 138 in the 1998 race and 37 in both. Cardiac dimensions increased in the cyclists competing in both races, a finding which may readily be attributed to continued athletic remodelling of the myocardium following an additional 3 years of training. However, it was also noted that cardiac dimensions were greater in the 1998 cohort than in the cohort of 1995, despite the cyclists being similar in age and experience. It is now apparent that 1998 was perhaps the peak period of erythropoietin abuse and it is curious to speculate that the resulting increase in aerobic capacity may indeed be reflected in cardiac morphology. Thus, perhaps this represents a period in which the very extremes of capacity in endurance exercise training and racing were reached and thus the potential for exercise-induced proarrhythmic remodelling were also greatest.

Genetic Predisposition?

Another underlying factor could be genetic predisposition, since desmosomal mutations and alterations are known as the basis for familial ARVC. It is well established that exercise activity promotes the development of RV dysfunction and arrhythmogenicity in mutation carriers [34, 35], and a similar relation has recently been described for left cardiomyopathies due to lamin A/C mutations [36]. Therefore, it is obvious to suspect that the similar phenotypes found in high-level athletes and in familial ARVC are due to (unmasking of latent) mutations. We systematically evaluated the five desmosomal genes for mutations (by sequencing) and larger genetic rearrangements (by multiplex ligation-dependent probe amplification, MLPA) in a cohort of 47 athletes, of whom 87 % had definite or probable criteria for an ARVC phenotype [37]. The proportion with desmosomal mutations was much lower than that described for familial ARVC (13 % vs. ~50 %) [38–44]. If RV arrhythmogenicity were the early expression of a latent underlying genetic (desmosomal) mutation, we would have expected at least a similar prevalence as in familial forms. Moreover, familial ARVC was only present rarely (in 2/47 athletes).

Some have argued that there might be a lower mutation rate in sporadic ARVC cases than in familial cohorts, and that this could explain the low mutation rate in our cohort. Most familial ARVC studies have recruited a large number of unrelated ‘index cases’. Because it is principally a familial disease, it is clear that a proportion of index cases have a positive family history (between 21 and 38 %) [39, 42–44]. When analysing the four largest studies which have included index cases with and without a positive family history, the mutation rate varies between 34 and 56 % in index cases without a family history. In none of these studies does the rate of mutation differ between those with and without a family history.

A Spectrum from Familial to Exercise-Induced RV Arrhythmogenicity?

The Interplay of Genotype and Environment

Although other genetic predisposition cannot be excluded, we do not believe that ‘exercise-induced ARVC’ is simply unmasking of mutation-dependent ‘familial ARVC’. Our genetic findings strengthen our initial hypothesis that excessive strain on the RV by sports itself (i.e. an environmental factor) can be regarded as one side of a continuous spectrum where myocardial integrity

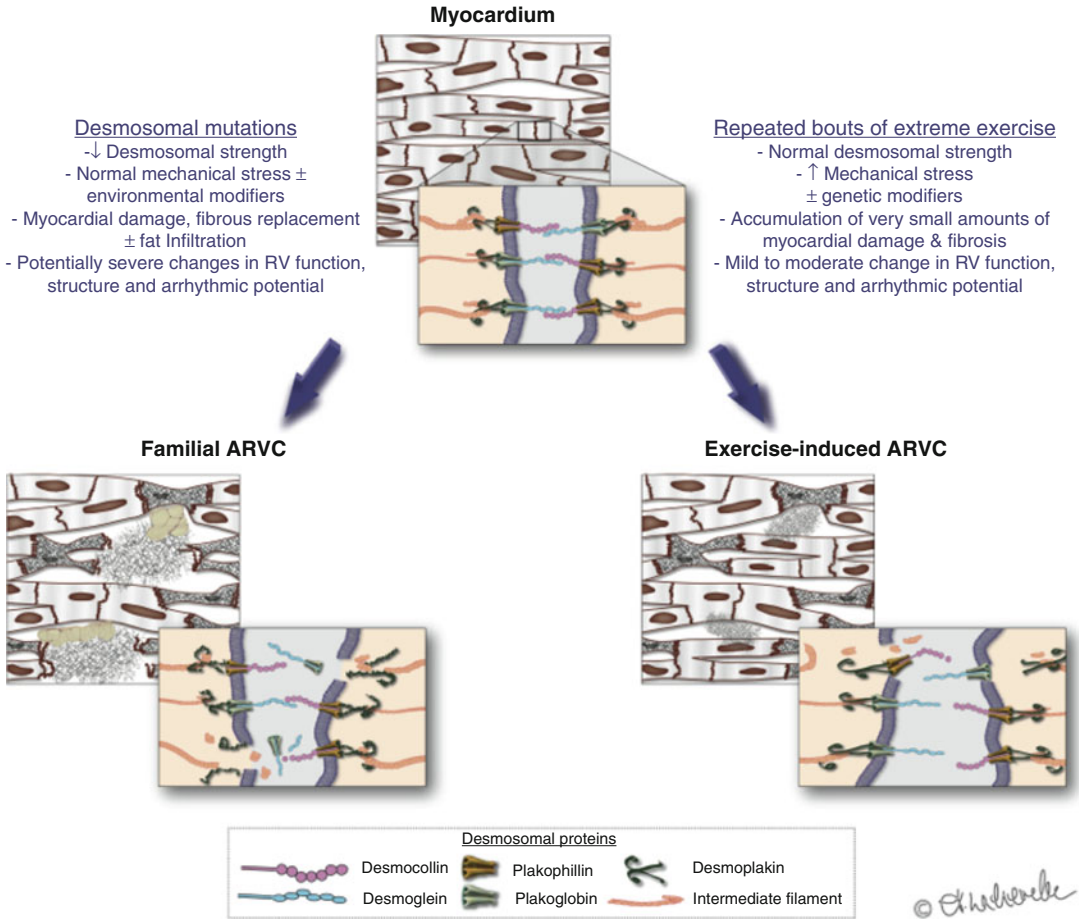

Fig. 3.3 Familial versus exercise-induced RV cardiomyopathy: a continuum? Integrity of myocyte junctions is critical to cardiac function, structure and electrical stability. These junctions can be compromised by genetic mutations of the desmosomal proteins (*left pane*) and/or by increased mechanical stress (*right pane*). Either mechanism, or a contribution of both mechanical and genetic factors, may predispose to apoptosis, fibrosis and arrhythmogenicity, which most commonly affects the right ventricle (Reprinted from Heidbuchel et al. [24]. With permission from BMJ Publishing Group Ltd.)

is perturbed due to a mismatch of strain and desmosomal integrity. With mutated desmosomes, normal levels of myocardial wall stress lead to cellular disruption and (fibro-fatty) repair, ending in familial ARVC. It is well-known that exercise facilitates the development of a desmosomal mutation phenotype, both in experimental as in clinical studies [35, 45]. But we propose that a similar phenotype may develop when excessive wall stress disrupts 'normal' desmosomes, i.e. in which the environmental factor plays the key role (Fig. 3.3). Like in other diseases, polygenetic factors, many outside the desmosomes, may interplay with environmental factors (here: exercise) to result in a phenotype. We do not believe however that cardiac monogenetic traits are or need to be the sole explanation for individual susceptibility. Retrospective data provided by James et al. definitely support interplay between exercise and genetic susceptibility to ARVC [46]. They reported that amongst patients with ARVC gene mutations, endurance athletes developed symptoms, arrhythmias and heart failure at an earlier age and were more likely to fulfil diagnostic criteria for ARVC than were non-athletic mutation carriers. Thus, it would seem that

endurance exercise can accelerate disease expression, promote phenotypic expression in carriers who may otherwise remain asymptomatic and, perhaps, create ARVC-like features in athletes with a mild and currently undetectable genetic susceptibility. Our description of an ARVC-like syndrome in athletes with no detectable genetic risk can be consistent with the assertion that there are genetic susceptibilities still to be found, or that extreme exercise by itself can be sufficient to promote proarrhythmic remodelling of the RV.

Recent studies have evaluated late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) in arrhythmia-free endurance athletes after an endurance race, but did not find its presence even when cardiac enzymes were elevated post-exercise [14, 17]. In our opinion, however, this does not exclude acute microstructural damage which is too small to be picked up by the limited resolution of the CMR examination. Moreover, the majority of symptomatic athletes in our studies with exercise-induced ARVC did not have overt fibrosis nor adiposis on CMR and only a minority showed histological fibroadiposis [3]. Hence, macrostructural fibroadiposis seems to be less a hallmark of exercise-induced ARVC than of familial ARVC.

Animal Models of Exercise as Sole Inductor of an ARVC Phenotype

The fact that exercise alone, without doping or genetic predisposition, could lead to the phenotype of exercise-induced ARVC, finds further credence in animal models. There is no perfect model of endurance athletic activity but two models have merit. Earlier findings were reported in a model based on an induced aortacaval fistula in pigs [47], leading to volume and pressure overload of the RV, a disproportionate increase in RV stroke work index relative to that of the LV (+216 % vs. +70 %), RV fibrosis and the development of RV dysfunction after 3 months. The pure LV volume overload was associated with hypertrophy based on myocyte length increase and increased local production of insulin-like growth factor. On the other hand, the RV showed more pronounced hypertrophy, increase in both myocyte length and diameter, and associated increased collagen deposition. Apart from IGF-I increase, there also was an increase in endothelin-I and angiotensin-II production. The authors postulated that the differential loads led to different gene expression and different structural changes [47].

More recently, the Barcelona group of Mont and colleagues have established a rat model of endurance activity [48]. Although rats can be forced to run only for a maximum of 1 h/day (i.e. much shorter than humans), the running rats showed increased interstitial fibrosis in both atria and in the RV after 16 weeks, in contrast to none in the LV. This was associated with inducibility of ventricular arrhythmias in 42 % of the exercise rats, versus only 6 % in controls ($p=0.05$). Cessation of exercise reversed the fibrotic changes. The question is whether fibrogenesis can also be prevented in man with much longer-standing exercise history. Moreover, it remains to be seen whether administration of an ACE-inhibitor or angiotensin receptor blocker could also lead to reversibility or prevention, offering further prospect for clinical medicine. Kirchhof, Fabritz et al. showed that in a heterozygous plakoglobin-deficient mice model of ARVC, exercise facilitated the development of the phenotype and arrhythmias [35]. Later, they showed by a controlled trial in this model that preload reduction using nitrates plus diuretics prevented development of ARVC, rendering preload-treated heterozygous plakoglobin-deficient mice undistinguishable from their wild-type littermates [49]. No data however are available so far on possible preventive or reversible effects of these drugs in athletes with supraventricular or ventricular arrhythmias, although a clinical trial with preload reducing therapy in familial ARVC is underway [50].

Molecular Mechanisms

It has been suggested that the molecular pathogenesis for the two components of ARVC, i.e. cardiac dysfunction and fibroadiposis, is different. Cardiac dysfunction is primarily due to impaired myocyte-to-myocyte attachment [51].

The pathogenesis of fibroadiposis involves partial nuclear translocation of plakoglobin and subsequent suppression of canonical Wnt signaling, which is involved in the development of the RV and its outflow tract, the predominant sites of involvement in familial ARVC. This pathogenic pathway may not be at work in athletes, whereas the myocyte-to-myocyte disruption is common to both. This requires further study. The exact incidence and significance of sub-clinical (microscopic) fibrosis in athletes is difficult to quantify given that myocardial biopsies are rarely performed and those in whom biopsies have been performed belong to cohorts with more severe symptoms or changes in cardiac structure or function [3, 37, 52]. An interesting recent exception to this is a study by Dello Russo et al. [53] in which athletes with ventricular arrhythmias but no overt structural heart disease were investigated with electroanatomical guided myocardial biopsy. There were histological abnormalities in all 13 of the athletes, which the authors attributed to ARVC, myocarditis or substance abuse. Whereas pathologic examination often shows fibrofatty replacement predominantly in the epicardial surface, probably because of increased wall stress on the outer surface, it is not known whether this is the case for exercise-induced ARVC and whether this is different from familial ARVC, since biopsies are taken endocardially and not transmurally. In our experience however, there is rarely endocardial voltage abatement in athletes with exercise-induced ARVC in contrast to those with familial ARVC forms. Data on epicardial mapping in athletes are lacking.

Why the Right Ventricle?

This brings us to a third pathophysiological predisposing mechanism on why exercise may lead to selective RV pro-arrhythmic remodelling, which may lie *outside* the heart. There are more and more data that especially in the RV, a mismatch between wall stress and desmosomal integrity develops during high intensity sports (as postulated above). As already mentioned in Chapter 3, we and others have observed that intense physical exercise is associated with an increase in pulmonary arterial pressures, which is much more pronounced in trained athletes than in volunteers [54, 55]. Studies using invasive pressure measures have demonstrated that although both ventricles have to realize the same cardiac output, the pulmonary vascular bed can only reduce its resistance by 30–50 % during exercise as compared with greater reductions in systemic vascular resistance (usually in excess of 75 %) [56, 57]. There is a strong relationship between non-invasive pulmonary artery pressure estimates and cardiac output [54, 58, 59]. This relationship is steeper and more linear than the comparable pressure/output relationship in the systemic circulation. Furthermore, this relationship is similar in athletes and non-athletes, i.e. training does not lead to adaptation to reduce afterload for the RV during exercise [54, 60]. Thus, irrespective of athletic status, the harder the exercise, the greater the RV pressure demands and the larger the proportional difference between the demands placed on the RV and the LV. Given that athletes are trained to attain higher cardiac output than controls, they achieve significantly higher peak pulmonary pressures as compared with non-athletes (Fig. 3.4).

The higher pulmonary pressures during exercise lead to a greater RV load and stroke work during exercise than for the LV [54, 55]. Based on the Laplace equation, and including chamber size and wall thickness estimates from cardiac MRI, we estimated the resulting wall stress in both ventricles. Compared to rest, the RV wall stress at peak exercise rises in athletes by 170 % compared to rest, with only a 23 % increase in the LV wall stress [60]. Furthermore, we observed RV hypertrophy (both wall mass and dilation) which was proportionally greater than LV hypertrophy in athletes as compared with non-athletes, thus confirming a link between acute hemodynamic load and chronic ventricular remodelling [60]. It also stands to reason that single bouts of extreme and prolonged hemodynamic stress may result in RV fatigue or transient damage, thus potentially explaining both the ‘leak’ of enzymes

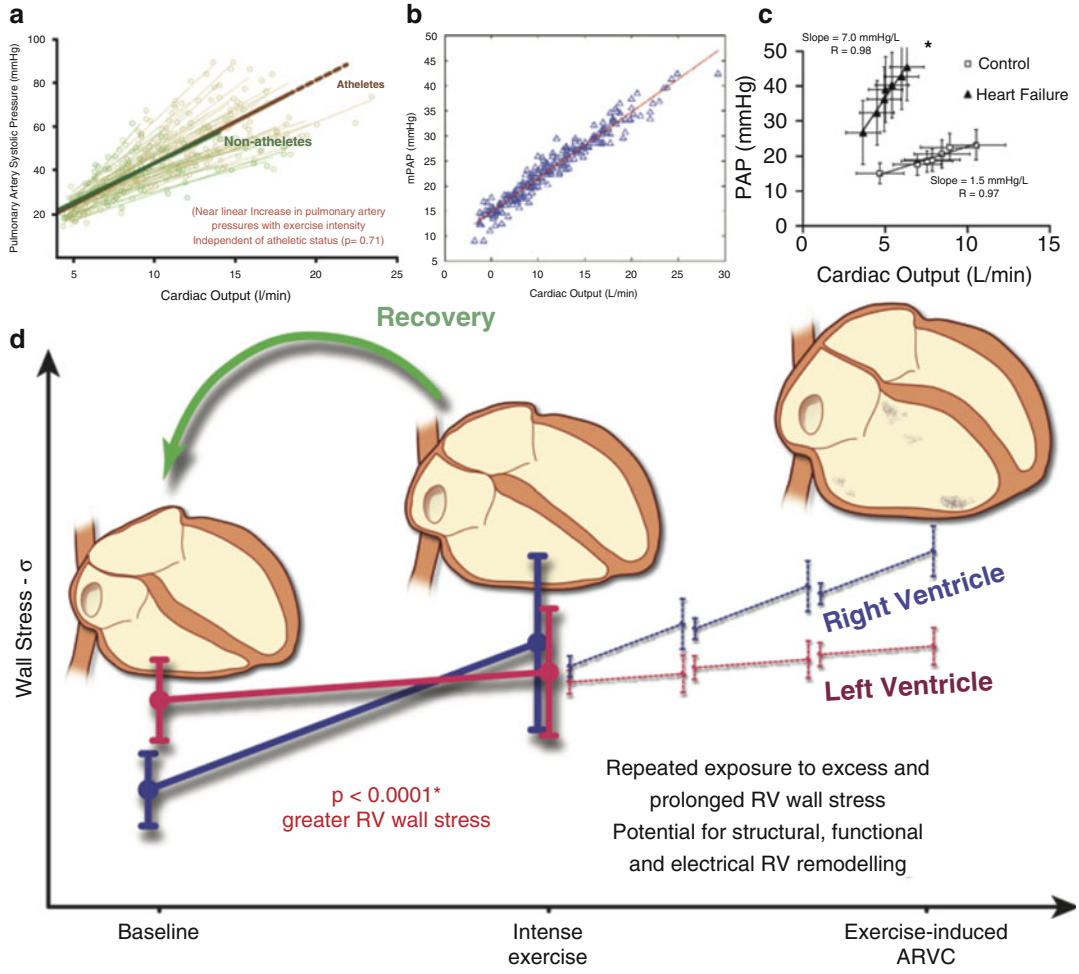

Fig. 3.4 Disproportionately greater RV pressures and wall stress give rise to RV remodelling. Data from two echocardiographic studies – panels (**a**, **b**) [54, 58] – and one invasive study – panel (**c**) [61] – demonstrate a consistent relationship between increases in cardiac output and pulmonary pressures. Although there were methodological differences between the studies, all three studies converge upon an approximately linear increase of 1.5 mmHg of mean pulmonary artery pressure for every 1 L increase in cardiac output. As compared with the LV, relative increases in wall stress are greater for the RV during intense exercise, the result of which is healthy cardiac remodelling with a very slight RV dominance, which diminishes with de-training – panel (**d**). Repeated bouts of excessive and prolonged RV wall stress may result in cumulative RV damage, which may predispose to arrhythmias. The degree to which this adverse remodelling may recover with de-training is unclear

and transient RV dysfunction following endurance sports. As mentioned, we have found that the enzyme rise correlates with the degree of transient RV dysfunction, whereas no such correlation exists with LV measures [23]. Myocardial inflammation, substrate deficiency and oxidative stress have all been proposed as potential mediators of post-exercise cardiac injury [62]. We contend that the primary cause is the mechanical and metabolic stress of the prolonged intense exercise and that this triggers cellular pathways of injury and/or repair in the RV more than the LV. The 'marathon rat' study of Benito, Mont and colleagues [48] supports this premise.

We described above that the pulmonary vasculature has similar properties in athletes and non-athletes. Nevertheless, based on transit of microbubbles, two distinct groups of pulmonary

vascular behaviour can be distinguished [54]. At rest, no athlete or control showed microbubble passage through the lungs. In contrast, in about half of the population microbubbles pass the lung vasculature during exercise. Again, this proportion is similar in athletes and non-athletes, and thus it does not seem to be a 'trainable' characteristic. Interestingly, those athletes that show bubble transfer during exercise attain 16 % higher peak cardiac outputs with lower peak pulmonary pressures and resistance, and an attenuated BNP rise. The physiological basis of this bubble transfer is still unclear (opening of shunts or distension of pulmonary capillaries?). But it is evident that such physiology results in less RV wall stress for a comparable workload. We may speculate that such a pulmonary vasculature is less prone to induce RV wall damage, but this hypothesis needs further study.

Perspectives and Clinical Relevance

The recognition that the RV may get overtaxed during high-intensity sports does not necessarily negate the benefit of physical activity on cardiovascular morbidity and mortality. Sport is good and essential for all. But we may have to realize that adaptation of the athlete's heart is not always able to accommodate the sustained haemodynamic loads placed upon it. In some, intense endurance activity can lead to cardiac sports injury in the form of supraventricular or ventricular arrhythmias. Although the number of data is increasing, the prevalence of life threatening arrhythmic problems is definitely small. But like other sports injuries, recognizing the problem in an early phase can prevent disaster and may lead to measures that allow safe and enjoyable continuation of sports participation.

Diagnosis of RV arrhythmogenicity is not straightforward. Even in athletes with documented arrhythmias, confirming RV damage and proving compromised prognosis (i.e. differentiating it from benign idiopathic RV outflow tract extrasystoles) is cumbersome. It requires an extensive work-up with expert electrophysiological insight. The diagnosis mainly resides on electrical findings (including an invasive EP study in some) rather than imaging (with CMR normal in many patients). However, first-line physicians should develop an alertness when they hear suspicious symptoms (like exertional sudden dyspnoea or light headedness), see negative T-waves beyond V2, or record ventricular premature beats (VPB) with a left bundle branch morphology on ECG, note ≥2,500 VPB on a 24 h Holter, or see exercise-induced arrhythmias during an exercise test.

Modern training regimens include high altitude training, real or simulated in hypobaric oxygen chambers. This may result in improvements in endurance performance but we wonder whether this may also lead to an increase in the potential for cardiac 'over-training', particularly of the RV. It is well known that subjects living at high altitude (more than 3,000 m) have higher resting pulmonary pressures and that these pressures increase to even significantly higher levels during exercise (29–60 mmHg in high-altitude subjects vs. 12–18 mmHg in sea level subjects) [63]. If our hypothesis is true that increases in arterial pulmonary pressures put a strain on the RV, high altitude training will exacerbate this [16]. Modern training regimens therefore may promote RV dysfunction, which therefore should be closely monitored and better studied. Moreover, if our hypothesis is correct, the athletic community in general should reflect on the appropriateness of ever increasing demands on athletes. Young cyclists undertake gruelling training and competition schedules, often biking more than 200 days per year for more than 5 h. Recreational athletes engage in ever longer and harder activities. There is a social aura of competitiveness and excess performance during sports, rather than to highlight the important social and healthy merits of moderate physical activity. Certainly, the spirit of competition is an undeniable part of the human spirit but it cannot simply be assumed that the drive for "faster and further" is healthy for all body systems, all the time…

Most of the data on RV function in athletes are measured at rest, or derived indirectly from echocardiography during exercise (like pressure

estimates). Although good correlations between these echocardiographic measures and invasive pressure measurements have been shown, direct and combined pressure-volume measurements during exercise are desirable [64]. Such studies, combining RV imaging during exercise and invasive pressure measurements, are now starting based on novel techniques for cardiac MRI imaging during uninterrupted exercise and without breath-holding, as mentioned in Chapter 3. They may shed more light on this intriguing pathophysiology and help us to define risk patterns. Early recognition of those at risk would not only help prevent accidents, but also mostly help to reassure many others that they can enjoy their athletic endeavours safely. And based on the clinical insights and data from animal experiments, the time may be ripe to start clinical trials of drug-therapy for those who have been affected in order to slow or stop progression.

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Right Ventricular Pathobiology

4

Evan L. Brittain and Anna R. Hemnes

Abstract

Right ventricular (RV) function is a strong independent determinant of outcomes in a broad range of cardiopulmonary diseases. Despite this recognition, the underlying pathobiology of RV failure remains poorly understood and no RV-specific therapies exist for RV dysfunction. The variable response of RV function to different medical therapies and among etiologies of pulmonary hypertension suggests that elevated afterload is not the sole determinant of RV function. Various molecular mechanisms have been identified that contribute to RV failure. RV ischemia, neurohormonal activation, maladaptive myocardial hypertrophy, metabolic remodeling, and mitochondrial dysfunction are key pathogenic mechanisms that have been demonstrated in both experimental models and humans with RV dysfunction. Genetics may also contribute to RV dysfunction as in heritable pulmonary arterial hypertension and arrhythmogenic RV dysplasia. Metabolic dysregulation and neurohormonal antagonism are currently being tested as RV-specific therapeutic targets in PAH. More detailed understanding of the molecular underpinnings of RV failure will lead to additional therapeutic avenues. Molecular imaging tools such as positron emission tomography may provide a more mechanistic understanding of RV pathophysiology *in vivo* and allow translation of basic science findings to humans.

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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 non-ischemic 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

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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 little studied, but undoubtedly powerfully affect outcomes in situations of RV stress and may be independent targets of therapy. This chapter will focus on the pathobiology of right heart failure in chronic pulmonary hypertension and highlight areas of recent advances in our molecular understanding of RV function and dysfunction.

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 disease, 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 the mechanisms mediating RV decline and recovery will improve our understanding of RV failure and aid in 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 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 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, the 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 diseases such as scleroderma-associated PAH has disproportionate RV failure [11, 12] may point to different patterns of RV pathology in this disease.

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, and maladaptive myocyte hypertrophy. Ultimately, many of these processes potentiate one another leading to a cycle of worsening myocardial failure (Fig. 4.1). 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

Patients with PH develop increased myocardial wall stress due to increased RV pressure and dilation resulting in an increased myocardial oxygen demand [13]. 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 [14]. Right ventricular myocardial ischemia has been documented in PAH using myocardial scintigraphy and correlates directly with increases in RV diastolic pressure [15]. 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 [16].

Additional factors may contribute to supply/demand mismatch in PAH such as coronary compression from increased wall tension, hypoxemia due to impaired gas exchange, microvascular dysfunction, and impaired NO signaling [17]. Capillary loss and failure of new capillary growth in proportion to myocyte hypertrophy have recently been shown to differentiate angio-proliferative models of experimental PAH from RV pressure-overload models. In an

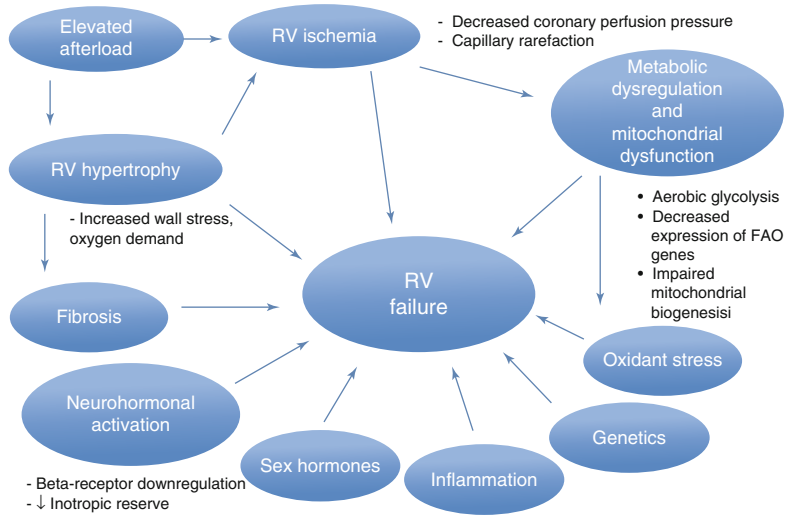

Fig. 4.1 Molecular mechanisms of RV failure. Alone or in combination, the various mechanisms pictured have been implicated in the development of RV failure. Several molecular mechanisms of RV failure such as RV ischemia and hypertrophy occur primarily as a result of elevated RV afterload. However, others such as metabolic dysregulation and mitochondrial dysfunction may by inherent features of PAH

experimental model of PAH using the vascular endothelial growth factor (VEGF) receptor blocker SU5146 and hypoxia (SuHx model), 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 [18]. These data suggest that VEGF production in PAH may be insufficient to induce adequate angiogenesis relative to cardiac hypertrophy, resulting in RV ischemia.

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 RAAS activation. As in left heart failure, the initially compensatory mechanisms of sympathetic system and RAAS activation ultimately become detrimental in patients with right heart failure. After prolonged stimulation, this results in down-regulation 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 [19], increased plasma norepinephrine levels [20], decreased β_1-receptor density in the RV in PAH, and increased muscle sympathetic nerve activity [21]. In addition, hyponatremia, an indirect marker of renin-angiotensin-aldosterone systemic activation is associated with reduced survival and RV failure in PAH [22].

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 beta-blockers would impair both chronotropic and inotropic reserve. However, recent evidence from preclinical models of RV failure suggests a potential benefit from beta-blockers. In the SuHx and monocrotaline PAH models, carvedilol, a $\beta_{1,2}$- and α(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. Similarly, the β_1-receptor blocker bisoprolol improved RV function in experimental PAH [23]. Early-phase clinical trials are now underway testing the effect of beta-blockade on RV function in patients with PAH. Elevated pulmonary aldosterone expression is present in PAH and correlates directly with endothelin-1 secretion [24]. Treatment with aldosterone antagonists in the SuHx and monocrotaline PAH models reduces pulmonary pressure and PVR without significant systemic side effects [25].

A common clinical dilemma in the treatment of RV failure is the choice of inotrope or vasopressor during acute decompensation. There are no specific recommendations in published guidelines and no clinical trial data to support evidence-based use of a specific inotrope. Recent findings regarding adrenergic remodeling in animal models of RVH may provide some guidance. PAH-associated (maladaptive) RVH as compared to RVH secondary to pulmonary artery banding is associated with downregulation of β_1, α_1, and dopamine-1 receptors resulting in reduced inotropic reserve. As a result of superior coupling to adenylyl cyclase, dobutamine outperformed dopamine as an RV inotrope in both *in vivo* and ex vivo models [26]. Larger clinical trials are needed to translate this data to humans, but this study demonstrates the influence of neurohormonal activation on myocardial response to inotropic therapy.

Right Ventricular Metabolism and Mitochondrial Function

In patients with PH, chronically increased pulmonary pressure and PVR results 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. Emerging 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 are associated with increased utilization of glycolysis for ATP production, even in the setting of abundant oxygen when oxidative metabolism would otherwise be used [27, 28]. 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 [29]. Direct measurement of increased RV glycolysis has been demonstrated in the monocrotaline PAH model [30]. Increased glycolysis (and decreased glucose oxidation) in this model is shown to be due to increased pyruvate dehydrogenase kinase (PDK) activty, 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) [31–33]. Although this suggests an increase in glycolysis given 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's cycle [34]. 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 [35, 36]. It is unclear whether therapeutic strategies that impair fatty acid oxidation either directly or by increasing glucose oxidation will benefit patients with PAH.

Recent evidence suggests that 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 [37]. 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 [38].

While changes in mitochondrial metabolism shifting from fatty acid oxidation to glycolysis in RV failure are clearly present, the underlying triggers for this shift are unknown. Understanding the influence of RVH on metabolic adaptation, and the potential for metabolic modulation as an RV-specific therapeutic strategy for RV failure are areas of intense investigation and hold promise for future therapies in RV failure from many causes, not just PAH.

Myocyte Hypertrophy

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 [39]. The molecular mediators of this shift from adaptive to maladaptive hypertrophy and RV failure are presently unknown, but animal models are beginning to provide some insight by comparing models of adaptive and maladaptive hypertrophy. Bogaard et al. has used pulmonary artery banding as a tool to study chronic pressure overload of the RV and compared the effects with the sugen + hypoxia model [9]. They found that in the pulmonary artery banding model, there is little mortality compared with the SuHx model, RV hypertrophy is present but to a lesser degree and there is less fibrosis in pulmonary artery banding. In the pulmonary artery banding model, cardiac output and tricuspid annular plane systolic excursion are preserved for up to 22 weeks. These studies have allowed better interpretation of animal models, suggesting that pulmonary artery banding is most informative as a model of early, adaptive hypertrophy. This paper suggests that angioproliferative pulmonary hypertension in SuHx is associated with capillary rarefaction in the RV, which is not present in pulmonary artery banding. The RV consequences of ischemia have been described and include normoxic HIF signaling [40] and mitochondrial metabolic changes discussed in the section on metabolism above. With inefficient production of ATP through glycolysis, there is postulated to be less substrate availability for myocardial cell growth required for hypertrophy. There is some animal data that dichloroacetate may reverse maladaptive hypertrophy associated with mitochondrial dysfunction in RV failure and ongoing human trials will provide much anticipated information about the utility of this other RV-directed metabolic interventions in the future [27].

Ischemia associated with reduced capillary volume may underlie the transition from adaptive to maladaptive hypertrophy, but alternative or contributory mechanisms have been implicated including altered electrophysiology [30] and perhaps geometry. Other hypertrophy triggers that are thought to be unrelated to ischemia have also been reported. Recent work by Nagendran et al. has demonstrated upregulation of endothelin-1 protein expression and endothelin receptor A in the hypertrophied human RV and in animal models of pulmonary hypertension [41]. Similarly, the phosphodiesterase 5 inhibitor sildenafil has been shown to increase cardiac index in its pivotal PAH trial [42]. Animal data suggests that increased NO signaling though PDE5 inhibition attenuates maladaptive RV hypertrophy in rodent models of right ventricular hypertrophy [43, 44]. The clinically evident RV effects of these disparate pharmaceutical classes has led to interesting insight into molecular basis of RV failure and may point to future therapeutics or new uses of older drug classes.

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 [45]. 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 [47, 48]. The role of sex hormones the development of RV failure may also be important given the observation that PAH is more prevalent in females but associated with worse outcomes in males. Recent data from our group has shown that testosterone negatively regulates right ventricular function in the pulmonary artery banding model of RV hypertrophy and that testosterone deprivation via castration is associated with prolonged survival in this model [49]. Castration was associated with reduced myocyte hypertrophy and reduced expression of natriuretic peptides associated with hypertrophy in this model. It is possible that the worse survival in male PAH patients is mediated by this negative effect of testosterone on RV hypertrophic responses.

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 disease. Transgenic models would facilitate a more detailed molecular dissection of the signaling pathways key to development of RV failure. Archer et al. have used the fawn-hooded rat to identify the key metabolic derangements in RV failure [50]. We have recently described worse survival in patients with heritable PAH compared with idiopathic PAH that may be due to impaired RV compensation in heritable PAH [51, 52]. Heritable PAH is most commonly associated with mutations in the bone morphogenic protein receptor type 2 (BMPR2), for which there are transgenic rodent models [53, 54]. In unpublished data 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, 56]. Moreover, hypertrophic responses in this strain appear to be impaired. The use of transgenic models to study RV failure will facilitate a deeper molecular understanding of the mechanisms that drive development of this syndrome and potentially point to new, effective therapeutic targets.

ARVC/D

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ACRC/D) is an inherited cardiomyopathy characterized by replacement of myocardium with fibrofatty tissue [57]. The genetic underpinnings of ARVC/D primarily involve mutation in desmosomal proteins resulting in disruptions in cell-cell adhesion and intracellular signaling; over a dozen unique mutations have been identified to cause disease [58]. Clinical manifestations typically occur in early adulthood and often the first manifestation is life-threatening ventricular arrhythmia or sudden cardiac death. Although ARVD is not known to be common in PAH or other WHO pulmonary hypertension groups, it is a genetic cause of RV-related disease. Its study may aid in understanding how the RV fails in the absence of load stress, as patients with this condition do not have pulmonary hypertension.

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 (trials of carvedilol on clinicaltrials.gov: NCT01586156, NCT01723371; trial of dichloroacetate:

NCT01083524). 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 [59]. 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 non-invasive 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 cardiopulmonary fitness [60, 61] and may bear fruit in the study of RV failure.

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Experimental Models

5

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Abstract

There is need for animal models that can represent changes in the right ventricle that closely mimic the human situation. The availability of an animal model of pressure overload-induced right ventricular (RV) hypertrophy (e.g. the pulmonary artery banding model) provides a valuable tool to aid understanding of the differences between adaptive and maladaptive RV hypertrophy and to expand our knowledge about the direct effects on the heart of current therapies for pulmonary arterial hypertension. Here, we discuss the role of such models in investigating the physiological/pathophysiological mechanisms involved in adaptive and maladaptive RV hypertrophy.

Abbreviations

COPD	Chronic obstructive pulmonary disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CYP3A4	Cytochrome P450
FDG	^{18}F-fluorodeoxyglucose
FHR	Fawn-hooded rat
LAD	Left anterior descending
LV	Left ventricular
MCT	Monocrotaline
MCTP	Dehydromonocrotaline
MI	Myocardial infarction
MMP	Matrix metalloproteinase
OSA	Obstructive sleep apnea
PA AcT	Pulmonary artery acceleration time
PAB	Pulmonary artery banding
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RV	Right ventricle
RV	Right ventricular
SUHx	Sugen plus hypoxia
TAC	Transverse aortic constriction
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
VEGF	Vascular endothelial growth factor

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Introduction

The right ventricular (RV) function is the most important determinant of prognosis in pulmonary arterial hypertension (PAH) patients, although the main pathological abnormalities are found in the pulmonary vasculature [1–4]. Our knowledge about the molecular physiology and pathophysiology of RV hypertrophy and failure in response to pressure or volume overload is still limited and most data are derived from research on the left heart. However, molecular mechanisms involved in left ventricular (LV) remodeling cannot be generalized to the right ventricle because the right and left ventricles differ greatly in their size, shape, architecture, and function. Furthermore, despite recent advances in the treatment of PAH the prognosis for patients is still poor. Currently available therapies for PAH are considered to act principally via vasodilation, and although offering symptomatic benefit and some improvement in long-term outcome, their true impact on disease progression is considered limited [5–7]. The development of novel therapies that directly target the fundamental processes involved in chronic pulmonary vascular remodeling and maladaptive RV structure/function represents a key aim in this disease. The development of novel PAH and heart failure therapies requires testing of the putative therapeutic strategies in appropriate animal models. Because pulmonary vascular and RV remodeling is a complex and multifaceted process, the study of a single animal model will never fully represent all the changes that occur in patients. Researchers need to combine both small and large animal studies as well as different models in order to unravel the key pathophysiological mechanisms of RV remodeling.

Although numerous studies have demonstrated the usefulness of large animal models for mimicking pulmonary hypertension (PH), including primates [8], calves [9], sheep [10], pigs [11], and dogs [12], small animal models of pressure overload are preferable. In some cases, large animals may be better model species for the human disease than rodents, and provide models of mechanisms that do not exist in rodents. Nevertheless, large animal models are often more expensive than rodents, and they are often less acceptable for ethical reasons [13]. The practical advantages of rodents are their short gestation period and the low cost of breeding and housing compared with other mammalian models. Additionally, the availability of genetically modified mice and rats allows us to perform more detailed pharmacological and molecular-mechanistic studies of the cardiovascular system and to better understand the physiology and pathology of the human disease. Indeed, for the best characterization of animal models, accurate cardiovascular phenotypic characterization, including adequate imaging approaches (e.g. echocardiography or magnetic resonance imaging) is needed. Recent technical developments have meant that noninvasive imaging techniques previously used in a clinical setting have been scaled down to allow high-resolution imaging of rodents, thus enabling serial studies to be performed in a single animal. Importantly, these techniques also allow us to monitor disease progression.

Previously published papers of our group [14] and later of Ryan et al.[13] suggest that rodent models of PH should be classified using nomenclature similar to that used by the World Health Organization to categorize human PH. However, some animal models are missing in this classification. Recently published reports and the latest advances in animal models of PH provide an opportunity to modify the existing classification of animal models (Table 5.1). Most animal models for PH and right heart hypertrophy (some of which also develop right heart failure), which are highlighted in Table 5.1 and 5.2, involve direct modification of the pulmonary (vascular) structure (Fig. 5.1) to increase the resistance the right heart has to work against. These models make it difficult to assess whether the effects of a drug on the right heart are secondary, due to RV unloading, or primary effects on right heart remodeling. An important animal model that has recently attracted attention, that exclusively induces RV hypertrophy without initially affecting other organ systems, is the pulmonary artery banding (PAB) model [15]. This surgical method has been employed not only in large animals such as pigs

Table 5.1 World Health Organization classification of PH and small animal models

Group of PH	Animal models
Group 1 PAH	MCT-induced PAH in rats
	MCT + pneumonectomy in rats
	Sugen + hypoxia in rats and mice
	Fawn-hooded rat
	Schistosomiasis in mice
Group 2 PH due to left heart disease	TAC in mice and rats
	Acute MI model
Group 3 PH due to lung disease and/or hypoxia	Hypoxia-induced PH in mice and rats
	Chronic intermittent hypoxia in mice
	COPD models or smoke exposure model in mice
	Bleomycin-induced pulmonary fibrosis
Group 4 CTEPH	Repeated microembolization with microspheres in rats
Group 5 PH with unclear and/or multifactorial mechanism	—

COPD chronic obstructive pulmonary disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *MCT* monocrotaline, *MI* myocardial infarction, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *TAC* transaortic constriction

and dogs [16] but also in small laboratory rodents such as rats [17, 18] and mice [19, 20]. In this model, the pulmonary artery is constricted to a smaller diameter, thereby increasing the resistance, which finally leads to extensive RV hypertrophy as well as cardiac fibrosis and finally RV failure. This model allows us to elucidate the effects of treatment on the right heart and define the pathophysiological mechanisms underlying RV hypertrophy and failure independently of the pulmonary vasculature.

Although our understanding of right heart hypertrophy and failure has improved in recent decades, knowledge is still limited about pathophysiological features of the RV response to pressure overload, and especially about mechanisms that underlie the transition from hypertrophy to dilatation in PAH-associated right heart failure, which has not as yet been well defined. Here we shall discuss the mechanisms of the physiological/pathophysiological response of the pulmonary vasculature in response to variety of chemical (e.g. monocrotaline [MCT]) and physiological (e.g. hypoxia) stimuli with special emphasis on the right ventricle in small animals.

Table 5.2 Animal models and the right ventricle

Animal model	Precapillary arteriopathy	Plexiform-like lesions	RVSP	RVH	RV function	RV fibrosis	RV vascularization
MCT rat model	↑+	—	↑+	↑+	↓+	↑+	↓+
MCT + pneumonectomy	↑+	↑+	↑+	↑+	↓+	NA	NA
Chronic hypoxia in rats	↑+	—	↑+	↑+	↓+	↑+	NA
Chronic hypoxia in mice	↑+	—	↑+	↑+	↓+	↑+	NA
SUHx in rats	↑+	↑+	↑+	↑+	↓+	↑+	↓
SUHx in mice	↑+	↑+	↑+	↑+	↓+	NA	NA
PAB in rats	—	—	↑+	↑+	↓ or ↔	↑ or ↔	↓ or ↔
PAB in mice	—	—	↑+	↑+	↓+	↑+	NA
Schistosomiasis	↑+	↑+	↑+	↑+	↓+	NA	NA
TAC	↑+	—	↑+	↑+	↓+	↑+	NA
MI	↑+	—	↑+ or ↔	↑ or ↔	↓+	↑+	NA
Smoke-exposure model	↑+	—	↑+	↑+	NA	NA	NA
Intermittent hypoxia	↑+	—	↑+	↑+	NA	NA	NA

MCT monocrotaline-induced pulmonary arterial hypertension, *MI* myocardial infarction, *NA* data not available, *PAB* pulmonary artery banding, *RV* right ventricular, *RVH* right ventricular hypertrophy, *RVSP* right ventricular systolic pressure, *SUHx* Sugen + hypoxia model of pulmonary arterial hypertension, *TAC* transaortic constriction, ↑+ present and increased, ↔ no change, ↓+ present and decreased, — not present

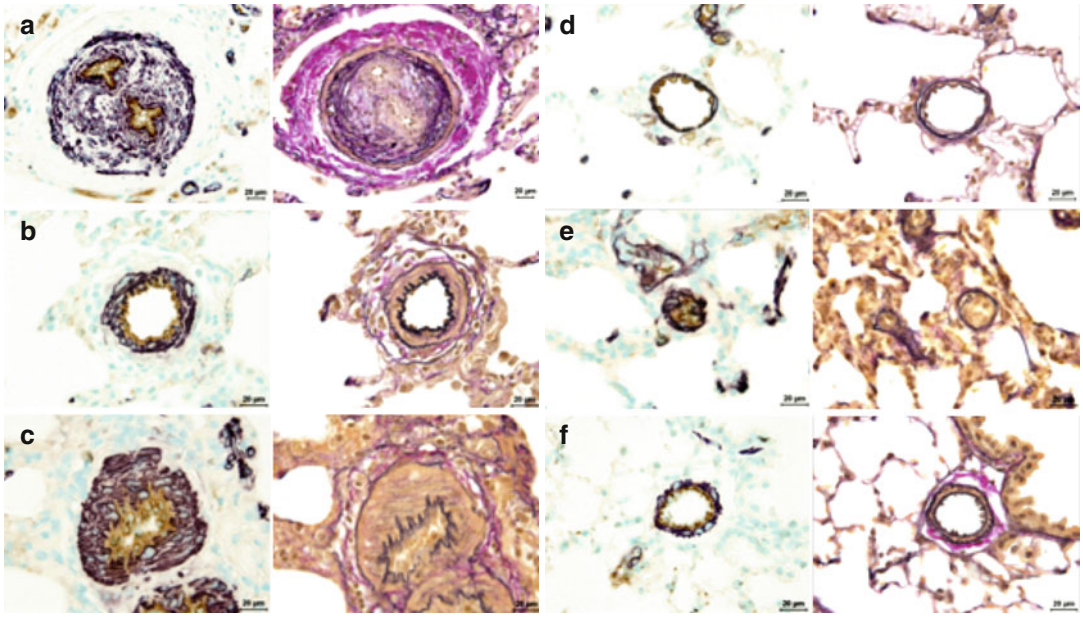

Fig. 5.1 Pulmonary vascular changes in animal models of pulmonary hypertension. Representative images of lung vessels from human idiopathic pulmonary arterial hypertension (PAH) (**a**) and different models of PH: monocrotaline-induced PAH (**b**); monocrotaline + pneumonectomy (**c**); Hypoxia-induced pulmonary hypertension in rats (**d**); Sugen + hypoxia (SUHx) induced pulmonary arterial hypertension in rats (**e**); Hypoxia-induced pulmonary hypertension in mice (**f**)

MCT-Induced PAH

MCT-induced PAH remains a frequently investigated model. MCT is an 11-membered macrocyclic pyrrolizidine alkaloid derived from the seeds of the *Crotalaria spectabilis* plant. After a single subcutaneous or intraperitoneal injection of MCT, the alkaloid is converted in the liver by cytochrome P450 (CYP3A4) to the reactive pyrrole metabolite dehydromonocrotaline (MCTP) [21–23], which in turn causes endothelial cell injury in the pulmonary vasculature with subsequent remodeling of the precapillary vessels (medial thickening and *de novo* muscularization of small pulmonary arterioles) and progressive PH and RV failure [24, 25].

The response to MCT is variable among species, strains, and even individual animals due to differences in the hepatic metabolism by cytochrome P450 [26]. Whilst MCT injection leads to severe PAH in rats, the injection or oral application of MCT in mice causes liver damage [27], modest pulmonary fibrosis [28–30], and immunotoxicity [31, 32], but not PH. This phenomenon can be explained by the fact that the liver metabolism of MCT to MCTP by the cytochrome P450 system may differ between rats and mice [22, 33]. However, our group has recently demonstrated that after MCTP injection mice develop a typical early-phase acute lung injury characterized by lung edema, neutrophil influx, hypoxemia, reduced lung compliance, and high mortality. In the late phase, MCTP-injection resulted in limited lung fibrosis and no obvious PH [34]. Therefore, the MCT rat model of PH remains a model favored by many investigators.

Although the MCT model has been in use for several decades, the basic mechanisms that underlie the induction of PH in this model remain unclear. It is known that the active MCTP rapidly causes pulmonary artery endothelial cell injury, pulmonary arterial medial hyperplasia, interstitial edema, adventitial inflammation, hemorrhage, and fibrosis [14, 26, 35, 36]. As a result, pulmonary vascular resistance (PVR) increases and RV hypertrophy and failure occur. Several

investigators demonstrated that a single MCT injection led to time- and dose-dependent abnormalities in the pulmonary vasculature and RV hypertrophy as well as abnormalities in function. It was shown that a single exposure of rats to MCT at a dose of 60–100 mg/kg results in PH and RV hypertrophy, dilatation, and failure in 3 or 4 weeks, and leads to mortality in most rats within 4–8 weeks [37–40]. In contrast, MCT at a dose of 30 mg/kg induces compensatory RV hypertrophy without signs of RV systolic dysfunction, but with diastolic dysfunction [39, 41], 4 weeks after injection. Recently, Ruiter et al. published an interesting observation [42]: the authors demonstrated that an injection of 40 mg/kg of MCT induces acute muscularization of the smallest pulmonary arterioles, together with high PVR, RV hypertrophy, and diminished RV function, as measured by echocardiography and confirmed by invasive hemodynamic measurement. However, 8 and 12 weeks after MCT administration pulmonary arteriolar abnormalities were resolved, accompanied by normalization of RV function, although cardiomyocyte hypertrophy was maintained. The authors concluded that MCT-induced PH is reversible after 4 weeks and does not resemble the progressive nature of human PH [42]. This observation needs to be confirmed in a large cohort of animals.

Nevertheless, numerous published reports have proposed that subcutaneous injection of 30–60 mg/kg of MCT in rats is appropriate to study compensatory and maladaptive RV remodeling. Many factors such as neurohormonal activation, oxidative and nitrosative stress, immune activation, myocardial ischemia, and cardiomyocyte apoptosis are involved in reprogramming the heart from adaptive to maladaptive remodeling. The underlying mechanisms of RV hypertrophy and failure in MCT rats are extremely complex and still not well defined. Several studies demonstrate that, despite a similar degree of pulmonary artery pressure (PAP) or RV systolic pressure in rats treated with MCT and rats subjected to PAB or Sugen plus hypoxia (SUHx), the severity of RV failure and mortality in MCT rats remains extremely high [17, 18, 43, 44]. It is still not clear whether RV failure is associated with heart inflammation/myocarditis due to direct effects of MCT on the RV myocardium [45, 46], or if it is a secondary effect due to pulmonary vascular injury and release of mediators which can increase stress on the right ventricle and lead to maladaptive RV hypertrophy.

Histomorphological evaluation of RV tissue demonstrated that MCT rats exhibit increased levels of RV interstitial and perivascular collagen deposition levels [18], which continuously increase throughout RV disease progression, being highest during RV failure [47]. In contrast, serial noninvasive measurements by scintigraphy with ^{99m}Tc-annexin, also confirmed by autoradiography and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay, show that in right ventricles of MCT rats cardiomyocyte apoptosis occurs at the early compensatory disease stage and declines, while still remaining significantly increased, when RV failure has occurred [47, 48].

Few reports have addressed the role of inflammation in RV remodeling in MCT-induced PH. It has been shown that progressive RV failure is associated with an increased number of leukocytes in the right but not the left ventricle [46, 49]. However, in rats subjected to a low dose of MCT (40 mg/kg) the number of CD45-positive leukocyte cells was comparable with that in healthy control animals [42, 46]. Additionally, it was reported that inflammation, assessed noninvasively by ^{67}Ga (an agent that binds to transferrin, leucocyte lactoferrin, bacterial siderophores, inflammatory proteins, and cell membranes in neutrophils), is elevated at an early compensatory stage of RV hypertrophy, reaches its highest levels at the stage of RV dilatation, and remains elevated compared with baseline throughout disease progression to RV failure [50]. In parallel, high immunoreactivity and elevated levels of matrix metalloproteinase (MMP)-2 and MMP-9 were found in RV tissue of MCT rats [51]. Electrophysiological studies revealed that in MCT rats, all of the above-mentioned changes in the failing heart can lead to RV electrical remodeling, arrhythmias, and even spontaneous ventricular fibrillation, which may be considered as the main reasons for high mortality in this model [52–54].

Additionally, there is growing evidence that an oxygen supply/demand mismatch and metabolic changes in the right ventricle play an important role in adaptive or maladaptive RV remodeling [55]. RV capillary rarefaction is one phenomenon that leads to maladaptive RV remodeling. Interestingly, some studies examining capillary density in MCT rats demonstrated reduced numbers of capillaries and down-regulated vascular endothelial growth factor (VEGF) expression in advanced MCT-induced RV failure [49, 55, 56]. In parallel, it was suggested that the failing right ventricle is characterized by abnormal metabolism due to the pressure overload. It was demonstrated that ^{18}F-fluorodeoxyglucose (FDG) uptake in the lungs of MCT animals increases with progression of the disease and MCT treatment also leads to reduction of oxygen consumption and increased glycolysis as well as FDG uptake in the failing right ventricle [43, 57]. Similar findings were observed in patients with idiopathic PAH and congenital heart disease [58, 59]. These studies indicate that increased FDG uptake by the lung and the right ventricle reflects the metabolic state of the small pulmonary arteries and the pressure-overloaded right ventricle, and therefore can be used as an early diagnostic marker of disease severity and might be useful for PAH monitoring.

MCT Plus Pneumonectomy

As mentioned above, the MCT rat model is the most frequently used model, in which animals develop PAH with endothelial damage, vascular smooth muscle hypertrophy, and severe RV failure. However, in this model the plexiform-like vascular lesions that are found in human PAH do not occur. Since the MCT model does not fully reflect the clinical or pathological picture seen in human PAH, efforts have been made to modify this model to induce progressive pulmonary vascular disease with neointimal changes. Thus, Okada et al. established a new animal model in which MCT administration is followed by unilateral pneumonectomy [60]. The authors compared the changes in pulmonary vasculature in MCT plus pneumonectomy animals with the changes in those receiving MCT or pneumonectomy alone. They found that neointimal changes developed in more than 90 % of all right-lung intraacinar vessels in rats subjected to MCT injection plus pneumonectomy, but not in animals receiving either MCT or pneumonectomy alone. Additionally, they demonstrated that animals with a neointimal pattern of remodeling developed more severe RV hypertrophy compared with animals receiving MCT or pneumonectomy alone [60, 61]. Importantly, other investigators were able to reproduce this observation [62–64]. Despite the fact that the exact mechanisms that lead to neointimal formation in this model are still unknown, it is clear that the combination of MCT-induced endothelial lung injury and the increased vascular shear stress and blood flow to the remaining lung due to pneumonectomy is necessary to produce neointimal formation.

White et al. administered MCT to young rats following pneumonectomy and found that younger animals develop a more severe phenotype and die earlier than in previously reported models [60, 65]. This more severe phenotype was associated with plexiform-like lesions, severe vascular pruning, and networks of disorganized capillaries. Unfortunately, none of these studies investigated the RV histomorphological changes and function in detail, and therefore additional studies are required to distinguish the mechanisms involved in the formation of occlusive and plexiform-like lesions in this model.

Hypoxia-Induced PH

Chronic hypoxia is the most commonly used physiological stimulus for PH development in animal models. This experimental model of PH represents group 3 of the PH classification. Exposure of animals to normobaric or hypobaric hypoxia for 2 weeks or longer induces PH in a wide variety of animal species including rats, mice, guinea pigs, dogs, cows, pigs, and sheep. The most commonly used species in laboratory models of PH are rats and mice. The hypoxia model is useful because it is very predictable and reproducible within the selected animal species as well as strain. However,

there is a great variability in responses to chronic hypoxia between species [26]. The most common pathological findings are muscularization of previously nonmuscularized vessels and a moderate medial thickening of muscular resistance vessels. Both pulmonary smooth muscle cells and adventitial fibroblasts proliferate under hypoxia [26, 66, 67]. These features are largely reversible on return to normoxic conditions.

Chronic Hypoxia in Mice

The mouse is a widely used species for the investigation of a growing number of disease states. In particular, the availability of knockout and transgenic mouse strains allows us to understand the molecular mechanisms of diseases more precisely. Chronic exposure of mice to a hypoxic environment leads to pulmonary vasoconstriction, endothelial dysfunction, extracellular matrix deposition, muscularization of previously nonmuscularized vessels, medial thickening of muscular resistance vessels, and subsequently to an elevation in PAP, PVR, and RV hypertrophy [68–71].

Despite the fact that many investigators have extensively studied the mechanisms of hypoxia-induced pulmonary vascular remodeling in rodents, the mechanisms underlying RV hypertrophy and failure in hypoxic models remain largely elusive. Recent advances in noninvasive high-resolution imaging techniques allow us to characterize heart function in rodent models of PH more precisely. Basic parameters such as RV internal diameter, pulmonary artery acceleration time (PAAcT) or ratio of PAAcT to pulmonary artery ejection time, cardiac output, and tricuspid annular plane systolic excursion were described and validated in humans and rodents [72–76].

The results of hemodynamic and echocardiographic studies in hypoxic mice showed that mice developed mild or moderate PH with shortened PA AcT, and RV hypertrophy with preserved systolic function [74, 77, 78] or in some cases mild systolic dysfunction [70, 79–81]. Only one study quantified collagen content in the right ventricle by immunohistochemistry, in which the authors showed increased collagen content in hypoxic mice [71]. However, it should be mentioned that responses to hypoxia in mice are strain specific, and that intraspecies comparisons could vary significantly depending on the strains compared.

Chronic Hypoxia in Rats

Hypoxic rats develop more severe PH than hypoxic mice. However, there is considerable variability in the magnitude of the response to chronic hypoxia exposure in different rat strains due to genetic origin. For example, the fawn-hooded rat (FHR) is a strain in which PH occurs spontaneously [82] and it appears to be more susceptible to the development of more severe PH than control rats even after exposure to only mild hypoxia [83]. FHRs show increased endothelin levels, enhanced serotonin-induced vasoconstriction, a platelet storage pool deficiency, excessive pulmonary artery smooth muscle cell proliferation, and mitochondrial dysfunction [83, 84]. FHRs have been described as having normal PAP until 20 weeks of age, but by 40 weeks, despite normal systemic blood pressure and oxygen partial pressure, they develop manifest PAH and RV hypertrophy. Moreover, normoxic FHRs show a leftward shift in the pulmonary vascular pressure–flow relationship, which is similar to that shown by Sprague–Dawley rats exposed to chronic hypoxia, and they display medial hypertrophy of resistance pulmonary arteries in a comparable manner [84]. In contrast, the Fischer 344 rat strain is relatively well protected from hypoxia-induced pulmonary vascular and cardiac responses compared with the Wistar Kyoto rat strain [85, 86]. However, the major limitation of the above mentioned animal models of PH is that they do not develop occlusive neointimal and plexiform lesions, even in rats exposed to longer periods of hypoxia [87].

Sugen 5416 Plus Chronic Hypoxia in Rats

A rat model that better mimics the pulmonary vascular changes seen in human PAH is the combination of a single subcutaneous injection of the

VEGF receptor inhibitor Sugen (SU 5416) with exposure to chronic hypoxia (SUHx) for 3–5 weeks [88, 89] followed by re-exposure to normoxia [88, 90].

It has been shown that SUHx rats develop progressive PH and vascular remodeling even after being re-exposed to normoxia [88, 91]. By 5 weeks (3 weeks of hypoxia and 2 weeks of re-exposure to normoxia) after the SU 5416 injection the rats had developed severe PH and RV hypertrophy accompanied by proliferation of apoptosis-resistant endothelial cells and occlusive neointimal but not plexiform-like lesions in precapillary pulmonary arterioles. Recently, Abe et al. demonstrated that rats receiving a single injection of SU 5416 followed by exposure to 3 weeks of hypoxia and an additional 10–11 weeks of re-exposure to normoxia (13–14 weeks after the SU 5416 injection) developed severe PAH accompanied by pulmonary arteriopathy strikingly similar to that observed in severe human PAH. In this study, the authors found that at a much later stage (13–14 weeks after the SU 5416 injection) the rats developed complex plexiform lesions [90]. Interestingly, the irreversible progression of the pulmonary vascular disease and RV failure in this model led to death in some but not all animals at different time courses [90].

SUHx rats develop severe RV hypertrophy, dysfunction, and failure. An echocardiographic evaluation of cardiac function showed that SUHx rats developed severe RV hypertrophy with deteriorated systolic and diastolic functions, which progressively worsened from day 21 to day 35 [89]. RV failure in SUHx rats was also accompanied by fibrosis, capillary rarefaction, cardiomyocyte apoptosis, and furthermore by decreased expression of genes encoding angiogenesis factors such as VEGF, insulin-like growth factor 1, apelin, and angiopoeitin-1, and increased expression of genes encoding a set of glycolytic enzymes [89, 92, 93]. It seems that the SUHx rat model may be useful for addressing the etiological mechanisms involved in endothelial cell hyperproliferation, which is a distinctive plexogenic arteriopathy characteristic in humans with severe PAH.

Sugen 5416 Plus Chronic Hypoxia in Mice

Recently, Ciuclan et al. established a mouse model in which PH is induced by the above-mentioned combination of VEGF receptor inhibition and chronic hypoxic exposure [81]. Compared with normobaric chronic hypoxia alone, treatment with SU 5416 resulted in markedly increased RV systolic pressure, increased RV hypertrophy, and increased muscularization of small pulmonary vessels. In addition, the authors found occlusive neointimal lesions of small vessels in SUHx mice, which do not occur in mice under hypoxia alone. The vascular remodeling process induced by a combined application of hypoxia and SU 5416 was paralleled by an increased caspase activity and an increased proliferation of endothelial cells. The authors also demonstrated that SUHx mice developed more severe RV dilatation and cardiac dysfunction compared with mice exposed to hypoxia alone. The authors addressed the question of whether the PAH pathologies in SUHx mice are reversible after returning mice to normoxic conditions. Thus, 10 days after normoxic exposure SUHx mice showed slight decreases in hemodynamic parameters, indicating that this model of PH is less severe than the one in rats. Two follow-up studies in SUHx mice confirmed this observation [94, 95]. Combined with the obvious ease of gene manipulation in mice, this new model of PH may prove to be useful in deciphering specific mechanisms and designing targeted therapies [96].

Schistosomiasis

Schistosomiasis is one of the most common causes of PAH: of the more than 200 million individuals chronically infected worldwide, 2–5 % have PAH [97]. Approximately 10 % of people chronically infected with *Schistosoma mansoni* develop hepatosplenic schistosomiasis, a syndrome of preportal fibrosis, and portocaval shunting [98]. Approximately 10–20 % of those patients with hepatosplenic disease, or two to five million people worldwide, develop PAH [99, 100]. Patients

who develop schistosomiasis-associated PAH have the signs and symptoms of this condition, primarily resulting from progressive right heart failure. The pulmonary histopathology of schistosomiasis-associated PAH has both similarities to and differences from other forms of PAH that are more common in the developed world, most classically idiopathic PAH [101]. Analysis of pulmonary tissues from patients who died from schistosomiasis-associated PAH revealed that all lung samples showed evidence of pulmonary vascular remodeling, arterial medial thickening, and plexiform-like lesions [102, 103].

It was demonstrated that up to 20 weeks after infection with *S. mansoni* in mice a time-dependent increase in liver and lung egg burden resulted, along with extensive pulmonary vascular remodeling and development of plexiform-like lesions despite the absence of significant PH and RV hypertrophy [104]. This was likely due to marked heterogeneity in the lung egg burden among individual animals. In individual animals the authors found a significant correlation between lung egg burden and the ratio of RV weight to LV plus septum weight, indicating that the RV index was higher in animals with a greater density of eggs in the lung. In another study, Crosby et al. demonstrated that at the late time point (25 weeks) chronic infection with *S. mansoni* leads to significant elevation of the RV systolic pressure and RV hypertrophy [105].

Until now, the pathogenic mechanism by which the combination of the parasite's effect on the host and the host's immune response to the parasite results in PAH remains unclear. However, local inflammation may contribute to the process of pulmonary vascular remodeling [105–107]. Further pre-clinical investigations are needed to uncover the pathophysiological mechanisms involved in the development of severe pulmonary vascular remodeling and RV hypertrophy.

PH Due to Left Heart Disease

PH due to left heart disease, classified as group 2 according to Dana Point 2008 [108], is the most common cause of PH and is associated with high morbidity and mortality. Three distinct subcategories based on etiology divide this group: left heart systolic dysfunction (e.g. ischemic cardiomyopathy, dilated cardiomyopathy), left heart diastolic dysfunction (e.g. hypertensive heart disease, coronary heart disease, hypertrophic cardiomyopathy), and left heart valvular diseases (e.g. aortic or mitral valve stenosis, aortic or mitral valve regurgitation) [108]. The backward transmission of increased left atrial pressure leads to pulmonary capillary and arterial remodeling, thereby challenging the pulmonary vascular structural integrity and functional properties [109]. Pathological changes in pulmonary veins and arteries, including muscularization of the arterioles and medial hypertrophy and neointima formation in the distal pulmonary arteries, then lead to an increase of PVR [110]. The right ventricle is the ultimate victim of these vascular processes and the elevated PVR: a common phenotype of end-stage heart failure patients is that of predominant RV failure with systemic venous congestion, renal dysfunction, and ascites [111]. Multiple mechanisms may lead to RV dysfunction in association with left heart disease: (i) by increasing pulmonary venous and ultimately pulmonary arterial pressure, LV failure increases the afterload the right ventricle has to work against [112]; (ii) the right ventricle may be affected by the same cardiomyopathic process as the left ventricle; (iii) both ventricles may be damaged by myocardial ischemia; (iv) LV dysfunction may lead to a decreased systolic driving pressure of RV coronary perfusion, which may be a substantial determinant of RV function [113, 114]; (v) due to septal dysfunction, ventricular interdependence may occur; and (vi) RV diastolic function may be restricted by LV dilation in a limited pericardial compartment. However, despite the relatively large number of affected patients and the link with poor outcome, there are currently no therapeutic options for patients with PH due to left heart diseases. International guidelines give little advice other than to manage systemic hypertension and volume status and to optimize underlying conditions. Additionally, the European Society of Cardiology and the European Respiratory

Society guidelines discourage the use of drugs approved for PAH in PH due to left heart disease, because of missing evidence for a favorable risk-to-benefit ratio [115, 116]. Therefore, further research is needed employing adequate animal models to identify and modify novel therapeutic options and/or targets in right heart insufficiency due to left heart failure.

The most commonly employed models of left heart failure use the response to a surgical intervention such as banding of the transverse aorta or ligation of a coronary artery to display the multisystem effects of LV heart failure. One major advantage of such surgical models is that they very closely replicate the specific disease situation of either myocardial infarction (MI; coronary artery ligation) or heart failure owing to hypertension or aortic stenosis (transverse aortic constriction). However, one demerit of those surgical models is that heart failure occurs rapidly post surgery in the context of the relatively young heart of a laboratory animal, whereas in humans the onset of the disease may be subtle, occurring over several years in the context of co-morbidities and age-related changes.

Myocardial Infarction (MI)

Both the left and right ventricles are involved in compensatory mechanisms after acute MI. RV hypertrophy may even occur in experimental models of MI if the right ventricle is initially spared [117]. Additionally, sufficient myocardial damage can be caused by RV infarction, finally resulting in heart failure, shock, arryhthmias, and death of the patient [118]. The chronic MI model was first described in rats by Pfeffer et al. in 1979 [119]. It resembles the pathophysiological changes of remodeling and deterioration of systolic and diastolic cardiac function in patients with ischemia-induced heart failure. The animals develop myocardial hypertrophy, inflammation, and fibrosis resulting in LV systolic and diastolic dysfunction with reduced contractility and increased LV end-diastolic pressure [77]. Since then the murine model of MI and ischemia-reperfusion has been described widely in the literature and a detailed procedure description was published by Michael et al. in 1995 [120]. The usual approach is to ligate the left anterior descending (LAD) coronary artery, the major vessel that supplies blood to the left ventricle [121]. Once the LAD artery is occluded, this results in MI of the anterior wall of the left ventricle and the anterior portion of the interventricular septum [122]. The size of the infarction site is dependent on the position of the ligation: for most studies, the LAD artery is ligated below the tip of the left auricle, which induces roughly 40–50 % ischemia of the left ventricle.

Few researchers have so far investigated the effects of left heart failure due to MI on PH and RV function. In 2000, Nguyen et al. reported that an early intervention with endothelin receptor antagonists following coronary artery ligation in male Wistar rats reduced the development of PH as reflected by a significant decrease in RV systolic pressure, despite the lack of improvement in LV function [123]. Ben Driss and colleagues showed that in compensated left heart failure induced by small MI in male Wistar rats, hemodynamics, vascular wall function, and structure were altered in the pulmonary artery but preserved in the thoracic aorta. They concluded that the pulmonary vascular bed is an early target of regional circulatory alterations in left heart failure [124]. Later, in 2003, Jasmin et al. found that rats with large MIs developed progressive PH and right heart hypertrophy due to important pulmonary structural remodeling, which was already apparent after 2 weeks after surgery [125]. They measured marked elevations in the RV systolic and diastolic pressures as well as an increased ratio of RV weight to LV plus septum weight in rats with MIs, changes that were completely reversed by therapy with an angiotensin II receptor antagonist [125]. In 2010, Jiang et al. studied the applicability of a single measurement of troponin T for early prediction of infarct size, congestive heart failure, and PH in an animal model of MI. They concluded that an early single plasma cardiac troponin T measurement correlated with the infarct size in rats, and provided good sensitivity and specificity to predict congestive heart failure with secondary PH [126]. In 2011 the

same working group investigated the effects of statins on PH and RV function in ischemic congestive heart failure. The authors found that statins reduced lung remodeling and dysfunction associated with heart failure, with prevention of RV hypertrophy and PH [127]. Also in 2011, Toldo et al. reported that acute MI led to hypertrophy and induced a significant acute decline in RV systolic function even in the absence of PH [128]. They concluded that RV dysfunction also develops independently of changes in RV afterload [128].

Transverse Aortic Constriction (TAC)

Numerous LV pressure overload models have been developed in rodents in recent decades, but the TAC model remains perhaps the most widely used, first described by Rockmann et al. in 1994 [129]. The aortic banding model induces a pressure overload physiology such as that which may be found in aortic stenosis, systemic hypertension, and coarctation of the aorta. Initially, TAC leads to compensated hypertrophy of the heart (left ventricle), which is often accompanied with an enhancement of cardiac contractility. However, over time the response to the chronic pressure overload becomes decompensated, finally resulting in dilatation and heart failure [130]. Within 2 weeks after TAC surgery, an approximately 50 % increase in LV mass can be observed, making this model a good choice to study the usefulness of pharmacological or molecular interventions that may have beneficial effects on hypertrophy, fibrosis development, and/or heart failure [131]. Several locations of the aortic arch may be used for the banding: by positioning a 25- or 26-gauge needle next to the ascending or transverse aorta, knotting a thread around both the artery and the needle, and removing the needle immediately afterwards, the aorta remains constricted to the diameter of the 25- or 26-gauge needle [121]. Once the aorta has been constricted to the predefined diameter, the resulting increased resistance leads to chronic pressure overload and subsequent pathological LV remodeling. The major drawback of this animal model for LV hypertrophy and failure is probably the acute onset with which the banding procedure induces increased resistance and severe hypertension, therefore lacking clinical relevance. A second demerit of the TAC model may be its variability in the LV remodeling responses among different mouse strains: C57BL6 mice develop rapid LV dilation after TAC that may not occur with other strains [132, 133]. Nonetheless, there are a lot of examples in the literature of how this model can be used to identify and modify novel therapeutic targets in heart failure.

LV failure and its effects on the pulmonary circulation and RV function have not as yet been studied widely. Few publications try to explain the finding that TAC-induced LV dysfunction is also associated with RV dysfunction: in 2012, Chen et al. reported that male C57BL/6 J mice with a TAC displayed right heart hypertrophy as well as fibrosis, increased RV end-diastolic pressure, and right atrial hypertrophy 8 weeks after surgery [134]. They stated that these findings were due to massive pulmonary fibrosis and vascular remodeling.

Chronic Thromboembolic PH (CTEPH)

CTEPH is a form of PH caused by unresolved thromboemboli from sites of venous thrombosis, which undergo fibrotic organization in the lung. Incomplete thromboembolic resolution results in endothelialized residua that obstruct or significantly narrow major pulmonary arteries [135]. Once lodged in the lung arteries, these residua can cause more clots to form (thrombosis) and add more resistance to the blood flow through the lung, thereby increasing the pressure inside the lung. This obstruction of proximal pulmonary arteries leads to an increased PVR, development of PH, and progressive RV remodeling and failure. Pulmonary endarterectomy, a surgical method that removes the obstruction from pulmonary vessels, is the treatment of choice for patients with CTEPH [136].

Much effort has been made to generate appropriate animal models for this disease in order to

better understand the pathophysiology of CTEPH and to test new therapeutic approaches. In contrast to CTEPH, acute pulmonary embolism is easily reproduced in several animal models: to study the pathophysiological mechanisms or drug effects within the first hour following embolization, various different materials including autologous blood clots have been employed [137–139]. The development of a chronic CTEPH model turned out to be extremely challenging because of very efficient endogenous fibrinolytic systems in the employed animal species [140, 141]. Additionally, Mitzner et al. reported that the systemic vascular response to chronic pulmonary vascular obstruction varies from species to species, with proliferation of bronchial arteries into the intraparenchymal airways in large animals or, in contrast, with proliferation of intercostal arteries into the pleural space in mice [140, 142]. CTEPH can be generated in dogs by repeated microembolizations of microspheres (e.g. Sephadex) [143, 144]. The vascular lesions can be targeted to vessels of different size based upon the size of the injected microspheres. Repeated administration can lead to a sustained rise in pulmonary pressure [144]. High PVR is the result of primary vascular mechanical obstruction and vasoconstriction [45, 145]. In pigs, Weimann et al. generated a different model employing three repeated embolizations with polydextrane microspheres, which led to sustained PH with sustained elevation in PAP as well as RV hypertrophy [144]. Another chronic model of CTEPH in dogs was described by Moser et al., who employed a combined approach: pulmonary emboli were released from autologous venous thrombi, and the endogenous fibrinolytic system was inhibited by administration of tranexamic acid [146] or plasminogen activator inhibitor type 1 [147]. Unfortunately, these attempts did not result in stabilization of the thrombus, but resulted in its resolution latest within 1 week. In 2013, Li et al. reported that this method was also efficient in Sprague–Dawley rats and induced a stable increase in RV systolic pressure, right heart hypertrophy, and fibrosis [148]. Other authors used a surgical approach, the unilateral PAB model, to mimic CTEPH in pigs [149]. Naturally, a partial stenosis of the right or left pulmonary artery leads to an increased pressure in the right ventricle with development of RV hypertrophy and fibrosis, but this type of model does not reproduce distal vascular remodeling in the non-obstructed pulmonary arterial bed as seen in the human disease situation, which finally leads to the development of PH. Recently, Mercier at al. developed a CTEPH piglet model, which consists of a primary left pulmonary artery ligation via a sternotomy followed by weekly transcatheter embolizations, under fluoroscopic control, of the tissue adhesive enbucrilate (Histoacryl) into the right lower lobe for a duration of 5 weeks [150]. The authors asserted that this model reproduced all the features of human CTEPH: increased PVR, increased mean PAP, increased medial thickness of distal pulmonary arteries in both obstructed and unobstructed territories, increased systemic blood supply through the bronchial arteries in the obstructed territories, RV hypertrophy, RV enlargement, and paradoxical septal motion [150].

To conclude, over recent decades several animal models for CTEPH have been developed, which have provided valuable insights into some aspects of the pathophysiology of CTEPH. Animal models that represent more closely the human situation need to be developed in future.

Pulmonary Artery Banding (PAB)

A wide spectrum of animal models has been used in order to assess the anatomical, pathophysiological, and molecular adaptations of the right ventricle. Animal models for RV hypertrophy and failure mostly involve a direct modification of the pulmonary vascular structure. An increase in resistance in the vascular bed of the lung results in a higher afterload for the right ventricle to work against (e.g. the hypoxia rat or mouse model and the MCT rat model). If researchers employ these models it is difficult to distinguish between the direct effects of drug treatment on the right heart and secondary effects that are due to RV unloading. The PAB model allows the elucidation of the effects of treatment on the right ventricle independently of the

pulmonary vasculature, as a partial stenosis of the pulmonary artery results in a constantly elevated afterload and resistance. The PAB model was first generated in larger animals such as dogs and piglets, but progress in microsurgical techniques allowed the model also to be employed in smaller laboratory animals such as rats [151, 152] and mice. In 1994 Rockmann et al. applied the pulmonary banding model for the first time in mice [129], but the first comprehensive publication was by Tarnavski et al. in 2004, who explained in detail the banding procedure [121]: by positioning a 26-gauge needle next to the pulmonary artery, knotting a thread around both the artery and the needle, and removing the needle immediately afterwards, the pulmonary artery remained constricted to the diameter of the 26-gauge needle. Other groups modified this method slightly by using a hemoclip applier and hemoclips instead of a needle and thread [153], which gives several advantages: (i) the hemoclip can be applied quickly; (ii) with no needle involved, complete constriction of the pulmonary artery does not occur, avoiding possible rapid decompensation of the right heart and/or pathological changes different from the ones intended; and (iii) this method is highly reproducible due to the stability of the clip, compared with the thread which might loosen.

Once the pulmonary artery has been constricted to a pre-defined diameter, the resulting increased resistance leads to chronic pressure overload and subsequent pathological RV remodeling (Fig. 5.2). Both structural and functional changes can be observed in the artificially pressure-overloaded right heart. Functionally, after a first rapid decline immediately after the banding operation, the RV ejection fraction recovers for up to 14 days, after which it starts to steadily deteriorate. Main structural changes are: (i) growth of the right ventricle; (ii) growth of the individual cardiomyocytes; and (iii) increase in collagen content, e.g. right heart fibrosis. Increased RV fibrosis is experimentally as well as clinically associated with a decreased RV ejection fraction [154] and diastolic heart failure [155], and resembled a predictor of diastolic and systolic dysfunction during exercise in hypertrophic cardiomyopathic patients who successfully underwent surgery [156]. A reduced compliance of the (right) heart is the result of the pathological increase in collagen levels that leads to myocardial stiffness [157, 158]. Additionally, the normally coordinated excitation–contraction coupling is disrupted by the development of massive fibrotic tissue, which interferes with the heart working as a syncytium [155]. Also, the left ventricle is affected by the changes in the pressure-overloaded right ventricle: not only does the LV mass diminish slightly, but the left ventricle is no longer able to expand to its original volume, which causes major impairment of the LV stroke volume. Compression of the left ventricle is a direct result of an increased pressure in the right ventricle, which in turn exerts pressure on the left ventricle, reflected by an elevated LV eccentricity index.

The response to the constriction of the pulmonary artery depends on the animal species employed: e.g. researchers may find more extensive changes in hemodynamics in rats compared with mice. In 2009, Bogaard et al. stated that isolated chronic RV pressure overload per se, which was induced by PAB, does not lead to severe RV dysfunction, myocardial fibrosis, or capillary rarefaction [17]. This is in contrast to the findings of other working groups: in 2009, Schäfer et al. investigated the effects of chronic inhibition of phosphodiesterase 5 on RV remodeling. They demonstrated that the PAB model drastically elevated the RV afterload, decreased cardiac index as well as stroke volume, and led to RV hypertrophy and dysfunction [159]. Kojonazarov et al. found in 2012 that the PAB model is associated with RV dilation, impaired RV function, increased fibrosis in the right ventricle, and capillary rarefaction [18]. Those findings were confirmed by Piao et al. [160, 161]. The authors additionally found that there is a mitochondrial switch from glucose oxidation to glycolysis due to myocardial ischemia in the right ventricle. The degree of the stenosis applied to the pulmonary artery may explain the discrepancy between the studies.

The major drawback of this animal model for RV hypertrophy and failure is probably the rapidity with which the banding procedure induces the increased resistance and afterload. One might

argue that this process reflects more the situation in acute pulmonary embolism rather than right heart insufficiency due to PH or other diseases of the lung, in which the resistance builds up gradually over a longer period of time. Nonetheless, because better models are lacking, the PAB model is still the gold standard method to elucidate changes and treatment effects directly on the RV, without concomitant changes in the pulmonary vascular structure. In summary, with the PAB model a reproducible animal model of right-sided heart hypertrophy and failure has been established to induce a mechanical overload of the right ventricle.

Other Models

Smoke-Induced PH

Cigarette smoke is the main preventable cause for chronic obstructive pulmonary disease (COPD), resulting in progressive proteolytic, inflammatory, and vasoactive responses that lead to emphysema, small-airway obstruction, and PH. Originally, it was believed that the increase in PAP is secondary to the lung pathology associated with COPD, as a result of hypoxia, emphysema, and loss of the vascular bed [162]. However, a recently published observation revealed that pulmonary vascular dysfunction, vascular remodeling, and PH precede the development of alveolar destruction [163]. In this paper the authors demonstrated that smoke exposure for up to 8 months resulted in the development of emphysema after 6 months in mice. Within 3 months, tobacco-smoke exposure caused increases in RV systolic pressure and the ratio of the absolute numbers of alveoli to the number of vessels, followed by RV hypertrophy: i.e., development of PH preceded the development of lung emphysema [163]. Also, guinea pigs exposed to cigarette smoke develop PH and RV hypertrophy at levels similar to those seen in animals exposed to hypoxia [164]. Although it has been shown that tobacco smoke leads to PH and RV hypertrophy, the effects of smoke exposure on the right ventricle still need to be elucidated.

Intermittent Hypoxia

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder and contributes to the emergence of systemic arterial hypertension, peripheral vascular disease, stroke, PH, and sudden cardiac death [165–167]. Based on human research, sympathetic activation, inflammation, and oxidative stress are thought to play major roles in the pathophysiology of OSA-related cardiovascular diseases. Exposure of rodents to brief episodes of hypoxia mimics the hypoxia and cardiovascular and metabolic effects observed in patients with OSA. Animal models of OSA have shown that endothelial dysfunction, vascular remodeling, systemic and pulmonary arterial hypertension, and heart failure can develop in response to chronic intermittent hypoxia. It was shown that 20–30 % of untreated OSA patients suffer from PAH. It was first thought that this phenomenon is restricted to patients with pulmonary co-morbidities such as COPD, but it is now widely accepted that OSA can itself lead to PH [168]. A histomorphometric study showed that mice exposed to chronic intermittent hypoxia develop characteristic features of PH such as elevated PAP, RV hypertrophy, and muscularization of small pulmonary arteries [169, 170]. Further research of chronic intermittent hypoxia in animal models is needed to enhance our understanding of the pathogenesis of OSA-related cardiovascular disease and PH and RV remodeling.

Summary

It is clear that there is no available perfect preclinical model of human right ventricular failure that fully reflects the complexity of the human disease situation and totally reproduces the full spectrum of the pathological changes found in human patients. In our opinion the different models have different strengths and weaknesses. Nevertheless, animal models can be used as valuable scientific tools to develop novel therapeutic strategies and to elucidate the pathophysiological mechanisms which play a role in the disease.

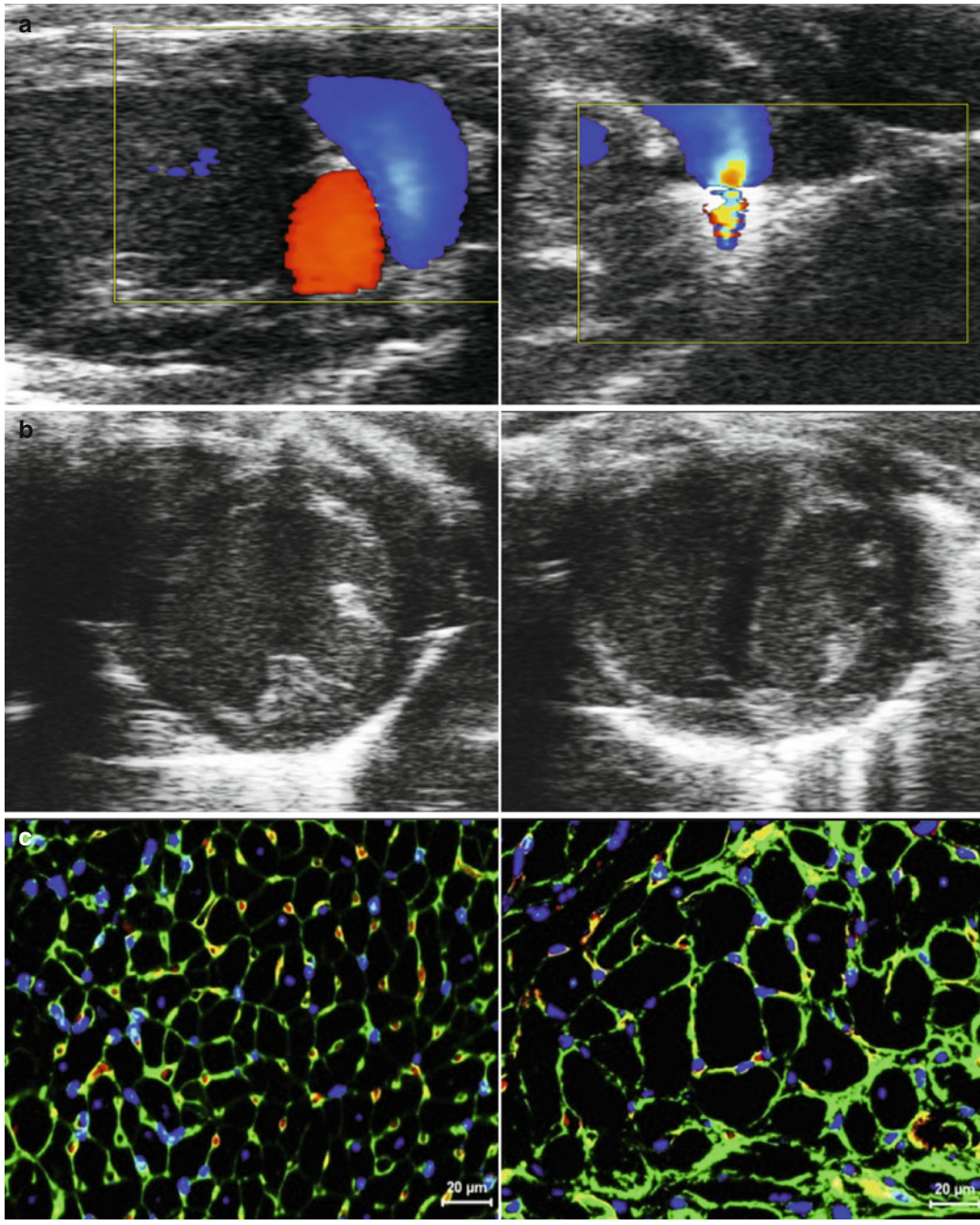

Fig. 5.2 Pulmonary artery banding (PAB) in mice. Representative echocardiographic images of the pulmonary artery and flow in healthy mice and mice subjected to pulmonary artery banding (PAB) (**a**); short-axis view on the level of pupillary muscles in healthy mice and mice subjected to PAB (**b**); representative images of the capillaries in healthy mice and in mice after PAB (**c**); representative images of right ventricular collagen in healthy mice and in mice after PAB (**d**)

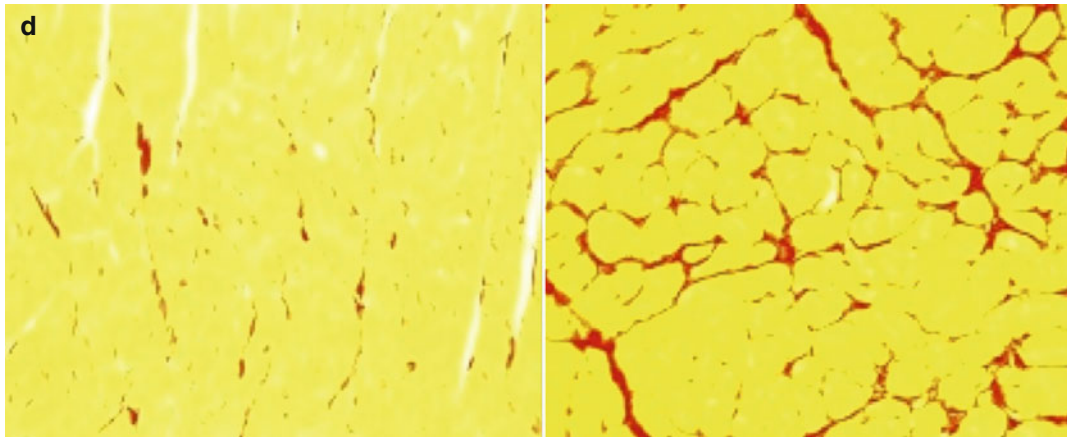

Fig. 5.2 (continued)

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Part II

Imaging the Right Heart

MRI of the Normal Right Ventricle at Rest

6

Melanie J. Brewis and Andrew John Peacock

Abstract

Cardiac magnetic resonance imaging (CMR) is perfectly suited to determination of right ventricular (RV) variables because the complex configuration of the RV is better described by three dimensional volume acquisition. This imaging modality has shown both accuracy and reproducibility for RV measurements and is, in most circumstances, superior to echocardiography. It is important to characterise normal variation in order to establish reference ranges for the healthy which can be used to determine abnormalities present in disease states. RV mass and volumes are affected by age, sex, race, and body size, and should be adjusted for patient demographics.

Abbreviations

BMI	Body mass index
BSA	Body Surface Area
CMR	Cardiac magnetic resonance imaging
LV	Left ventricular
MESA-RV	Multi-ethnic study of atherosclerosis right ventricle study
RV	Right ventricular
RVEF	Right ventricular ejection fraction
RVEDV	Right ventricular end diastolic volume
RVESV	Right ventricular end systolic volume
RVM	Right ventricular mass
RVSV	Right ventricular stroke volume
SSFP	Steady state free procession
SENC	Strain encoding
TAPSE	Tricuspid annular plane excursion

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Introduction

The role of Cardiac magnetic resonance (CMR) imaging is well established in the evaluation of wide range of cardiovascular diseases, both acquired and congenital. It is non-invasive and does not involve the use of ionizing radiation. Determination of ventricular volumes and function can be obtained by steady state free procession (SSFP) bright blood cine MRI without

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the need for contrast administration. Over the last two decades CMR has become recognised as the gold standard for assessing left and right ventricular structure and function with accuracy demonstrated in broad range of diseases [1–6] and in comparison to anatomical specimens [7]. It is particularly suited to the morphology of the right ventricle (RV) because the RV has a complex structure and contractile pattern which makes accurate assessment by 2D methods such as echocardiography more difficult. The high resolution, three dimensional images obtainable by CMR (Fig. 6.1) avoid the need for any geometrical assumptions and have been shown to have superior interstudy reproducibility for right ventricular volume and mass when compared with echocardiography. CMR is therefore an attractive modality for monitoring ventricular function in disease states [8–10]. More recently three dimensional echocardiography has emerged as a promising tool for assessment of RV volumes. Accurate volumetric data has been reported in variety of disease states including pulmonary hypertension (PH) and congenital heart disease. However reported accuracy in the literature has varied [11–15]. Challenges remain in acquiring good quality 3D data sets in patients with poor imaging windows and accuracy tends to decrease with increasing RV dilatation potentially limiting the use of 3D echocardiography in more advanced RV disease [16].

CMR also provides additional information on RV performance in the context of its loading conditions through assessment of intra-cardiac shunt, valvular regurgitation or stenosis from phase-contrast MRI, magnetic resonance angiography of the great vessels and finally myocardial disease from quantitative evaluation of segmental function, tissue characterisation with T1 weighted spin echo imaging for fatty infiltration or use of gadolinium contrast for regions of myocardial scarring and fibrosis.

CMR is not without limitation. It is less suitable for haemodynamic measurements than echocardiography due to more limited temporal resolution and, though accurate measurements can be made of flow, CMR cannot be used to measure pressure. It is expensive and less widely available in clinical practice. Incompatibilities with some ferrous implants such as cardiac pacemakers or aneurysm clips exist [17]. Claustrophobia, body habitus, long scan times and need for repetitive breath-holds for acquisition of images to reduce respiratory motion artefact may limit tolerance in some patients. However with advancing technology it is now possible to perform both single breath-hold techniques and real-time acquisitions with adequate resolution [18, 19].

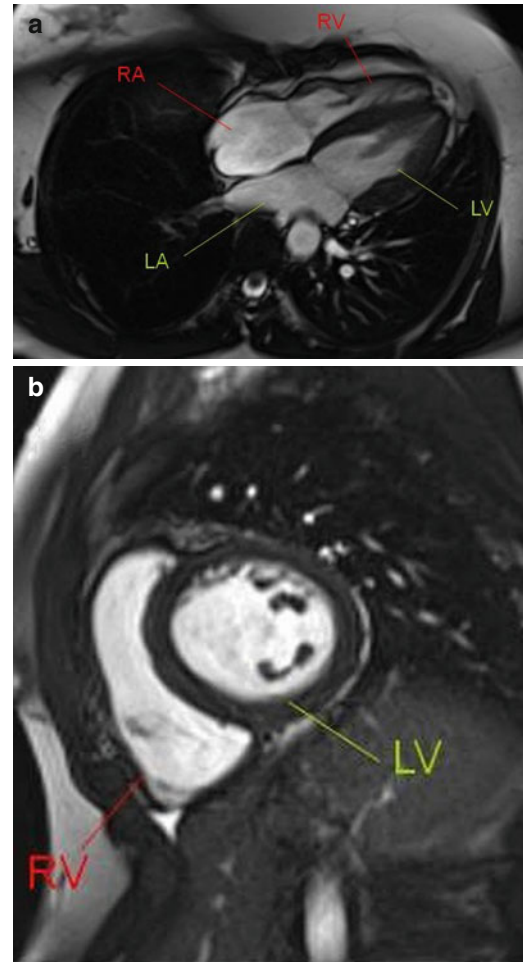

Fig. 6.1 Cardiac MRI images of normal subjects. (**a**) Four chamber or horizontal long axis view showing right and left atria (*RA* and *LA* respectively) and right and left ventricle (*RV*, *LV* respectively). (**b**) Short axis view

Measuring Ventricular Volumes, Mass and Global Function

Ventricular volume is determined using a "stack" of contiguous short axis slices 5–10 mm thick acquired during breath-hold (typically in region of 5–18 s), ECG-gated cine "bright" blood sequences (Fig. 6.2). This sequence gives good blood-myocardial contrast to allow tracing of endocardial and epicardial contours either manually or with use of semi-automated software on end-diastolic and end-systolic frames. Ventricular volume is calculated as sum of individual slice volumes (Simpson's rule). Ventricular mass is determined by multiplying myocardial volume by the muscle-specific density for myocardial tissue 1.05 g/cm^3. Inclusion or exclusion of the RV trabeculations as either mass or volume is source of interstudy variability and standardised approach is recommended [20]. Geometric shortening can be determined in both longitudinal and transverse planes. In the normal most of the RV contraction is longitudinal and is well described by echocardiogram derived tricuspid annular plane systolic excursion (TAPSE). However, transverse plane shortening has been shown to be superior to echo derived TAPSE as a surrogate for right ventricular ejection fraction (RVEF) in RV disease [21] and potential tool for monitoring RV performance [22]. Isovolumetric relaxation time can also be a marker of RV diastolic dysfunction which has been related to severity of disease in pulmonary arterial hypertension [23].

Interventricular interaction is another important consideration in RV dysfunction. In pulmonary hypertension, increased trans-septal pressure gradient causes bowing of the interventricular septum towards the LV (LVSB) which may affect LV filling [24]. CMR study in PH, using myocardial tagging techniques discussed below, has shown ventricular asynchrony with a left to right delay in myocardial peak shortening due to prolonged RV

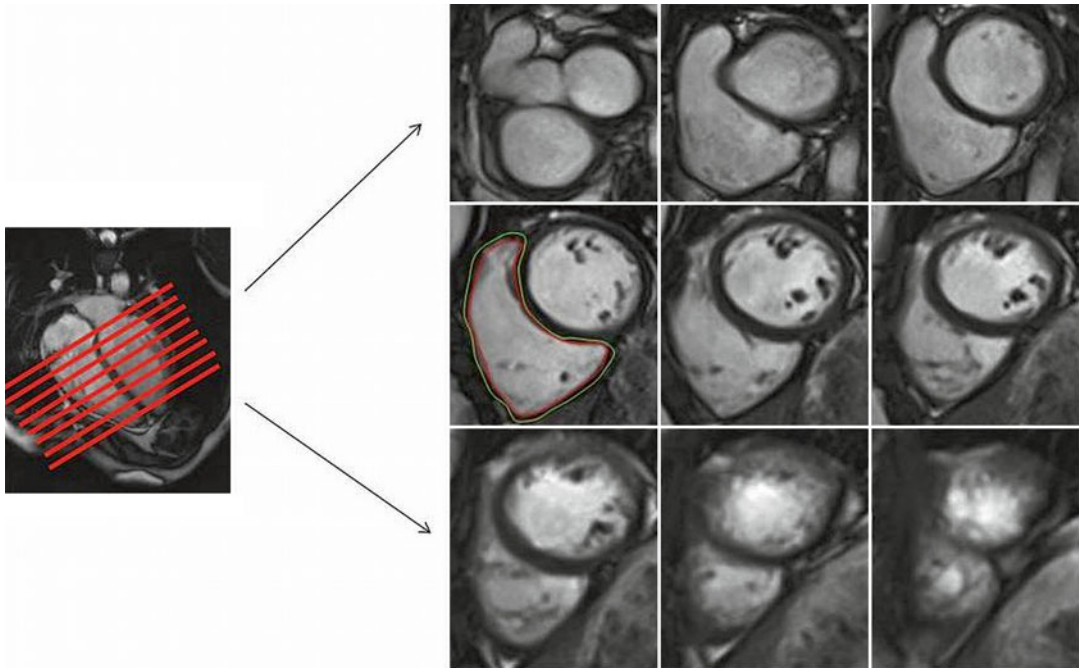

Fig. 6.2 Ventricular volume is determined using a "stack" of contiguous short axis slices 5–10 mm thick. Endocardial (shown in *red*) and epicardial contours (in *green*) are then traced on end-diastolic and end-systolic frames. Ventricular volume is calculated as sum of individual slice volumes (Simpson's rule). Ventricular mass is determined by multiplying myocardial volume by the muscle-specific density for myocardial tissue (1.05 g/cm^3). Ejection fraction is then calculated by end diastolic volume –end systolic volume (i.e. stroke volume) divided by end diastolic volume

shortening [25]. This is likely related to increased RV wall tension, and is a probable explanation of LVSB seen in PH due to ongoing RV contraction during LV relaxation phase.

Encoding the CMR signal phase for velocity (phase velocity mapping) allows assessment of flow velocities and volume. By multiplying blood velocity by the cross sectional area of chosen vessel, such as the main pulmonary artery, volumetric flow such as stroke volume (SV) can be calculated [26]. In addition this method can be used to quantify valvular regurgitant fractions ventricular ejection fraction, determine ventricular diastolic filling patterns and, by comparing aortic and pulmonary arterial flow, provide a measure of intra-cardiac shunt, [27]. Flow assessment by CMR has an advantage over echocardiography because it can be conducted in any orientation or plane whereas accurate echocardiographic assessment requires the flow to be parallel to the echocardiographic plane. Additionally it is better suited to interrogate eccentric regurgitant jets in valvular disease [17, 28, 29]. Phase contrast flow is however less accurate in the presence of cardiac arrhythmia or turbulent blood flow.

Measuring Regional Right Ventricular Function: Myocardial Tagging and Strain Mapping

The CMR equivalent to echocardiography tissue Doppler techniques to assess regional myocardial defects is myocardial tagging which can be used to determine three dimensional motion and deformation in the heart [30]. Tags are regions of tissue which are altered prior to acquisition so that they appear as dark regions in a grid-like pattern on CMR images. Changes of these dark areas during contraction provide information about myocardial shortening. *Strain* is defined as relative change in tissue length, expressed as a percentage. Longitudinal strain is measured from a four chamber tagged slice. Radial and circumferential strain are determined from short axis images [31, 32]. *Strain rate* (change in strain per unit time) can also be determined and give clues to diastolic RV dysfunction [33]. In addition to quantitative strain maps, direct visual assessment of myocardial contractility is possible using *strain encoding* (SENC) imaging which provides colour coded, high resolution map of through plane strain [34]. Tissue tagging in the RV in comparison to the left ventricle (LV) is challenging due to reduced RV wall thickness (normally 2–6 mm) which limits the number of tag lines for strain analysis although improving techniques have demonstrated good inter and intra-observer variability [35]. In healthy volunteers, a non-homogeneous pattern of regional longitudinal and circumferential deformation has been demonstrated with reduced apical peak systolic circumferential strain in comparison to mid and basal free wall regions [34, 35]. This may relate to weaker signal from the thin walled apex. Higher lateral free wall peak systolic longitudinal strain than anterior and inferior segments has also been reported in older individuals [34, 36, 37]. This may represent increase in circumferential function to compensate for reduction in longitudinal function which was previously shown in older subjects using colour Doppler imaging [38]. This requires further study.

CMR Guided Right Heart Catheterisation

CMR is ideally suited for the determination of RV pump function but cannot be used to determine the cardiovascular pressures which are required for assessment of more load-independent variables such as myocardial contractility. Pressure-volume (PV) relationships derived from RV PV loops provide additional information on RV pump function, mechanical interaction of the RV with its pulmonary vascular load (RV-PA coupling) and its contractile state. Recent advances in CMR have enabled a hybrid technique of real-time imaging CMR guided endovascular catheterisation (magnetic resonance fluoroscopy) which has allowed generation of RV pressure-volume loops with derivation of RV afterload and myocardial contractility allowing determination of RV coupling, the interaction

between the two variables [39]. Experiences described in the literature are limited to single centre experience but demonstrated reproducible assessment of PVR in patients with pulmonary hypertension (PH) [40]. Inefficient RV coupling in comparison to six control subjects has been shown in PH patients by this method despite higher myocardial contractility [41]. At present the technique of CMR guided catheterisation is a research tool only and has significant limitations due to costs and availability of CMR compatible equipment which may restrict eventual clinical applications. A simplified method of assessing RV-PA coupling non-invasively by CMR using the ratio of stroke volume to end systolic volume (SV/ESV) has been shown to be initially preserved in mild PH, then falls with increasing disease severity [42]. This surrogate measure potentially evaluates RV systolic function in a less preload dependent fashion than the traditional RVEF. However, this ratio assumes in its derivation that the volume intercept of the end-systolic pressure –volume slope is zero. Recent report in literature in PH has suggested this may not be true [43]. SV/ESV therefore requires further evaluation of its clinical application.

Defining Normal Values for Right Ventricular Mass and Volume

Accurate quantification of ventricular dimensions and function is crucial in distinguishing disease states from the normal. We have shown that the development of CMR has improved the measurement accuracy of RV parameters. Establishing what constitutes a "normal range" of RV volumes, mass and function is essential for the effective use of these measurements in clinical practice. LV mass and volumes are known to vary by age, sex and race and are typically adjusted for body surface area (BSA) [44–46]. Echocardiography and autopsy studies have demonstrated significant age and sex related differences in both cardiac function and mass in healthy subjects [47–49]. Autopsy studies have also shown that cardiac mass is related to subject weight, height and BSA [49, 50]. Establishing CMR RV mass, volume (RV end-diastolic volume [RVEDV] and RV end-systolic volume [RVESV]) and function (RVEF) references ranges therefore requires consideration of both absolute and "normalised" values in a diverse healthy reference database. Over the last decade a number of studies have reported normal values for right ventricular structure and function but have been limited by small sample size over a narrow age range with varying acquisition techniques [9, 51–53]. More recently, the multi-ethnic study of atherosclerosis (MESA)-right ventricle study, a multicentre prospective cohort study of over 4,000 participants without evidence of clinical cardiovascular disease at baseline [54], have evaluated a number of patient demographics that should be considered in CMR value interpretation: including body size, age, sex and race, physical activity and obesity

Scaling Right Ventricular Size and Function for Body Size

Extensive evidence exists from both the animal kingdom and human autopsy study that cardiac size and function varies with body size and scaling of functional cardiac variables such as cardiac output is common clinical practice. Conventional cardiovascular scaling approach uses a ratiometric method of dividing indices such as RV mass by a measure of body size such as height or BSA. Body composition has significant effects on the relationship between body mass, surface area and cardiac structure. For example we do not adjust for large volumes of adipose tissue in the obese or extravascular fluid in heart failure patients, These entities have little metabolic demand and it is postulated therefore that they do not impact on cardiac adaptation whose function is to provide efficient circulatory supply of metabolic substrates. Fat free mass or lean body mass has been proposed therefore as a more appropriate method of scaling to body size. Clinical use of lean body mass is however limited because accurate measurement requires additional assessment of body composition through methods such as dual-energy x-ray absorptiometry

(DEXA) or hydrodensitometry [55]. Superiority of height indexed LV mass measurements over BSA indexed LV mass has been demonstrated [56]. Height may therefore be preferable as a method of indexing RV variables rather than BSA because it is not affected by volume of adipose tissue. However autopsy study has shown weight or BSA to be superior to height in predicting cardiac mass [49] and CMR study has shown worse correlation coefficients in healthy subjects between RV mass, volumes and height than weight or BSA, although this appears population dependent [51]. Fat free mass may also vary considerably for subjects of identical height. It is therefore current clinical practice to adjust RV variables for BSA.

Ratiometric scaling relies on linear relationship between RV variables and body size variables. This method has been proposed to have several limitations for cardiovascular scaling and allometric scaling, where the cardiovascular variable is divided by the body size variable raised to a scalar exponent is suggested as a superior alternative [55]. This has been modelled in LV parameters of cavity dimensions and mass where the relationship between BSA and LV volume and mass were better described by the allometric method [57, 58]. Currently scaling methods for the RV are uncertain and a subject of research.

Ageing and the Right Ventricle

In autopsy studies, increasing age is associated with myocyte loss and decreases in LV mass and volume in males but not females [50]. Atrophy of the ventricles may occur because of age-related hormonal change such as reduced testosterone levels in males (explaining the sex differences observed) or as a result of decreasing levels of physical activity. Absolute and indexed CMR derived RV mass and volumes have also been shown to be lower with increasing age [59–62]. Larger effects are observed in males than females, but significant changes have been reported in both sexes albeit not consistently. In the MESA-RV study, ~5 % lower RV mass was observed per decade of increasing age. Age related increase in right ventricular ejection fraction is also seen (about 1 % per decade in MESA-RV). Changes in RV diastolic function defined by decreased early peak filling rate (PFR_E) and increased active peak filling rate (PFR_A) are also reported [62]. Both reflect a degree of right ventricular stiffening with age.

Sex

In large population studies of healthy individuals free from cardiovascular disease absolute right ventricular volumes are consistently greater in men than women [59, 63]. Differences in RV mass have been reported variably [51, 52, 59, 60, 62, 64] but in larger cohort studies RV mass seems to be higher in males. RV mass has been reported as up to 8–15 % lower and RV volumes 10–25 % lower in females [59, 60]. These differences have been shown to persist despite adjustment for the larger BSA seen in men [62]. As previously mentioned, greater age related decline in RV mass and volume is seen in men and one study has reported restriction of this decline to the male sex only [60]. In general no sex differences have been reported in RVEF, with the exception of the larger MESA-RV study where males had 4 % lower RVEF after adjustment for age and ethnicity [59]. These sex differences are likely hormonal related [65, 66]. Higher levels of estradiol are associated with better RV systolic function in healthy postmenopausal woman taking hormone replacement and higher levels of androgens in both males and postmenopausal women are associated with greater RV mass, higher stroke volume and larger RV volumes [67].

Race

The influence of ethnicity on CMR RV parameters has been less well studied. MESA-RV has reported lower RV mass in African Americans and higher RV mass in Hispanics in comparison to Caucasians in a population free of cardiovascular disease [59]. After adjustment for LV mass, only lower RV mass in African Americans

remained significant suggesting a RV specific effect. Hispanics had larger RVEDV and RVSV, African-American men only had smaller RVEDV after adjustment for covariates age and sex. African Americans had lower RVEF than Caucasians but greater increases with older age suggesting greater age-related right ventricular stiffening. Chinese ethnicity has also been shown to be associated with lower RV volumes after adjusting for BSA than Caucasians, although mass was not reported in this study [63].

Physical Activity (in the Non-athlete)

Long term high intensity exercise in elite athletes is well documented to cause adaptive changes in cardiac structure characterised by increases in LV mass, volume and wall thickness with a small number of CMR studies showing increases in RV mass and volume, the so called "athlete's heart" which will be discussed in a later chapter [68–71]. Levels of physical activity in non-athletes however have also been shown to influence RV mass and volumes. The MESA-RV cohort has been used to interrogate levels and intensity of activity from household chores, gardening and walking to sports and leisure activities [72]. Higher levels of moderate and vigorous physical activity were associated with greater RV mass and volumes after age, body size and sex adjustment, although the absolute value was low (1 g of RV mass from lowest to highest quintile of activity, and 7 % increase in RVEDV) which remained significant after adjusting for LV size.

Obesity

Obesity is independently associated with increased cardiovascular morbidity and mortality and is a growing health problem in the western world. Echocardiography is often suboptimal for evaluation of cardiac structure and function due to limited acoustic windows CMR is therefore an ideal tool to investigate impact of obesity on the right ventricle. Obesity is associated with increases in blood volume, cardiac output and direct infiltration of fat in the myocardium, termed the cardiomyopathy of obesity [73, 74]. RV mass and volumes determined by CMR are higher in obese individuals even after adjustment for the corresponding LV variable and demographics. Chahal et al. demonstrated an 14 % absolute and 8 % LV adjusted higher RV mass, 16 % higher RVSV, larger RVEDV and slightly lower RVEF in healthy obese individuals without reported symptoms suggestive of a sleep disorder [75]. Persistence of greater RV mass and volumes after adjustment for LV variables or height suggests these increases could not be attributed to increased body size alone. BMI is linearly correlated with RV variables after demographic adjustment. A 5 kg/m^2 increase in BMI was associated with 1.3 g higher RV mass, 8.65 ml greater RVEDV and 0.5 % lower RVEF. There was a BMI related increase in RV mass out of proportion to RVEDV again suggesting remodelling rather than simply increase in cardiac size. Earlier CMR studies in the obese have also shown higher RV mass and volumes but preserved RVEF [53]. These studies potentially could be inaccurate because subclinical sleep disorder was not excluded. Nocturnal hypoxic vasoconstriction could result in increased RV afterload or directly affect the RV [76]. It is however likely that obesity-related increase in blood volume impacts on cardiac output and ultimately causes adaptive change in RV morphology [77]. Additionally obesity results in changes in adipokine levels which have effects on RV morphology and fatty infiltration of myocardium and increased mass is also seen [78, 79].

Normative Equations for RV Variables

MESA-RV study has derived sex-specific reference equations for RV mass, RV volumes and RVEF from a subset of 441 healthy, non-obese, never smokers which incorporate age, height and weight adjustment [59]. While these equations need to be validated before clinical use they may in future serve as reference values in defining

abnormal RV morphology and function. Three large cohort studies including MESA-RV have now published age and sex specific CMR right ventricular reference ranges for mass, volume and function [59, 60, 62].

Conclusion

CMR is well suited for the determination of RV variables because the complex configuration of the RV is better described by three dimensional volume acquisition. CMR has shown excellent accuracy and reproducibility for RV measurements and is superior to echocardiography. It is important to characterise normal variants in order to establish healthy reference ranges which can be compared with disease states and in serial studies adjust for confounders. The normal range of RV mass and volumes vary with age, sex, race, body size, levels of physical activity and obesity. Interpretation of CMR RV variables should be considered in the context of patient demographics.

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Right Ventricular Structure and Function During Exercise

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André La Gerche, Guido Claessen, and Alexander Van De Bruaene

Abstract

Right ventricular (RV) function is relatively unimportant in the healthy circulation at rest when little work is required to generate flow across the low-resistance and high compliance pulmonary circulation. However, during exercise RV work increases disproportionately. Even in healthy subjects, pulmonary artery pressures increase with exercise intensity due to an increase in left atrial pressure and limitation in vascular recruitment, dilation and distension within the pulmonary vasculature. This increase in afterload during exercise demands an increase in RV contractility if normal ventricular-arterial coupling is to be maintained and stroke volume is to increase during exercise. The assessment of RV function during exercise is therefore of great interest, but is difficult. Recent advances and novel approaches to echocardiographic and magnetic resonance imaging provide excellent tools with which to quantify changes in RV function during exercise. RV stroke volume increases during exercise in healthy subjects in spite of the exercise-induced increases in afterload. However, if exercise is prolonged it seems that RV dysfunction develops as evidenced by the consistent demonstration of RV impairment after endurance exercise. In patients with pathological increases in RV afterload, the RV may be observed to dilate and fail early during exercise and may explain symptom severity better than resting measures. Pulmonary vasodilator therapy has been demonstrated to improve exercise capacity in patients with increases

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in pulmonary vascular resistance and in healthy subjects at altitude, but not in healthy subjects at sea level. Assessments of cardiac performance during exercise cannot ignore the RV and pulmonary circulation.

Introduction: Why Is Right Ventricular Function Important During Exercise?

In health and disease, exercise capacity is limited by the extent to which the working muscles receive and utilise oxygen. With the exception of patients with severe pulmonary disease, the most important factor in the supply of oxygen to the muscles is cardiac output (CO). Traditionally, investigators have sought to explain exercise-induced increases in CO (often termed "cardiac reserve") by means of increases in heart rate, augmentation in the left ventricular (LV) function and vasodilation of the systemic circulation [1, 2]. Often overlooked is the fact that *cardiac output is only as good as your worst ventricle*. This statement grossly simplifies important ventricular-arterial and ventricular-ventricular interactions but, nonetheless it is important to realise that overall cardiac performance is determined by two circulations in series. If, for example, the systemic ventricle only receives 3 L/min of input due to limitations in the pre-systemic circulation then, at best, it can only deliver 3 L/min. This highlights the fact that dysfunction of the pre-systemic circulation can impair overall CO and that a more holistic approach to cardiac function needs to consider the entire circulation. This chapter will highlight the complex interaction between the RV and its vascular load and how their inter-dependence means that any increase in pulmonary vascular pressures results in increased work for the RV. Moreover, we will discuss how in most situations the work of the RV increases disproportionately during exercise such that the RV contributes little to the maintenance of CO at rest, but is critical to cardiac reserve during exercise.

The consideration of RV function during exercise is of prime clinical relevance. The majority of our patients experience breathlessness with exertion rather than at rest, and yet the majority of assessments are made in the resting state. Thus, resting measures may be a poor surrogate. This concept seems to be well appreciated for some conditions such as myocardial ischemia whereby functional studies are the clinical standard by which the induction of electrical changes, regional myocardial impairment or hypoperfusion during exercise indicates an insufficiency of blood supply to meet the increased metabolic demands of exercise. The same rationale has not yet become routine in the appraisal of breathlessness and when exercise studies are used they all too often neglect the possibility that the pre-systemic circulation may be contributing. We often use the slogan "to assess exertional breathlessness, you must exert the breathless" as a means of remembering that the functional characteristics of the resting heart and circulation may change dramatically during exercise. In Fig. 7.1, the importance of exercise testing is illustrated in two patients who had no symptoms at rest but developed severe breathlessness and pre-syncope with exercise. Only mild changes were evident at rest but marked RV dysfunction and resulting impairment in LV filling occurred with exercise – correlating with the onset of symptoms.

The study of RV function during exercise also has potential benefits beyond understanding the pathophysiological mechanisms underpinning exercise-related breathlessness. It has been repeatedly demonstrated that RV functional measures are independent predictors of outcome in various cardiac pathologies such as valvular heart disease, myocardial infarction and congestive heart failure [3–7]. However, of even greater intrigue is the finding that RV reserve is perhaps an even more important determinant of clinical outcomes [8–12] and exercise capacity [13, 14], even amongst the very fittest of athletes [15, 16].

This chapter will review the physiological rationale underpinning the assertion that the RV and pulmonary circulation are critical

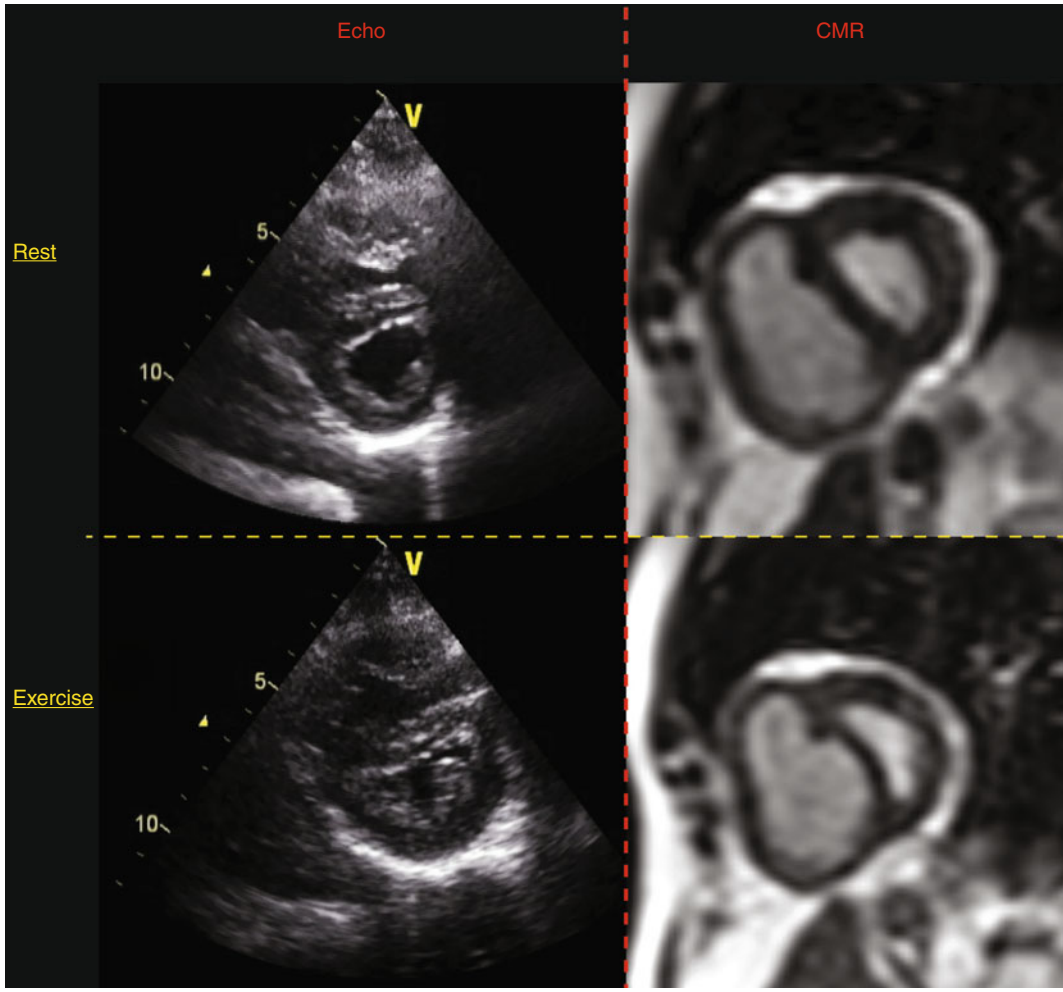

Fig. 7.1 Two patients with exertional symptoms correlating with exercise-induced right ventricular dysfunction. Patient 1 underwent exercise echocardiography to investigate severe exertional breathlessness. Resting examination suggested mild pulmonary hypertension. Exercise CMR was performed in Patient 2 who had mild chronic thromboembolic pulmonary hypertension and was limited by pre-syncope on relatively mild exercise. In a similar manner, short-axis images acquired at a mid-ventricular level during early diastole demonstrate only mild RV dilation and septal flattening at rest. However, during exercise the RV becomes more dilated and there is prominent septal shift which greatly impairs LV filling during early diastole. As a result of the reduced RV ejection and reduced LV filling, cardiac output is markedly impaired. Thus, as compared with rest, the exercise pathophysiology better explains the severity of the symptoms

determinants of exercise performance in health and disease. We will discuss established and evolving techniques for the assessment of RV function during exercise and clinical situations in which RV functional capacity may be insufficient to meet the metabolic demands of exercise. Finally, the promise and limitations of maximising exercise capacity via therapies targeting the RV and pulmonary circulation will be discussed.

Physiology of the RV and Pulmonary Circulation and Its Relevance to Exercise

In order to understand ventricular function, one must consider the venous preload which facilitates output by means of elastic recoil (Starling effect) and the arterial load against which it must pump. In the resting circulation the healthy RV has slightly

lower preload [17] and substantially lower afterload [18] than the LV. In fact, in the resting state, the afterload against which the RV must work is so slight that a near-normal CO can be maintained by means of venous preload and the increase in RV pressure resulting from ventricular inter-dependence. This has been demonstrated by animal studies in which the RV has been electrically isolated [19], replaced by a non-contractile patch [20], or by the Fontan palliation in which surgical 'by-pass' directly connecting the venous circulation to the pulmonary arteries is compatible with near-normal resting haemodynamics [21]. Although the ventricular work required may be sufficient to maintain trans-pulmonary blood flow in the healthy resting circulation, this does not apply when there is an increase in afterload [20] or during exercise when an increase in ventricular stroke volume and pressure is required [22]. Whilst the Fontan circulation is often cited as evidence of the RV's limited role in generating cardiac output, it must be remembered that a circulation without a sub-pulmonary pump has grossly inadequate reserve during exercise.

Although the pulmonary circulation shares much in common with the systemic circulation there are also some important differences. The pulmonary circulation receives the entire cardiac output but has a pressure of approximately one fifth that of the systemic circulation, a figure which is remarkably consistent across mammalian species [23]. The relationship between pressure (P), flow (F) and resistance (R) can be simplified as: $F \propto P/R$ which is a simile of Ohm's Law for electric circuits and is often referred to as the simplified Poiseuille's law in vascular circuits. Thus, the lower pressure pulmonary system equates to a lower resistance system. This lower resistance is a product of a number of unique features: firstly, there is rapid and prolific branching of vessels in the pulmonary circulation. Total vascular resistance may be quantified as the sum of the reciprocal of the resistance of each branch (i.e. $1/R_{total} = 1/R_1 + 1/R_2 + 1/R_3$ …….) such that the greater the number of parallel branches the lower the total resistance. Also, the pulmonary arteries and arterioles are thinner-walled than their systemic counterparts. This has a very important implication in that the thinner walled vessels are more compliant and this greater compliance causes a further reduction in resistance and pressure. This concept is summarized in the Windkessel model of vascular flow [24, 25]. This model predicts that compliance is inversely proportional to resistance and thus the "stretching" of compliant vessels with pulsatile flow serves to decrease the resistance and blunt pressure rises. Therefore, the differences between the pulmonary and systemic circulations are that the former forms a more extensive and earlier parallel circuit and is more compliant, both serving to make RV afterload low.

Another potential difference is that there is relative independence between the pressures of the arteriole and venule pressures in the systemic system. The high systemic arteriolar pressures mean that systemic venous pressures would need to be very high before exerting a "back-pressure effect". In the pulmonary vasculature, however, there is much greater back-pressure effect such that increases in left atrial pressure have a strong bearing on pulmonary artery pressures. It has been suggested that left atrial pressures explain approximately 80 % of the variance in pulmonary artery pressures in the absence of pulmonary vascular disease [17]. This may be of particular importance during exercise. Descriptions of heart failure are often dichotomized into those with abnormalities in lusitropic and contractile dysfunction in whom left atrial pressures increase during exercise and those with healthy heart function in whom filling pressures do not increase [26]. Augmentation in CO during exercise requires increasing filling volumes within shorter diastolic filling times. This can be achieved by means of greater ventricular suction, greater atrial pressures, or both. Nonogi et al. demonstrated that early diastolic ventricular suction increases during exercise [27]. They demonstrated that active ventricular relaxation (time constant of relaxation – tau) improved and that early-diastolic and mid-diastolic ventricular pressures were lower during exercise as compared with rest. However, these differences were relatively modest and it would seem unlikely that this degree of "suck" could generate the massive outputs (in excess of 40 L/min [28, 29]) generated by well-trained athletes during exercise. Rather, it is most likely that an increase in atrial pressure is also required to "push" blood across the atrioventricular valve during exercise. Relatively few

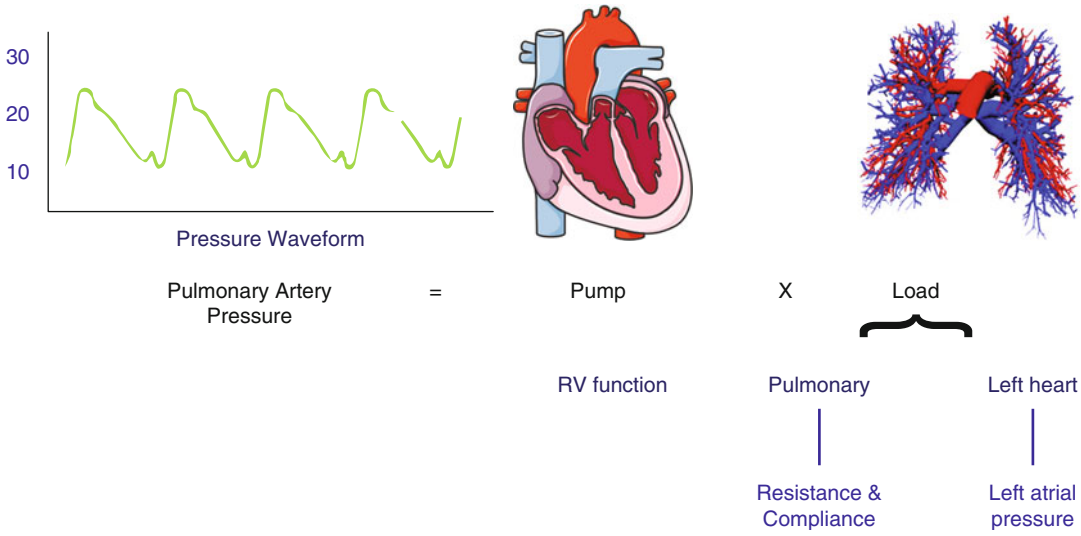

Fig. 7.2 The relationship between pulmonary artery pressures, right ventricular function and vascular load. Pulmonary artery pressures are determined by both the ability of the RV pump to generate pressure and by the load against which this pump must push. The RV afterload is determined by pulmonary vascular factors (resistance, compliance and impedance) and by left atrial pressures

studies have assessed left atrial pressures during exercise in healthy subjects and those studies that exist have used pulmonary artery balloon occlusion ('wedge') catheters as a surrogate of left atrial pressure, a method that has potential limitations during vigorous exercise. Nonetheless, existing data supports the premise that exercise-induced increases in cardiac output require an increase in left atrial pressure. Reeves et al. measured right atrial and pulmonary artery occlusion pressures (PAOP) in eight healthy volunteers during intense exercise and found a fairly strong correlation between these measures and CO [17]. Interestingly, the four subjects with the highest oxygen consumption (VO_2max) had PAOPs between 19 and 35 mmHg. More recently, Lewis et al. also observed a strong correlation between PAOP and CO in control subjects and determined the relationship PAOP (mmHg) = 1.1 × CO (L/min), albeit within a group with substantially more modest exercise capacity [12]. However, if one were to extrapolate the relationship derived by Lewis et al. to the athletes studied by Reeves, there is considerable agreement in the range of values. It would seem reasonable to conclude that the idea that left atrial pressures do not increase in healthy subjects is likely to be false. Rather, it may be more correct to state that left atrial pressures will increase in all subjects and that it is the relationship between filling pressures and CO that is the more precise discriminator.

Thus, one cannot focus on ventricular filling pressures without context. The heart failure patient may have elevated left atrial pressures whilst walking up a flight of stairs whilst an athlete may have similar left atrial pressures whilst running record pace. In both cases, the subjects are breathless, ventricular filling pressures increase, CO is close to maximal and is insufficient for the metabolic demands of the working muscles. The difference is the work level and cardiac output at which cardiac function is maximised. "Heart failure" represents a continuum in which relatively arbitrary clinical cut-offs are set to distinguish normal cardiac performance from failure.

The concept of exercise-induced LV filling pressures is extremely relevant to the further discussion regarding performance of the pulmonary circulation and RV during exercise. The increased LV filling pressures are relayed "upstream" and contribute to the afterload against which the RV must pump. Thus during exercise, the RV is faced with the increased afterload of the sum of LV filling pressures and any additional flow-induced increase in pulmonary artery pressures (Fig. 7.2).

Exercise Causes a Disproportionate Increase in RV Pressures, Wall Stress and Work

There are differences between the RV and LV in the arterial load imposed by exercise and in the ventricular capacity to counter that load (i.e. maintain ventricular arterial coupling). As illustrated in Fig. 7.3, at rest the LV contracts against a systemic circulation with moderate resistance and compliance as compared with the low resistance and high compliance of the pulmonary circulation. During exercise, CO increases many fold (as much as eightfold in well-trained athletes [28, 29]) and therefore vascular pressures would be expected to increase unless sufficiently counter-balanced by decreases in resistance and increases in compliance. However, the pulmonary vasculature has very low resistance at rest and it has somewhat limited capacity for further decreases [30, 31]. Recruitment of upper lobe vessels in combination with flow-mediated and neurohormonal vasodilation affect a reduction in PVR of approximately 20–50 % [30]. Such changes are limited compared with the profound reductions in systemic vascular resistance which is enabled by the greater capacity for redistribution to vascular territories of low resistance. The moderating effect of vascular compliance may also be less than anticipated. During exercise, the vasculature is distended by the high flow rates meaning that compliance (the ability to further distend the vessels with any given change in pressure) is reduced [7, 32, 33]. Therefore, vascular pressures increase and, these increases are greater for the pulmonary circulation than for the systemic circulation [34, 35].

A number of studies have reported substantial increases in pulmonary artery pressures during exercise using echocardiographic estimates [34–38] and direct invasive measures [12, 31, 39]. Figure 7.4 summarises data from four recent studies which demonstrate remarkable consistency in the linear regression derived for the relationship between mean pulmonary artery pressure (mPAP) and CO. Using direct catheter measures, Lewis et al. [12]. observed an increase of 1.5 mmHg in mean pulmonary artery pressure for each litre increase in CO. Less steep mPAP/CO relationship have been observed in the younger and fitter cohorts of Argiento et al. [37], and La Gerche et al. [35]. Other potential confounders such as the postural effects on pulmonary vascular recruitment [30] and differences in both pulmonary artery estimates (echocardiographic vs. catheter) and CO estimates (thermodilution vs. echo Doppler vs. exercise MRI) may explain the variance in the mPAP/CO relationships observed. Despite this, there is considerable consistency in these results which predict significant increases in pulmonary artery pressures during intense exercise. For example, an increase in CO of 30 L/min would equate to a mean pulmonary artery pressure exceeding 50 mmHg – representing an increase of threefold or more from rest. Furthermore, the relationship between pulmonary artery pressures and CO appears similar regardless of athletic conditioning (Fig. 7.4a). However, because athletes have greater exercise capacity they are able generate higher outputs and higher pulmonary artery pressures [35]. This represents a disproportionately large increase in RV afterload compared with mean arterial pressure increases which rarely exceed 50 % in the LV.

We sought to assess this seemingly disproportionate ventricular load using a combination of magnetic resonance and echocardiographic imaging at rest and during exercise to quantify RV systolic wall stress, as compared with that of the LV [34]. Using the simple construct of the LaPlace relationship, we found that during exercise increases in both pressures and volumes were greater for the RV, whilst increases in wall thickness were relatively less than for the LV. As a result, RV wall stress estimates increased 125 % during exercise as compared with a modest 14 % increase in LV wall stress [34]. Thus, it may be contended that the stress, work and metabolic demands placed on the RV during exercise are relatively greater than that of the LV.

Such substantive afterload would seem a significant burden for the contractile reserve of the RV and raises the possibility that in the extremes of exercise the RV/pulmonary vascular unit may limit output just as it does in some

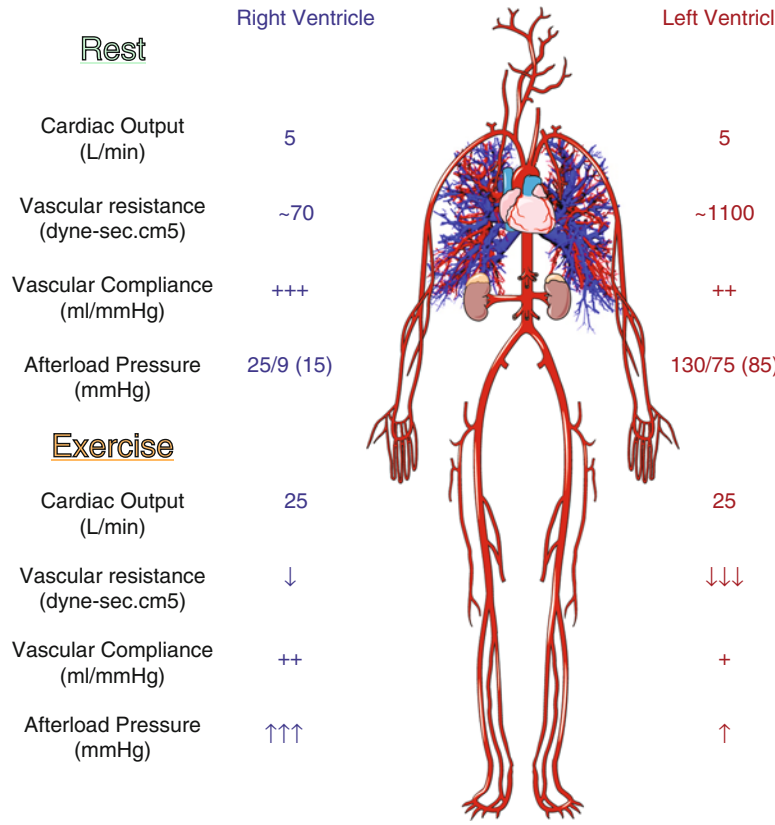

Fig. 7.3 Comparison between the load and function of the pre-systemic and systemic ventricles at rest and during exercise. Relative to the LV, the RV is a low-pressure chamber subject to low afterload at rest. However, during exercise, pressures in the RV increase disproportionately due to relatively less capacity for the pulmonary circulation to dilate, distend and recruit new vascular territories

disease states [13, 14]. At rest, RV measures of mass and contractility are one-third to one-fifth those of the LV and this appropriately matches the pressure requirements of each [40, 41]. This lesser myocardial mass of the RV suggests that it may have a diminished contractile reserve and may be less able to accommodate marked changes in loading. This is supported by studies which demonstrate that afterload increases result in a marked reduction in RV stroke volume but only a slight decrease in LV stroke volume [42, 43]. MacNee at al. quantified the relative reductions in stroke volume in either ventricle at rest with increasing afterload. The ~30 % reduction in RV stroke volume compared with ~10 % fall in LV stroke volume suggest that the RV has less contractile reserve to accommodate afterload increases. Given the potential limitations in RV reserve and the far greater increases in RV afterload relative to the LV, one might hypothesize that the RV could limit CO during intense exercise. This hypothesis has been raised previously [44–46], but has not been actively pursued over the last three decades, perhaps due to limitations in imaging the RV during exercise.

How Can RV Function Be Assessed During Exercise?

One of the major issues in attempting to appraise the hypothesis that the RV may serve as an important limitation to CO during exercise is the difficulty in assessing the RV during exercise. The RV has complex geometry, relatively heterogeneous regional function and is situated behind the sternum, thereby limiting echocardiographic windows. Of perhaps greatest importance, particularly during exercise, is the profound influence of loading conditions on the RV and thus it is important for functional measures to either be load independent or to incorporate an assessment of load.

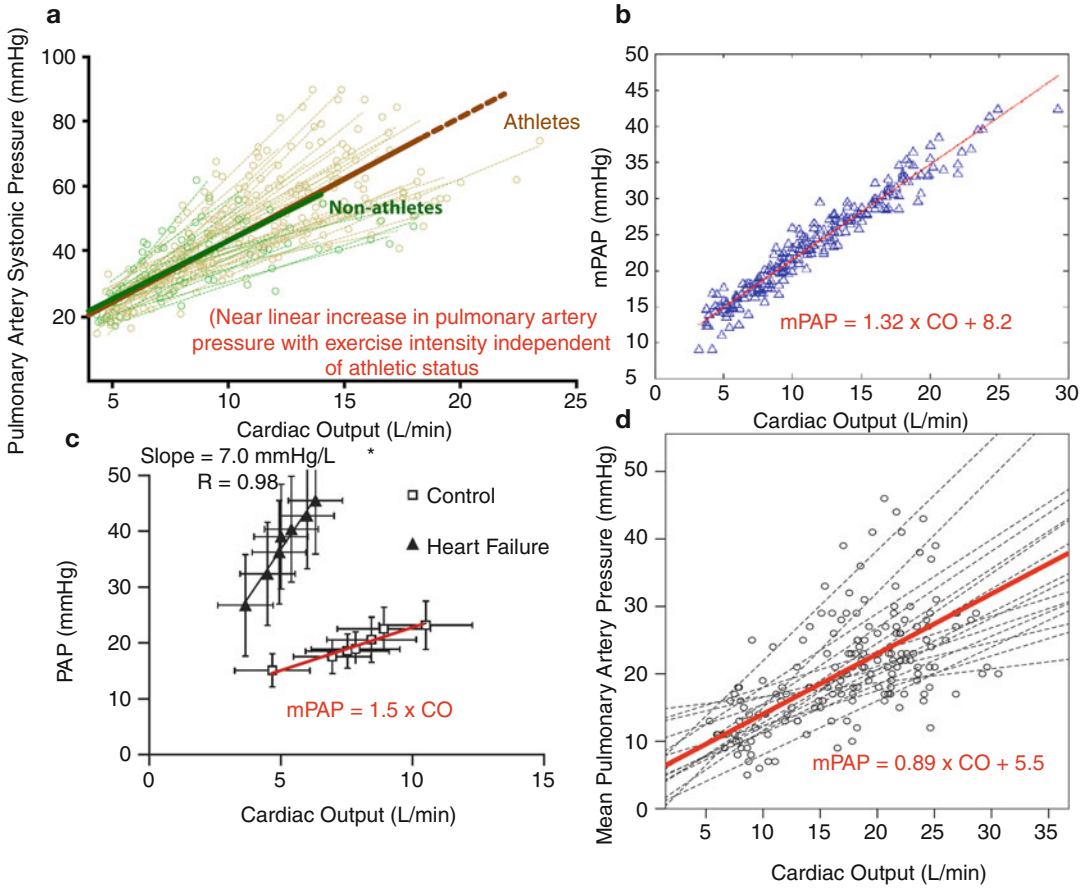

Fig. 7.4 A consistent near-linear relationship between increases in pulmonary artery pressures and cardiac output during exercise. Echocardiographic estimates of pulmonary artery pressures (*PAP*) – panels (**a**, **b**) – demonstrate a near-linear relationship between increases in PAP and cardiac output (*CO*). These findings have been validated in untrained and trained subjects using direct invasive pulmonary artery pressure measures – panels (**c**, **d**) (Adapted from original publications [12, 35, 37] and the authors' own unpublished data (panel **d**) in which invasive PAP and Exercise-CMR derived CO were measured in healthy athletic and non-athletic subjects)

The earliest attempts to define the RV response to exercise utilised radionuclide ventriculography. Morrison et al. used radiolabelled red cells and acquired steady-state data over 2 min during four stages of exercise of increasing intensity [47]. In nine healthy volunteers, they observed a progressive increase in RV ejection fraction (EF%) and an inverse relationship between RVEF% and pulmonary vascular resistance (PVR), thereby concluding that RVEF is strongly influenced by afterload. Hirata et al. advanced this hypothesis further by examining radionuclide RVEF in subjects with variable pulmonary vascular resistance as a result of atrial septal defects or rheumatic mitral stenosis. They found a strong inverse relationship between the change in RVEF% during exercise and PVR [48]. Radionuclide ventriculography was well suited to the investigation of RV function given that the technique relies on geometry independent count-based techniques. However, limitations include overlap of counts from the atria and LV, lack of detail in regard to RV morphology and the need for prolonged steady-states for gated acquisitions. Moreover, there is substantial radiation exposure involved, particularly when repeated measures are acquired.

Echocardiography is a readily accessible, safe and adaptable imaging technique but RV imaging presents some unique challenges given the irregular geometry and retrosternal positioning of the RV. Nonetheless, a number of investigators have sought to assess RV function during exercise. Given the considerable load dependency of the RV, investigators have sought to evaluate RV contractility using relatively load-independent measures. RV strain rate measures the speed of myocardial deformation and has been quantified during intense exercise using vector imaging, 2D tracking and tissue Doppler techniques [16, 49]. However, these remain specialised measures with high variability and are exquisitely dependent upon the quality and temporal resolution of the dataset. Perhaps of greater appeal is the concept of combining functional and load measures in a manner akin to pressure-volume analyses. We combined pulmonary systolic pressure with RV end-systolic area (as a 2D approximation of volume) with the hypothesis that the change in pressure/area relationship could be considered a surrogate measure of contractility. In 40 athletes and 15 non-athletic controls, we demonstrated that whilst resting measures of systolic function were low in athletes, the change in RV pressure/area relationship was similar to non-athletes. We concluded therefore, that whilst resting measures may appear spuriously low in healthy athletes, contractile reserve is normal [16]. Extending this hypothesis that abnormal RV reserve may be able to be identified using echocardiography, Plehn et al. demonstrated that RV end-systolic volume reduced during exercise in healthy controls but not in patients with hypertrophic and dilated cardiomyopathies, and this attenuation in systolic performance did not seem to be accounted for by the slightly greater increases in pulmonary artery pressures [50]. Finally, unique insights into RV function can be extrapolated from the unique patient group with congenitally corrected transposition of the great arteries in whom the RV is subjected to systemic afterload and has a tendency to decompensate with time. Van der Bom et al. demonstrated that a combination of RV end-diastolic volume and peak exercise blood pressure was the strongest determinant of clinical events such as worsening heart failure [9]. These echocardiographic measures represent relatively simple research tools suggesting that RV reserve may be a particularly useful means of determining mechanisms of cardiac limitation and patient outcomes.

Cardiac magnetic resonance Imaging (CMR) is ideally suited to the assessment of the RV during exercise. Unlike with echocardiography, RV volumes can be accurately quantified during intense exercise in all subjects regardless of body habitus [28, 51]. The technique is technically demanding at present as traditional CMR relies upon gating and breath-holding to ensure that cardiac translation is minimised. However, recent advances have enabled real-time acquisitions in which ECG gating is not required and respiratory translation can be accounted for post-hoc such that biventricular volume quantification compares favourably with invasive standards [28]. Temporal resolution remains a constraint (approximately 7–8 frames/cardiac cycle during maximal exercise tachycardia) although advances in acquisition and processing methods are likely to result in substantial improvements in the near future [52].

Exercise CMR has provided some important insights into RV limitations to cardiac performance in patients with pulmonary vascular pathology. Holverda et al. observed that whilst RV end-systolic volume decreases with exercise in healthy control subjects, it remained unchanged or even increased in patients with pulmonary hypertension and patients with chronic obstructive airways disease [13, 14]. Thus, a lack of augmentation in RV stroke volume limits overall cardiac performance such that oxygen delivery to the working muscles is insufficient, resulting in premature anaerobic metabolism, breathlessness and fatigue.

Even with technical advances to enable wider use of exercise CMR, it is unlikely to become sufficiently accessible to influence routine clinical management. Whilst offering superb insights into the mechanics and quantification of impaired cardiac reserve, simpler tests are necessary to

identify those patients in whom RV functional reserve is reduced due to either RV dysfunction and/or pathological increases in pulmonary vascular load. To this end, indirect measures show promise. Lewis et al. elegantly demonstrated that ventilator efficiency (VE/VCO_2) on cardiopulmonary testing correlated well with pulmonary vascular resistance, determined by a combination of invasive pressure estimates and nuclear ventriculography [53]. Furthermore, they demonstrated a reduction in VE/VCO_2 following treatment with a pulmonary vasodilator but not in those receiving placebo suggesting that this non-invasive measure may reflect RV/pulmonary vascular coupling during exercise. Guazzi et al. have also demonstrated a relationship between RV functional measures during exercise and ventilatory efficiency in patients with left heart failure thereby supporting the hypothesis that those with greatest impairment in ventilatory efficiency may benefit from specific pulmonary vasodilator therapy in addition to traditional heart failure treatment [54, 55]. Trials addressing this hypothesis are currently underway [56].

Can the Healthy RV Cope with the Increased Pulmonary Vascular Load of Exercise?

As discussed in section Exercise causes a disproportionate increase in RV pressures, wall stress and work, there is a significant increase in RV afterload during exercise which increases RV wall stress and work. The question that arises, therefore, is whether the RV can generate the increased work that is required against the accumulating load of intense exercise? In healthy subjects during exercise of short duration, it would seem that the answer is yes. Using echocardiography and CMR during exercise, we have demonstrated that RV area progressively decreases as pulmonary artery pressures increase (using echocardiography) and that RV end-systolic volume decreases with exercise intensity (CMR) [16, 28] – see Fig. 7.5. This is perhaps not surprising given the near linear relationship that exists between cardiac output and exercise intensity suggesting that ventricular ejection augments despite increases in vascular load.

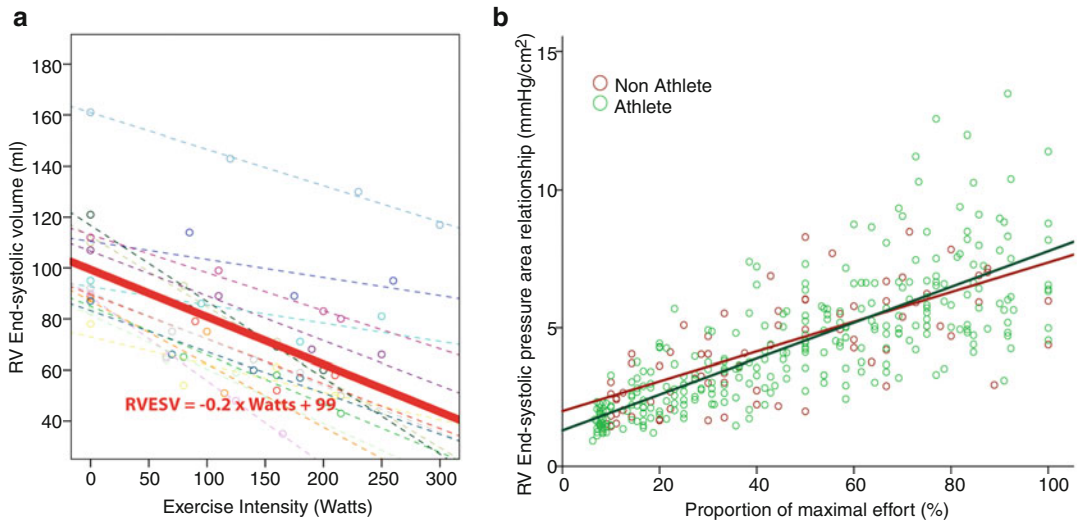

Fig. 7.5 Improvement in right ventricular functional measures despite exercise-induced increases in afterload. During exercise in healthy subjects, RV end-systolic volume (measured by exercise CMR) reduces in an approximately linear manner (panel **a**) despite consistent increases in pulmonary artery pressures (authors' own unpublished data). In panel (**b**), RV area is expressed as a ratio of pulmonary artery pressures thereby serving as a surrogate of function incorporating load (akin to contractility). The RV pressure/area ratio increases during short intense exercise suggesting that RV function is able to accommodate the exercise-induced increases in load

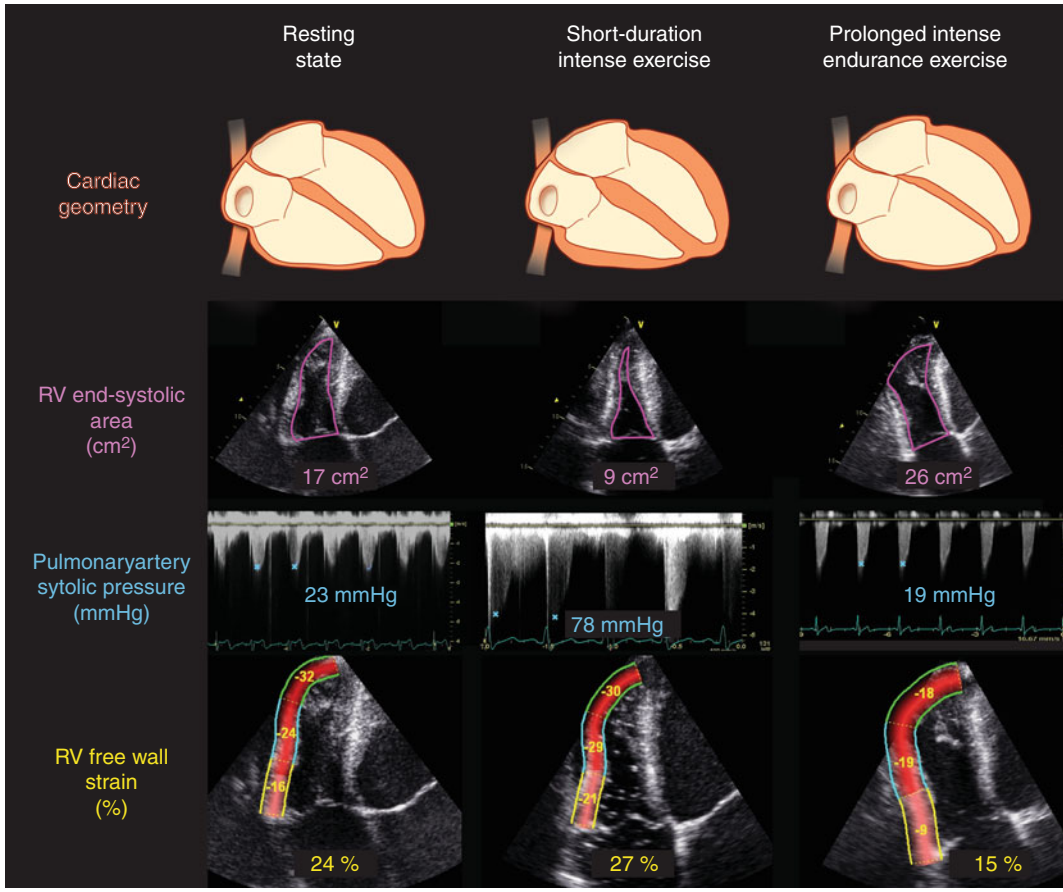

Fig. 7.6 Summary of right ventricular structural and functional changes during exercise of different duration. Typical changes in RV function at rest (*left*), during short-duration intense exercise (*middle*) and immediately following an ultra-endurance triathlon (*right*) are demonstrated using the example of a professional triathlete. At rest, the RV is moderately enlarged with normal pulmonary artery pressures and deformation. During exercise, large increases in cardiac output result in proportional increases in pulmonary artery pressures. RV function is able to match demand with systolic augmentation evidenced by a reduction in systolic area and a small increase in strain (larger increases in strain rate not shown here). After prolonged exercise it seems that these substantial RV work demands result in RV fatigue/injury reflected by RV dilation and systolic dysfunction as evidenced by an increase in systolic area and a reduction in strain

However, multiple recent studies have observed a decrement in RV function after more prolonged intense exercise suggesting that whilst the RV can maintain function against the disproportionate increase in vascular load during exercise of short duration, there is a point at which the RV fatigues. Given the observation that RV load, wall stress and work increase to a relatively greater extent than in the LV, it is perhaps not surprising that the RV fatigue precedes that of the LV. Studies in relatively amateur marathon runners [57–59] as well as well-trained ultra-endurance runners [60] and triathletes [61, 62] have consistently demonstrated significant decrements in RV function immediately following exercise, whereas LV function is preserved.

Figure 7.6 summarises the changes in RV function during exercise in the healthy person or healthy athlete. During short intense exercise there is an increase in RV pressures and sytolic function but when this exercise becomes protracted the RV can fatigue in response to working against a sustained increase in load. The exact mechanism of this fatigue is not known

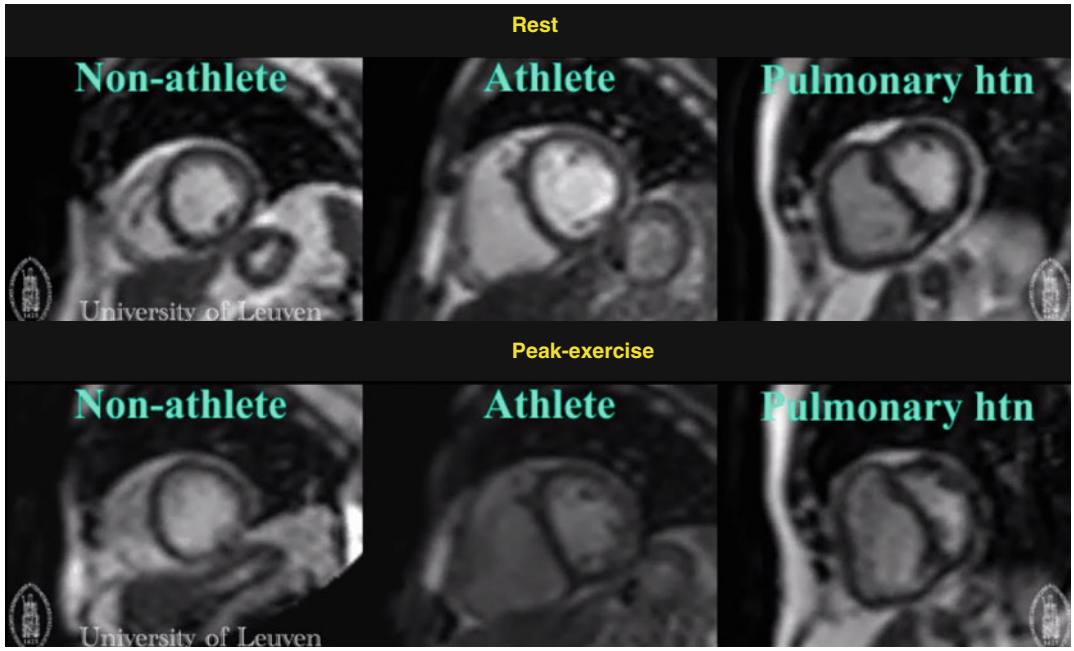

Fig. 7.7 Exercise cardiac magnetic resonance imaging providing an improved insight into pathophysiological changes in right ventricular function during exercise. Early diastolic mid-ventricular short-axis CMR images acquired at rest provide a comparison between a healthy non-athlete, an athlete and a patient with pulmonary hypertension. The RV:LV ratio increases and there is greater ventricular interaction (right to left septal shift) in the athlete, as compared with the non-athlete and even more so in the patient. However, these changes are far more obvious during exercise. In the athlete the RV is slightly more dilated and the septal shift becomes appreciable. In the pulmonary hypertension patient, these changes become marked

– substrate deficiency, beta receptor desensitization, inflammation or neurohormonal dysregulation are all potential candidates.

In the patient with pathology of the RV and pulmonary circulation there can be immediate failure of RV arterioventricular coupling during exercise. As discussed above, and as exemplified in Fig. 7.7, assessment of the RV during exercise may provide a better understanding of the pathophysiology underpinning the patient's symptoms. Most patients with pulmonary hypertension develop breathlessness during exertion, rather than at rest, and thus it makes sense to study the RV during exercise [63]. As discussed in section How can RV function be assessed during exercise?, the elegant studies of the Vonk Noordegraaf group have nicely illustrated how RV failure can be identified during exercise even when RV dysfunction is not appreciable at rest [13, 14].

Can Pulmonary Vasodilators Improve Exercise Tolerance?

The preceding sections detail a disproportionate increase in RV load during exercise and a predisposition for RV failure during exercise; either early in those with pathology of the pulmonary circulation, or only after very prolonged exercise in those with a normal RV and pulmonary circulation. This assertion that the pre-systemic circulation may limit cardiac performance during exercise would imply that pulmonary vasodilators may improve exercise performance by means of attenuating the disproportionate increase in RV load. Pulmonary vasodilators have proven efficacy in improving exercise tolerance in those patients with pulmonary arterial hypertension [32, 64] due to their ability to attenuate the pathological increases in RV load thereby improving RV function during exercise. However, taking

this one step further, one may even anticipate that these agents could improve exercise capacity in those with a normal pulmonary circulation.

Ghofrani et al. performed a randomised, double-blind placebo controlled trial assessing the efficacy of sildenafil in improving exercise haemodynamics in 14 healthy subjects during normobaric hypoxia (10 % O_2) and at altitude (Mount Everest base camp, 5,245 m above sea level). As compared with placebo, sildenafil resulted in a decrease in pulmonary artery pressures and an increase in exercise workload and cardiac output in both the hypoxic and high-altitude settings [65]. Further studies using both PDE5 receptor and endothelin antagonists have been consistent in demonstrating improvements in haemodynamics and exercise performance in hypoxic conditions but have failed to show any benefit in normoxia [66–68]. There are a number of reasons why pulmonary vasodilators may have limited efficacy in healthy subjects at sea level. One of the more likely hypotheses is that the pulmonary circulation is maximally dilated during exercise and there is little capacity for further decreases in pulmonary vascular resistance. This would perhaps explain why pulmonary vasodilators do not seem to improve exercise capacity at sea-level whilst increases in basal pulmonary vascular tone (with hypoxia and/or altitude) provide an opportunity for pulmonary vasodilators to reduce resistance, aid RV ejection and improve exercise parameters.

Conclusions

The RV appears to be a potential "Achilles' heel" for the exercising heart. The RV is subject to disproportionate increases in load during exercise and, as compared with the LV, impairment in function develops earlier and more significantly when exercise is prolonged. Separating and comparing function of various elements of the circulation ignores complex interactions and some of the data and theories presented may over-emphasize the limitations of the pre-systemic circulation. However, it is clear that a comprehensive understanding of exercise physiology needs a more holistic approach to cardiac function than has been previously considered. The importance of the RV and pulmonary circulation should not be overlooked. It may be an important component of exercise limitation and may even be the "weak link" in some settings. Fortunately we now have methodologies capable of quantifying RV function during exercise and an exciting new window into exercise physiology has been opened.

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Echocardiography of the Right Heart

8

Robert Naeije and Bouchra Lamia

Abstract

Echocardiography allows for accurate measurements of pulmonary vascular resistance and hydraulic load, and thus the estimation of afterload in severe pulmonary hypertension as a cause of right ventricular (RV) failure. The procedure also provides a series of estimates of RV systolic function, such as fractional area change, tricuspid annular plane excursion, tricuspid annulus tissue Doppler imaging of the velocities of isovolumic contraction and ejection, strain and strain rate. These indices help to evaluate the adequacy of RV systolic function adaptation to afterload (Anrep mechanism) but suffer from variable degrees of preload-dependency. Failure of RV-arterial coupling results in Starling's mechanism of preservation of stroke volume through increased myocardial fibre length, or end-diastolic volume. This can be appreciated by echocardiographic measurements of increased right heart chamber dimensions, dilatation and loss of inspiratory collapsibility of the inferior vena cava, and pericardial effusion, along with altered indices of left ventricular diastolic function such as prolonged isovolumic relaxation time, deceleration of E waves, and decreased ratio of E over A waves. Echocardiographic dimension measurements are currently limited to a series of planes, with difficult instantaneous volume reconstruction of the RV, which has an irregular crescent shape and inhomogenous contraction. Echocardiography is limited by operator-dependency, and is sometimes implemented in low clinical probability contexts. This may be a cause of false positive or negative diagnosis of RV

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failure. Recent advances in echocardiography technology open the perspective of RV volume measurements with assessment of regional function and asynchrony.

Introduction

Echocardiography of the pulmonary circulation and the right heart is essential for the screening, differential diagnosis and follow-up of pulmonary hypertension [1, 2]. However, the procedure is still perceived to be insufficiently accurate for the estimation of pulmonary vascular pressures or resistance [3–5]. This is now being improved with better Bayesian integration of measurements in a clinical probability context [6] and understanding that measurements by adequately trained examiners and updated equipment may fail on precision rather than on accuracy [7]. Echocardiographic measurements of the pulmonary circulation at rest and at exercise have recently contributed to a better functional understanding and definition of the limits of normal of the pulmonary circulation [8]. Echocardiographic indices of right ventricular (RV) systolic and diastolic function diagnostic and prognostic relevance are being developed [9, 10]. The advent of portable devices is improving the bedside diagnosis and follow-up of pulmonary hypertension and RV failure.

The present chapter will focus on the functional significance of current echocardiographic imaging of the right heart of patients with pulmonary hypertension, which is by far the most common cause of RV failure. Technical issues have been extensively reviewed in recent guidelines [9].

Measurement of the Pulmonary Circulation

Pulmonary hypertension is the most common cause of RV failure. Therefore, in the presence of a patient with signs and symptoms of RV failure, it is essential to evaluate the pulmonary circulation. The definition of pulmonary hypertension relies on the recording of a mean pulmonary artery pressure (PAP) higher than 25 mmHg [1, 2].

Mean PAP (PAMP) increases with any pulmonary vascular disease causing an increased resistance (PVR) to pulmonary blood flow (CO) but also with increased left atrial pressure (LAP)

$$\mathrm{PVR} = \left(\mathrm{PAMP} - \mathrm{LAP}\right) / \mathrm{CO}$$

$$\mathrm{PAMP} = \mathrm{PVR} \times \mathrm{CO} + \mathrm{LAP}$$

Therefore, the diagnosis and estimation of severity of pulmonary hypertension requires three measurements: PAP, CO and LAP.

Systolic PAP (PASP) can be estimated from the continuous Doppler maximum velocity of tricuspid regurgitation (TRV), in m/s, to calculate a trans-tricuspid pressure gradient, in mmHg using the simplified form of the Bernouilli equation and an estimate of right atrial pressure (RAP) [11].

$$\mathrm{PASP} = 4 \times \mathrm{TRV}^2 + \mathrm{RAP}, \mathrm{mmHg}$$

The assumptions of this measurement are that PASP and RV peak systolic pressures are equal, and that the Bernoulli equation is applicable [12]. RAP is estimated clinically, or, preferably from the diameter of the inferior vena cava and its inspiratory collapsibility [13].

PAMP can be calculated from PASP [14]:

$$\mathrm{PAMP} = 0.6 \times \mathrm{PASP} + 2 \ \mathrm{mmHg}$$

A limitation to estimates of PAP from TRV is that a good quality signal cannot always be recovered, especially in the presence of hyper-inflated chests and/or normal or only modestly elevated PAP [15]. However, the single use of TRV has disclosed a higher than normal frequency of increased pulmonary vaso-reactivity in family members of patients with pulmonary arterial hypertension (PAH), independently of identified mutations [16]. The single use of TRV to estimate exercise-induced pulmonary hypertension has been shown to be of prognostic relevance in patients with aortic or mitral valvulopathies [17, 18]. The approach combined with estimates of CO and LAP at exercise has contributed to the understanding of normal pulmonary vascular mechanics in normoxia or hypoxia, with resistance and compliance determinations that were in good agreement with previous invasive studies [19–23].

Since PAP is a flow-dependent variable, it is important to couple it with a measurement of cardiac output (CO). This can be measured from the left ventricular outflow tract (LVOT) diameter and velocity time integral (VTI) multiplied by heart rate (HR) [24].

$$\mathrm{CO} = [0.785 \times (\mathrm{LVOT\,diameter})^2 \times \mathrm{LVOT-VTI}] \times \mathrm{HR}$$

It is also possible to record a pulmonary flow-velocity sampled in the RV outflow tract (RVOT), but the calculation of a volume flow at that site is less stable than at the LVOT, especially at exercise. However, RVOT and TR flows can be combined to calculate pulmonary vascular resistance (PVR) [25].

$$\mathrm{PVR} = 0.1618 \times 10 \times \mathrm{VTI}_{\mathrm{RVOT}} / \mathrm{TRV}$$

For the direct calculation of PVR, it is also necessary to know LAP. This can be calculated from the ratio of trans-mitral Doppler and mitral tissue Doppler E and e′ waves [26].

$$\mathrm{LAP} = (1.24 \times \mathrm{E} / \mathrm{e}') + 1$$

The echocardiographic PVR calculated from measurements of PAMP, LAP and CO has been recently shown to be more accurate than that based on the $\mathrm{VTI_{RVOT}}$/TRVratio [27].

The simplified form of the Bernouilli equation has also been applied to pulmonary insufficiency jets to calculate mean and diastolic PAP [9]. While this may be useful for derived pulmonary arterial compliance (Ca) calculations, this measurement is relatively uncommon.

Perhaps a more useful independent method to estimate mean PAP is based on the pulsed Doppler measurement of the acceleration time (AT) of pulmonary flow (sampled at the RVOT) [28].

$$\mathrm{PAMP} = 79 - (0.6 \times \mathrm{AT})$$

Given the importance of a reliable estimate of PAP for the diagnosis of pulmonary hypertension, and given the uncertainties encountered with the sampling of good quality TR or pulmonary insufficiency, it may be surprising that internal controls based on AT are uncommonly reported [15].

There has been less validation of PAMP calculated from the AT against invasive measurements than reported on the basis of TRV. Accurate estimates of PAMP are less reliable when AT exceeds 100 ms, the lower limit of normal, and the measurement may need a correction for ejection time at high heart rates [12]. However, there are data suggesting that AT may be more sensitive than TRV to early or latent pulmonary vasculopathy [29]. This may be due to its sensitivity to changes in pulmonary vascular impedance more than PVR [12, 15]. The advantage of the measurement of PAP on the basis of the shape of pulmonary flow is in a quasi 100 % recovery of good quality signals [15], independently on the level of PAP. In addition to AT, the shape of the flow wave is of interest, as pulmonary hypertension is associated with a deceleration of flow in late or in mid-systole (notching) [15]. A decreased time to notching has been reported to identify proximal obstruction in patients with chronic thromboembolic pulmonary hypertension (CTEPH) [30]. Notching is explained by wave reflection [31]. The impact of the first reflected wave on the forward wave may be caused either by a proximal reflection site, such as in CTEPH, or by increased wave velocity on severe pulmonary arterial stiffening caused by high PAP, such as in advanced PAH [31]. The presence of mid-systolic notching indicates a high likelihood of a PVR > 5 Wood units and associated RV dysfunction [32]. An acceleration time < 90 ms has been shown to be highly predictive of a PVR ≥ 3 WU [33].

Accuracy of Echocardiographic Measurements of the Pulmonary Circulation

Previous validation studies of Doppler echocardiographic measurements of pulmonary vascular pressures and flows have much relied on correlation calculations [3–5, 11, 24–28]. This is misleading, as correlation coefficients largely reflect the variability of the subjects being measured. If

one measurement is always twice as big as the other, they are highly correlated but do not agree. Bland and Altman addressed this problem by designing difference versus average plots. This analysis has since become gold standard to compare methods of measurements [34]. Two crucial information are provided: (1) the bias, or the difference between the means and whether it is constant over the range of measurements, and (2) the limits of agreement, or the range of possible errors. Bias informs about accuracy, and agreement informs about precision.

Two previous studies which concluded that echocardiography was insufficiently accurate when compared to catheterization for the assessment of pulmonary hypertension [3, 4] reported Bland and Altman plots showing almost no bias, thus actually good accuracy, but large limits of agreement, rather indicating insufficient precision. More recently, D'Alto et al. compared PAP, LAP and CO measured by echocardiography and right heart catheterization performed within an hour in 151 patients referred for a pulmonary hypertension [7]. The results showed nearly identical means and almost no bias, confirming accuracy of echocardiographic measurements compared to invasive measurements. However, the limits of agreement appeared to be wide, indicating potentially insufficient precision. This may be a problem for single-number-derived decision in relation to guidelines [1, 2].

Agreed statistics are straightforward when one of the two methods of measurement is a recognized reference, or "gold standard". There is currently a consensus that right heart catheterization provides gold standard measurements of the pulmonary circulation [1, 2]. However, routine right heart catheterization most often relies on the use of fluid-filled catheters, which have an insufficient frequency response. Adequately flushed and calibrated fluid-filled catheters compared to true gold standard high-fidelity micromanometer-tipped catheters have been shown to be accurate (no bias) but may lack precision (agreement of ±8 mmHg on pulse pressure) [35]. Cardiac output measured by thermodilution has no bias with respect to gold standard direct Fick method (rarely used) but limits of agreement are of ±1 L/min [36]. Estimation of LVEDP from a PAWP has an expected bias of –3 mmHg, but limits of agreement vary from −15 to +8 mmHg [37].

In summary, echocardiography at rest provides accurate measurements of the pulmonary circulation, therefore suitable for population studies. Insufficient precision may be a problem for individual decision making based on single numbers, such as a PAMP > 25 mmHg to diagnose PH or a PAWP > 15 mmHg to diagnose left heart failure [1, 2]. It may then be necessary to take the clinical context into account, and to use repetition of measurements and internal controls.

There has been no study comparing echocardiography and right heart catheterization for measurements of the pulmonary circulation during exercise. However, in 136 normal subjects compared to 25 controls, invasive and non invasive measurements produced the same results, and agreed on PAMP-CO relationships of 3 mmHg/L/min as the upper limit of normal [8, 23]. Echocardiographic measurements of pulmonary vascular pressure-flow relationships in a healthy volunteer are illustrated in Fig. 8.1.

Right Ventricular Afterload

There are three possible and equally valid measurements of afterload [38, 39]. The first is maximum ventricular wall stress, which is approximated by the maximum value of the product of volume by pressure, divided by wall thickness. This is a transposition of Laplace's law for spherical structures, and thus problematic for the RV because of considerable regional variations in internal radius. The second is hydraulic load, summing the forces that oppose flow in the pulmonary circulation, which requires integration of arterial pressure and flow waves. The third is arterial elastance (Ea) as it is "seen" by the ventricle and thus graphically determined on a ventricular pressure-volume loop by dividing the pressure at maximal elastance by stroke volume (SV).

The echocardiographic measurement of PVR divided by HR would offer an approximation of Ea on the assumption that PAMP is equal to RV pressure at the point of maximum RV elastance.

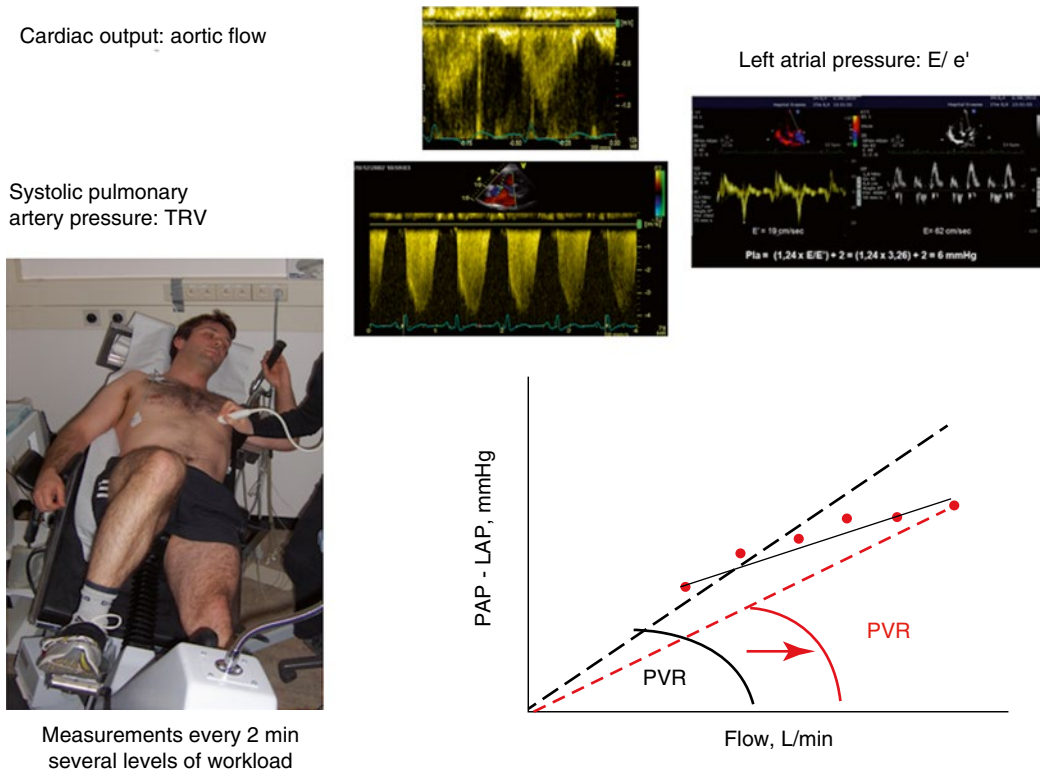


Fig. 8.1 Exercise stress echocardiography of pulmonary vascular pressure-flow relationships in a healthy volunteer. Pressure-flow coordinates do not follow a slope predicted by the PVR equation, but rather a slightly curvilinear adjustment corresponding to decreased PVR calculation at increased cardiac output. *TRV* tricuspid regurgitant velocity, *Ppa* mean pulmonary artery pressure, *Pla* left atrial pressure

This assumption is not correct, and the error on the estimation of Ea potentially large and unpredictable [40]. Hydraulic load calculated on pulmonary artery pressure and flow curves may be more adequate, but requires a spectral analysis to integrate the pulsatile and steady components of the work [39].

Afterload defined as a hydraulic load is determined by a dynamic interaction between resistance, compliance and wave reflection [41]. Recent studies have shown that the product of PVR by Ca, or time constant of the pulmonary circulation (RC-time) is invariable over a wide range of severities, types and treatments of pulmonary hypertension [42]. Accordingly, the pulsatile component of pulmonary arterial hydraulic load, or RV work, can be predicted to be constant as well, and has been shown to be on average of 23 % of the total RV work [43]. Steady-flow RV stroke work (RVSWsteady) can be calculated as

$$\mathrm{RVSWsteady} = \mathrm{PAMP} \times \mathrm{SV}$$

and total RVSW (RVSWtot) as

$$\mathrm{RVSWtot} = 1.3 \times \mathrm{RVSWsteady}$$

It is interesting that the constancy of the pulmonary arterial RC-time rules out a significant impact of wave reflection on RV afterload.

The RC-time has actually been reported to be decreased in patients with an increased PAWP [44] and also in patients with proximal CTEPH [45]. Experimentally, the RC-time has been shown to decrease from 0.8 s in peripheral pulmonary vascular obstruction (microembolization) to 0.3 s in proximal pulmonary arterial obstruction (ensnarement), with extremes of the oscillatory component of RV hydraulic load of 15 and 39 % [35]. Accordingly, the constant for the calculation of RVSWtot from RVSWsteady may vary from 1.2 to 1.4, which remains an acceptable approximation.

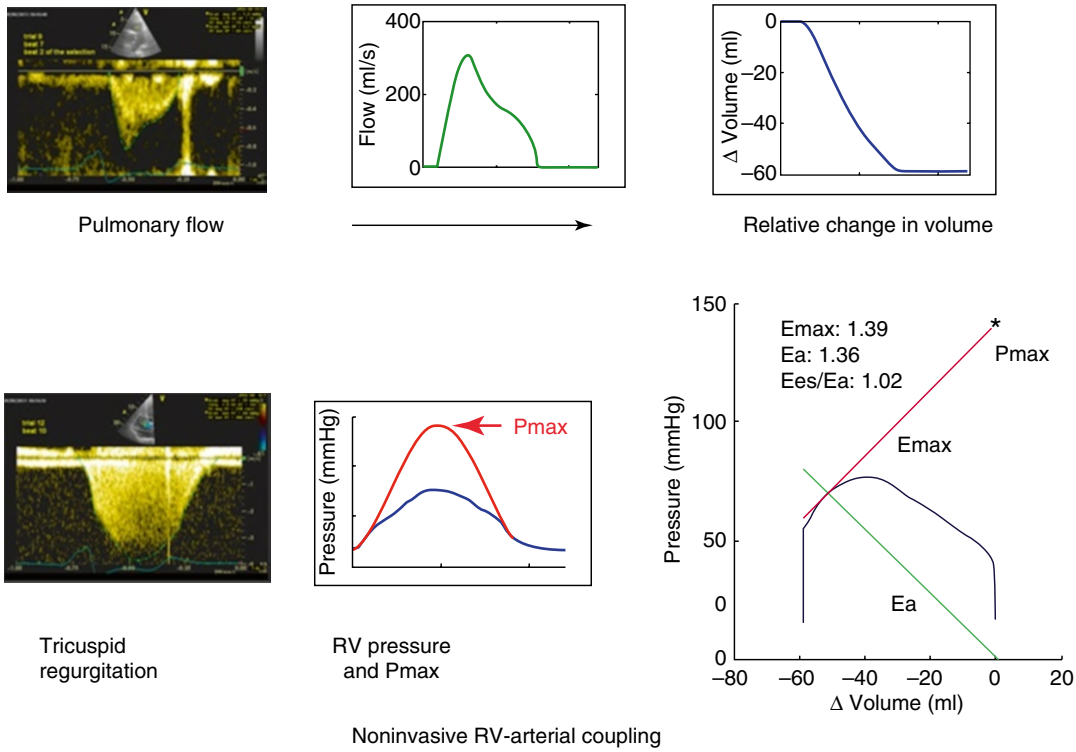


Fig. 8.2 Single-beat method applied to echocardiographic measurements of pulmonary flow and tricuspid regurgitation (TR) for the calculation of right ventricular (*RV*) maximum elastance (*Ees*) and arterial elastance (*Ea*) in a patient with pulmonary hypertension. A RV pressure curve is synthetized from the envelope of the TR wave. A relative change in RV volume is derived from the integration of the pulmonary flow wave

Thus RV afterload can be estimated from echocardiographic measurements of PAMP and SV. We are not aware of studies having yet exploited this possibility.

RV Systolic Function and RV-Arterial Coupling

The gold standard measurement of contractility in an intact being is maximal elastance (Emax), or the maximum value of the ratio between ventricular pressure and volume during the cardiac cycle [38–40]. Left ventricular (LV) Emax coincides with end-systole, and is thus equal to the ratio between end-systolic pressure (ESP) and end-systolic volume (ESV). End-systolic elastance (Ees) of the LV is measured at the upper left corner of a square-shape pressure-volume loop [46]. Because of low pulmonary vascular impedance, the normal RV pressure-volume loop has a triangular shape and Emax occurs before the end of ejection, or end-systole [47]. However, a satisfactory definition of RV Emax can be obtained by the generation of a family of pressure-volume loops at decreasing venous return [47]. Instantaneous measurements of RV volumes are difficult at the bedside, and so are manipulations of venous return. This is why single beat methods have been developed, initially for the left ventricle [48] then for the RV [49]. The single beat method relies on a maximum pressure Pmax calculation from a nonlinear extrapolation of the early and late portions of a RV pressure curve, an integration of pulmonary flow and synchronization of the signals. Emax is estimated from the slope of a tangent from Pmax to the pressure – volume curve (Fig. 8.2).

It is important to note that this graphic analysis uses relative changes in volume without

assumption on absolute volumes. This is acceptable because Emax is essentially preload, or end-diastolic volume (EDV)-independent [40]. As contractility is homeometrically adjusted to afterload [38–40], its adequacy is best evaluated as a ratio of Emax to Ea, which defines RV-arterial coupling. The optimal mechanical coupling of Emax to Ea is equal to 1. The optimal energy transfer from the RV to the pulmonary circulation is measured at Emax/Ea ratios of 1.5–2. Patients with PAH and no clinical symptomatology of heart failure may present with a several-fold increase in Emax matching increased Ea, so that RV-arterial coupling is relatively maintained or only slightly decreased [50, 51]. A similar observation of maintained RV-arterial coupling has been reported in an asymptomatic patient with congenitally corrected transposition of the great arteries (CCTGA) [52].

The maintenance of RV-arterial coupling in pulmonary hypertension varies considerably from one patient to another, depending on rate of increase and levels of PVR. Whether or not there has been post-natal decrease in RV afterload may matter. The RV may fail after a few symptomatic weeks in rapidly evolving idiopathic pulmonary arterial hypertension, but maintain satisfactory coupling to afterload for a few decades in CCTGA, or in congenital left-to-right shunting and subsequent Eisenmenger syndrome. Uncoupling of RV systolic function to afterload is more likely to occur in patients with severe PAH associated with scleroderma, probably in relation to myocardial involvement of this systemic disease [51]. The critical values for RV-arterial uncoupling associated with onset of RV failure are not known.

A RV pressure curve can be recalculated from point-by-point application of the Bernouilli equation to the envelope of the TRV signal [53]. This has been used to derive peak positive and negative dP/dt [54] and a delayed time to peak pressure as an indirect index of decreased dP/dt and depressed systolic function [55].

A preliminary study suggests that it is possible to calculate a Emax/Ea ratio using the single beat method applied to the envelope of a TRV signal and a relative change in RV volume derived from the integration of a synchronized pulmonary flow measurement (Vanderpool 2013, personal communication). An example is shown in Fig. 8.2. This approach is currently under evaluation.

Echocardiographic Indices of RV Systolic Function

Right ventricular systolic function is usually estimated at echocardiography by the fractional area change (FAC) measured in the 4-chamber view, tricuspid annual plane systolic excursion (TAPSE), tissue Doppler imaging (TDI) of the tricuspid annulus systolic velocity S wave and isovolumic acceleration (IVA) or maximum velocity (IVV), strain or strain rate measurements and even SV calculated from aortic flow-derived cardiac output divided by heart rate [9].

RVFAC is determined from the planimetric areas of the RV end-systole and end-diastole from the apical 4-chamber view. RVFAC does not require geometric assumptions and correlates with RVEF, but incomplete visualization of RV cavity and suboptimal endocardial definition are causes of high inter- and intra-observer variability [9]. This explains why RVFAC was only recently shown in one study to be of prognostic relevance in patients with idiopathic PAH [56].

Because of the predominantly longitudinal contraction pattern of the RV, a more suitable measure of systolic function is TAPSE, which can be derived from 2-D and M-mode echocardiography, is easy to perform and highly reproducible. A decreased TAPSE has been shown to be associated with a decreased survival in patients with left heart failure [56, 57] and with PH [56, 58].

A TDI measurement of the longitudinal velocity of RV contraction measured at the tricuspid annulus, or S wave, correlates with TAPSE and RVFAC [59, 60], and offers an additional internal control measure of systolic function.

The problem of RVFAC, TAPSE and S wave is preload-dependency. This may be less of a problem for isovolumic phase indices such as the IVA or IVV [61]. IVV was recently reported to be superior to other echocardiographic indices of RV function such as TAPSE to predict survival in

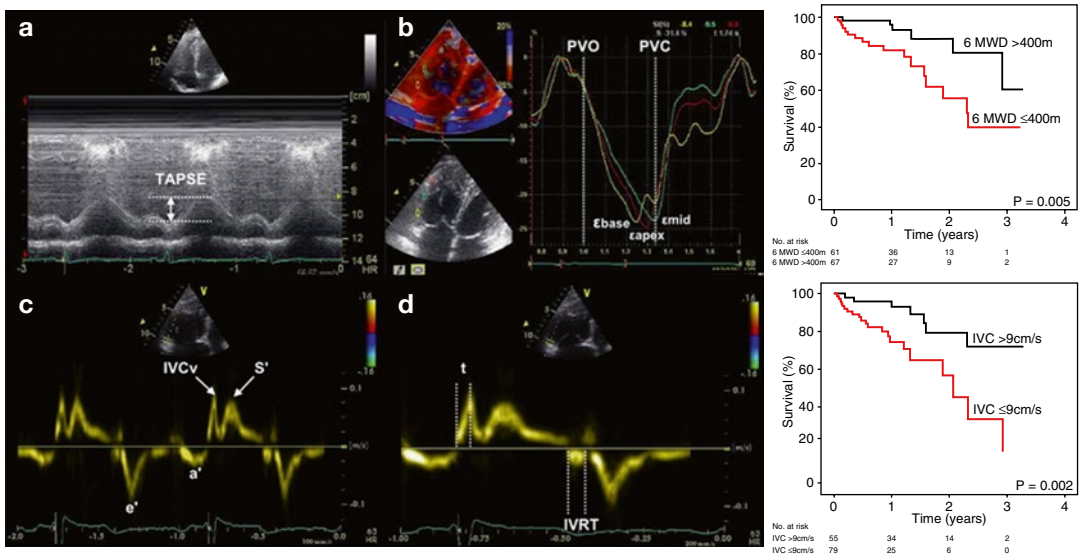


Fig. 8.3 Maximum velocity of isovolumic contraction (*IVCV*) and 6-min walk distance (6MWD) were the only independent predictors (multivariable analysis) of survival in 146 patients with severe pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Survival was also predicted (univariate analysis) by the tricuspid annular plane systolic excursion (*TAPSE*) (**a**), tissue Doppler imaging (TDI) of systolic strain of the RV free wall (ε) (**b**), and TDI of tricuspid annular velocity S' (**c**) and isovolumic relaxation time (IVRT) (**d**). *PVC* pulmonary valve closure, *PVO* pulmonary valve closure (Reprinted from Ernande et al. [62]. With permisssion from Elsevier)

a series of 142 patients with PAH or CTEPH [62]. This is illustrated below (Fig. 8.3).

In the search of better indices of RV systolic function, strain and strain rate measurements have been shown to be closely correlated with myocardial contractility in in vitro and in vivo experimental settings, with minimal preload-dependency [63]. Strain is defined as percentage change in myocardial deformation, while its derivative, strain rate, represents the rate of deformation of myocardium over time [9]. Strain and strain rate are decreased in patients with severe pulmonary hypertension [64, 65] and rapidly improve with only partial reversibility during testing with inhaled pulmonary vasodilators [66]. However, strain measurements suffer from large inter- and intra-individual variability so that the limits of normal are not exactly known [9]. The addition of speckle tracking has made strain measurements less angle and operator-dependent, and as such emerge as potent predictors of functional state and outcome in patients with severe pulmonary hypertension [67, 68].

An integrated index of systolic and diastolic function of the right ventricle is given by the so-called Tei index, which is the ratio of the sum of isovolumetric time intervals to ventricular ejection time [69]. The Tei index has prognostic relevance [69, 70], but does not allow to evaluate the components of RV-arterial coupling and diastolic function adaptation in the presence of increased afterload.

Not surprisingly, a decreased TAPSE < 18 mmHg or a S wave < 15 cm/s predicted a SV index of less than 30 ml/m, underscoring that SV reflects RV systolic function [58, 71]. As such, SV predicts survival similarly to other indices of systolic function [72], An echocardiographic measure of SV is easily obtained by dividing CO by HR but, as such, has not been evaluated as it has been by magnetic resonance imaging (MRI) [72].

It is difficult to propose a hierarchy of echocardiographic indices of systolic function, even though

there might be a logic for preference of immediate preload-dependent IVA, IVV and strain. There have been no validation studies of these indices against true gold standards in patients with RV failure.

Echocardiography of RV-Arterial Coupling

Most recently, in an attempt to evaluate RV systolic function in terms of adequacy of coupling to afterload, Guazzi et al. simply corrected TAPSE for systolic RV pressure measured on TR, and showed this index to be of prognostic value in patients with heart failure [73].

There has been interest in evaluating the contractile reserve of the RV. Contractile or ventricular reserve determined using exercise of pharmacological stress tests (typically an infusion of dobutamine) has been shown to be a strong prediction of outcome in heart failure [74]. A preserved contractile reserve of the RV in PH would indirectly indicate adequate coupling to afterload. Grunig et al. thought of RV systolic pressure measured on TR at exercise as an index of RV contractile reserve, which is simple, and straightforward. These authors showed in patients with severe PH that an exercise-induced increase in RV systolic pressure ≥30 mmHg was associated with a much better survival, reflecting the importance of RV systolic function to afterload in these patients [75].

It has also been reasoned that a ratio of elastances can be simplified to a ratio of volumes, as Emax and Ea have a common term, which is RV pressure at end-systole or at maximum elastance [76]. However, ESV may not be the same as RV volume at the point of maximum elastance, excepted possibly when afterload is markedly increased. The pressure-volume relationships of the RV chronically exposed to increased PAP tend to resemble LV pressure-volume loops, with decreased difference between Emax and Ees [50, 51]. Sanz et al. measured ESV and SV by MRI and showed that the SV/ESV ratio is initially preserved in patients with mild pulmonary hypertension, then decreases with increasing severity of the disease [76]. The measurements of RV volumes using 3D echocardiography are much better, and currently appear accurate when compared to MRI [77].

A problem with the SV/ESV ratio is the inherent assumption that the ESP-ESV relationship is linear and crosses the origin. This is incorrect, because ventricular volume at a zero filling pressure is not zero but has to be positive [78]. Furthermore, the RV Emax curve is slightly curvilinear, with decreased slope at increased volumes [79]. Therefore the ESP/ESV may be insufficiently accurate. The SV/ESV as a simple volume measurement of RV-arterial coupling requires further evaluation and estimation of functional and prognostic relevance.

A recent study reported on the negative impact on outcome of decreased RVEF measured by MRI in spite of targeted therapies-associated decreased PVR in patients with PAH [80]. Systemic vasodilating effects of targeted therapies in PAH may increase systemic venous return and increase EDV, which decreases EF if SV remains essentially unchanged, while increased cardiac output may decrease PVR without any change in the functional state of the pulmonary circulation [41]. There might be interest in comparing the effects of targeted therapies on changes in 3D echocardiography measurements of SV/EDV and SV/ESV and their prognostic relevance in patients with severe PH.

RV Dimensions and Diastolic Function

The heterometric adaptation of the RV inevitably results in a competition for space with the LV within the relatively indistensible pericardium. This diastolic interaction is usually quantified by an apical 4-chamber view as a ratio of RV and LV diastolic surface areas. The RV/LV ratio is normally 0.5–0.7, increasing to 0.8–1.0, 1.1–1.4 and >1.5 in mild, moderate and severe RV dilatation [9].

The dilatation of the RV compressing the LV can also be measured by an end-systolic parasternal

short axis view of a D-shape instead of circular shape of the LV, with an increased ratio of parallel to perpendicular to septum LV diameters, called eccentricity index (EI). The EI is normally equal to 1, and increases to 1.1–1.4, 1.5–1.8 and >1.8 referring to mild, moderate and severe septal bowing respectively. However, some degree of septal flattening is invariably present in patients with pulmonary hypertension, and actually also reflects a delay in the time to peak RV contraction [81]. An increased EI enhances the prognostic impact of a given degree of RV systolic dysfunction [82].

Impaired relaxation and filling of the RV is also a consequence of altered systolic function and increased dimensions, which causes an increase in the RV isovolumic relaxation time (IVRT), with reversal of trans-tricuspid flow and tricuspid annulus velocity E and A waves. Compression of the LV by an enlarged RV alters LV diastolic compliance, with prolonged mitral E wave deceleration, inversed E/A and, eventually an increasesd E/E' indicating increased LV end-diastolic pressure (LVEDP). Altered diastolic function of the LV as a consequence of RV failure is sometimes called the "inverse Bernheim effect", after the initial report more than a century ago of altered RV function by LV failure [83].

Dilatation of the RV under pressure is inevitably associated with tricuspid insufficiency. The greatest degrees of tricuspid regurgitation are observed in dilated RV on severe PH. The combination of a marked tricuspid regurgitation and depressed TAPSE is of particularly poor prognosis in patients with severe pulmonary hypertension [56].

Right atrial enlargement is component of right heart failure. An increased RA area has been shown to predict decreased clinical stability and shorter survival in idiopathic PAH [84]. Whether the dilatation of the RA is more than just the mechanical consequence of RV dilatation and tricuspid insufficiency is not exactly known. Right atrial enlargement goes along with inferior vena cava dilatation and decreased inspiratory collapse.

The presence and severity of pericardial effusion is another important sign of RV failure. It is the consequence of increased central venous pressures, with increased coronary capillary filtration,. It may be aggravated by coexistent inflammation in patients with PAH associated with connective tissue diseases. Pericardial effusion predicts clinical worsening and decreased survival [84].

RV Dyssynchrony

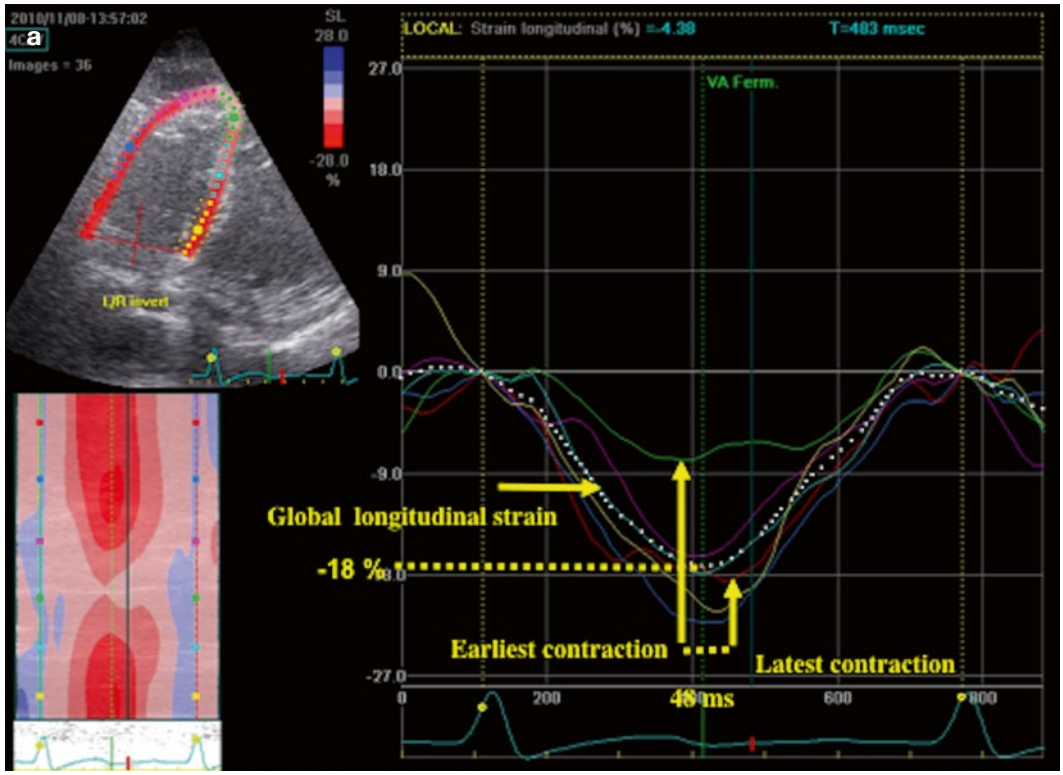
Studies using MRI imaging with myocardial tagging have shown that RV failure in patients with severe PH is characterized by prolonged systolic shortening with late peaking, and that this contributes to septal bowing, decreased LV filling and decreased SV [81]. This inter-ventricular asynchrony causes a typical aspect of post-systolic shortening on the TDI imaging of tricuspid annulus tissue velocity [85].

However, RV failure is also associated with regional contraction abnormalities responsible for dyssynchrony, as can be shown by speckle tracking strain measurements. This is illustrated in Fig. 8.4.

The speckle-tracking analysis is used to generate regional strain from echocardiographic images [86, 87]. A region of interest is traced on the endocardial and epicardial border of the right ventricle apical 4-chamber view, using a point-and-click approach. Natural acoustic markers, or speckles within the region of interest are tracked over the cardiac cycle. The location shift of these speckles from frame to frame, which represents tissue movement, provides the spatial and temporal data. Longitudinal strain is calculated as the change in length/initial length between endocardial and epicardial trace. Accordingly, in the longitudinal view, RV myocardial shortening is represented as negative strain and myocardial lengthening as positive strain. The software then automatically divides the RV long axis image into six standard segments and generates global and individual strain-time waveforms for basal septum, mid septum, apical septum, basal free wall, mid free wall and apical free wall segments. Peak strain and time to peak strain from each of six time-strain curves are determined with dyssynchrony defined as the difference between earliest and latest segments as previously described [88–90]. Global longitudinal RV septal wall strain is

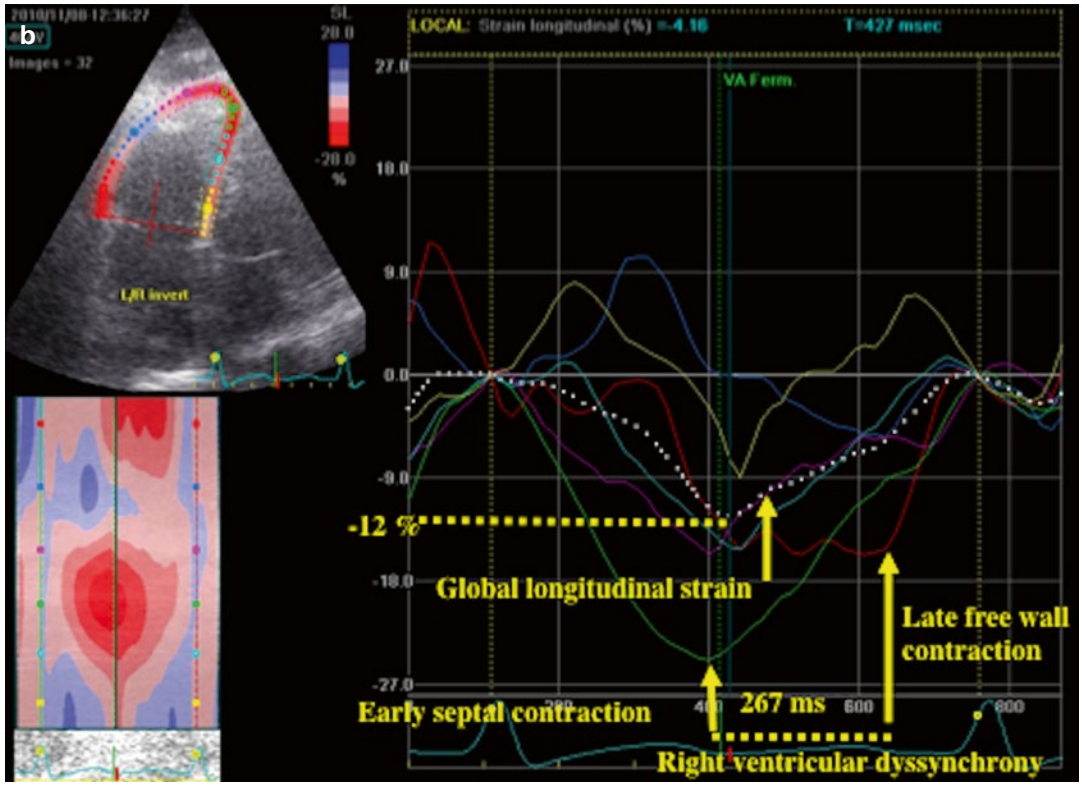
calculated as averaged longitudinal strain from three septum segments. Global longitudinal RV free wall strain is calculated as averaged longitudinal strain from three free wall segments. Finally, global longitudinal RV strain is calculated as averaged longitudinal strain from six segments. The maximum time difference from the earliest to latest peak strain among six segments, as a measure of contraction synchrony is increased in pulmonary hypertension patients.

Asynchrony and dyssynchrony decrease the efficiency of RV contraction, and thus depresses global indices of systolic function such as FAC or TAPSE, even though this has not until now been systematically evaluated. Asynchrony also impairs LV diastoilc filling.



CI	3.79 l/min/m^2
RAP	6 mmHg
MPAP	23 mmHg
PVR	1.4 WU

Fig. 8.4 Regional right ventricular function analyzed with speckle tracking strain in a control (**a**) and a patient with pulmonary hypertension (**b**). Global strain and individual segments are color- coded: global longitudinal strain (*dashed white curve*), basal (*yellow curve*), mid (*cyan curve*) and apical (*green curve*) segments of the right ventricular septum and basal (*red curve*), mid (*blue curve*) and apical (*magenta curve*) segments of the right ventricular free wall. Note that some segments shorten early and the remaining segment shorten late, similar to dyssynchrony. Hemodynamics, global, early and late segmental contraction and dyssynchrony are reported below each example. *CI* cardiac index, *mPAP* mean pulmonary arterial pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *SVI* stroke volume index



CI	1.28 l/min/m^2
RAP	9 mmHg
MPAP	39 mmHg
PVR	15.6 WU

Fig. 8.4 (continued)

Conclusions

Echocardiography is essential for the diagnosis and serial assessments of pulmonary hypertension and RV failure.

The echocardiographic approach provides accurate assessments of the pulmonary circulation and RV function. The precision of echocardiographic measurements is limited by operator-dependency, inherent instability of physiological measurements and recalculation of variables or indices, which is necessarily fraught with variability. Adequate accuracy but limited precision limits the use of echocardiography for single number decision making.

Echocardiography must be understood as an extension of clinical examination.

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Part III

Causes of Right Heart Dysfunction

Right Ventricle and High Altitude

9

Jean-Paul Richalet and Aurélien Pichon

Abstract

At high altitude, as hypoxia induces pulmonary vasoconstriction and increases ipulmonary arterial pressure, right ventricular (RV) function will be affected. The right ventricular function may be affected directly by the hypoxaemic challenge or indirectly through a pressure overload due, in turn to changes in the pulmonary circulation. Both animal and human studies show that moderate or transient hypoxia results in adaptive changes in right ventricle that are reversible with re-exposure to normoxic conditions and RV dysfunction is mainly due to mechanical overload from the pulmonary circulation. When hypoxia is more severe or more prolonged, it may directly impact ventricular diastolic or systolic function through mechanisms that remain to be unraveled. Chronic exposure to hypoxia in high-altitude natives suffering from Monge's disease may lead to RV hypertrophy, RV failure and overall cardiac failure. The adrenergic system may be involved, as well as HIF, PKC or phospholamban. More studies using the latest imaging technology should give us a better understanding of RV systolic and diastolic function in humans exposed to altitude hypoxia including acute, chronic or chronic intermittent hypoxia.

Introduction

The function of the right ventricle (RV) is tightly related to the physiology of pulmonary circulation. As hypoxia induces pulmonary vasoconstriction and possibly pulmonary hypertension, right ventricular function will be affected. A great number of studies have addressed pulmonary circulation changes induced by altitude exposure but only rarely have studies explored the potential direct effect of hypoxia on RV function. We will review RV function in humans and in some animals in acute and chronic hypoxia

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and discuss the role of RV dysfunction in some diseases such as Chronic Mountain Sickness (CMS). Its possible role in limiting exercise performance at high altitude will be mentioned. Finally, the mechanisms of an eventual RV dysfunction at high altitude will be discussed: is the (right) heart hypoxic at high altitude?

The Effects of Hypoxia on the Heart, Experimental Studies

Exposure to altitude hypoxia triggers physiological reactions involving all organs and systems. Physiological responses to hypoxia may occur at the cellular level, as well as at an integrative level involving the autonomous nervous system or endocrine system. Acute, intermittent or chronic hypoxia may have distinct effects on the heart.

Three main effects of hypoxia on the heart can be identified as:

1. Direct effect, by genes with *hypoxia-responsive elements*, inducing the production of HIF1α, VEGF, EPO, and other regulatory proteins.
2. Indirect effect of hypoxia via adrenergic activation and autonomous nervous system imbalance.
3. Indirect effect through the increase in afterload due to pulmonary hypertension.

These effects are usually combined during altitude exposure. The first two are common to the right and the left (LV) ventricles while the third one is only relevant for the RV.

Chronic increase in afterload leads to a progressive hypertrophy of RV while LV remains generally retains a normal size.

The response of RV often differs from LV. For example, intermittent hypoxia (7,000 m, 8 h/day for 25 days) induced a marked hypertrophy of RV in rats, while gelatinolytic activity of matrix metalloproteinase-2 (MMP-2) and protein levels of carbonic anhydrase IX (a marker of hypoxia) were significantly enhanced. Activation of p38-Mitogen activated protein kinase (p38-MAPK) was decreased in the RV and moderately increased in the LV. As compared with the controls, total content of c-Jun N-terminal kinases (JNKs) was increased in the RV of the hypoxic rats, while expression of JNKs in the LV was down-regulated. The results demonstrate that adaptation of rat hearts to chronic intermittent hypoxia is associated with distinct changes in the levels and/or activation of several regulatory proteins in two ventricles, probably because of distinct load constraints [1].

Exposure of rats to intermittent high altitude (IHA, 5,000 m, 4 h to 10 days) led to an increased expression of Heme oxygenase-1 and transforming growth factor (TGFβ-1) in all regions of the heart. Lactate dehydrogenase-A was up-regulated in RV, lactate dehydrogenase-B up-regulated in RV, but down-regulated in LV and atria. Vascular Endothelial Growth Factor (VEGF) was up-regulated in RV, LV and lungs, but down-regulated in the atria. Its receptor Flk-1 mRNA was increased in the atria and RV only. Expression of c-fos was found in the LV and RV only after 4 h of hypoxia. C-jun was increased in the LV but decreased in the atria. Therefore, intermittent hypoxia modulates gene expression under physiological conditions by regulating the expression of distinct genes in the heart [2].

In wild type mice however, no change was reported in the RV or LV weight after short term chronic hypoxia [3] but has been recently observed in long term chronic hypoxia with a critical role of the MAPK kinase kinase-2 [4] and MAPK phosphatase-1 pathways [5]. Erythropoietin (Epo) deficiency has also been shown to be deleterious for both LV and RV under chronic hypoxia due to depressed HIF-1alpha and EPO receptor pathways. Moreover, Epo seems to be expressed and involved in heart adaptation during chronic hypoxia or heart failure [3, 6].

Exposure to hypoxia activates the adrenergic system, which leads to profound changes in the receptors involved in the control of chronotropic and inotropic function of the heart. A desensitization of the beta-receptor pathway rapidly occurs with a downregulation of betareceptors and adenosinergic receptors, and an upregulation of muscarinic receptors both in RV and LV [7]. These effects of chronic hypoxia seems to be reinforced in animals adapted to high altitude as Andean guinea pigs or Plateau Pikas for example

[8, 9]. Gi protein is upregulated mainly in RV, while functional activity of Gs protein is decreased in both RV and LV [10]. These changes fully explain the decrease in chronotropic response to adrenergic activation at high altitude [11], as well as the reduction in maximal heart rate at exercise [12]. Moreover, this desensitization of heart response to adrenergic activation is a remarkable protecting mechanism of the heart against a possible unbalance of oxygen availability to cardiac tissue in conditions of severe environment hypoxic conditions. During exercise, the right ventricle is therefore partially protected against the double constraint of high afterload (due to pulmonary hypertension) and tachycardia.

Two periods of intermittent exposure for 2 months to hypoxia (either 24 h in hypoxia (428 Torr) then 24 h in normoxia; or 48 h in hypoxia, then 24 h in normoxia) led to RV hypertrophy and downregulation of alpha1-adrenoceptor in RV and LV in rats, with RV hypertrophy being greater and alpha1-adrenoceptor density being lower in the group with prolonged exposure to hypoxia [13].

RV and LV also respond differently to hypoxia for glucose metabolism and ion gradient and function. Indeed, according to isolated rat heart experiments, RV seems to be more prone to hypoxic damage than LV because it is less efficient in recruiting glucose as an alternative fuel and is particularly dependent on the efficient Na, K-ATPase function [14]. In these experiments RV showed also a greater oxidative stress under chronic hypoxia as compared to LV. However, in whole body experiment and under chronic hypoxia leading to RV pressure overload the RV showed a downregulation of fatty acid metabolism and an increase in glucose metabolism, while left ventricular metabolic gene expression suggested restoration of fatty acid metabolism [15].

The remodelling (at morphological and electrophysiological levels) induced by chronic hypoxia in the RV can be decreased by the natural aging process [16]. The extent of RV hypertrophy was less in older animals. RV cell size and pericellular fibrosis showed a significant increase in 2- and 6-month-old exposed rats but not in the 18-month-old exposed rats compared with control. A decrease in the transient outward potassium current (Ito) density was observed in RV cell only in the 2-month-old exposed group. The norepinephrine content in the RV was decreased in each age group exposed to hypoxia when compared with their age-matched control group [16] (Fig. 9.1).

The function of the hypertrophic RV was studied in an isolated RV working heart preparation from rats with hypoxic pulmonary hypertension induced by intermittent high-altitude (IHA) exposure. Elevated RV systolic pressure and maximum rate of pressure development were observed at various levels of preload or afterload. The peak indices of mechanical performance were almost doubled in these animals when compared with the normoxic group, while the index of contractility remained unchanged. Maximum ventricular performance was linearly related to RV weight. No evidence of RV pump dysfunction was detected in rats exposed to IHA; moreover, the ability of the ventricle to maintain cardiac output against increased pulmonary resistance was markedly improved. Therefore, the increase of the RV mass in IHA-exposed rats may serve to improve maximum ventricular performance, in order to overcome elevated pulmonary resistance without disturbing the pump function [17].

RV mass is commonly related to the level of hypoxia-induced pulmonary hypertension, either directly or via Fulton's ratio (RV/(LV+septum)). For example, when reducing pulmonary hypertension by drugs such as calcium channel blockers (nifedipine), RV mass is reduced in rats exposed for 2 weeks at 380 mmHg. The α1-adrenergic receptor (AR) and protein kinase C (PKC) may play an important role in the signalling pathway leading to RVH. In both ventricles, hypoxia decreased α1- and β-AR density and increased muscarinic receptor density. The development and regression of pulmonary hypertension and RV hypertrophy were also related to the expression of PKC isoforms (epsilon, delta and zeta) [18].

Dehydroepiandrosterone (DHEA) has been shown to prevent chronic hypoxia-induced pulmonary hypertension as well as RV dysfunction in rats [19]. DHEA abolished RV diastolic

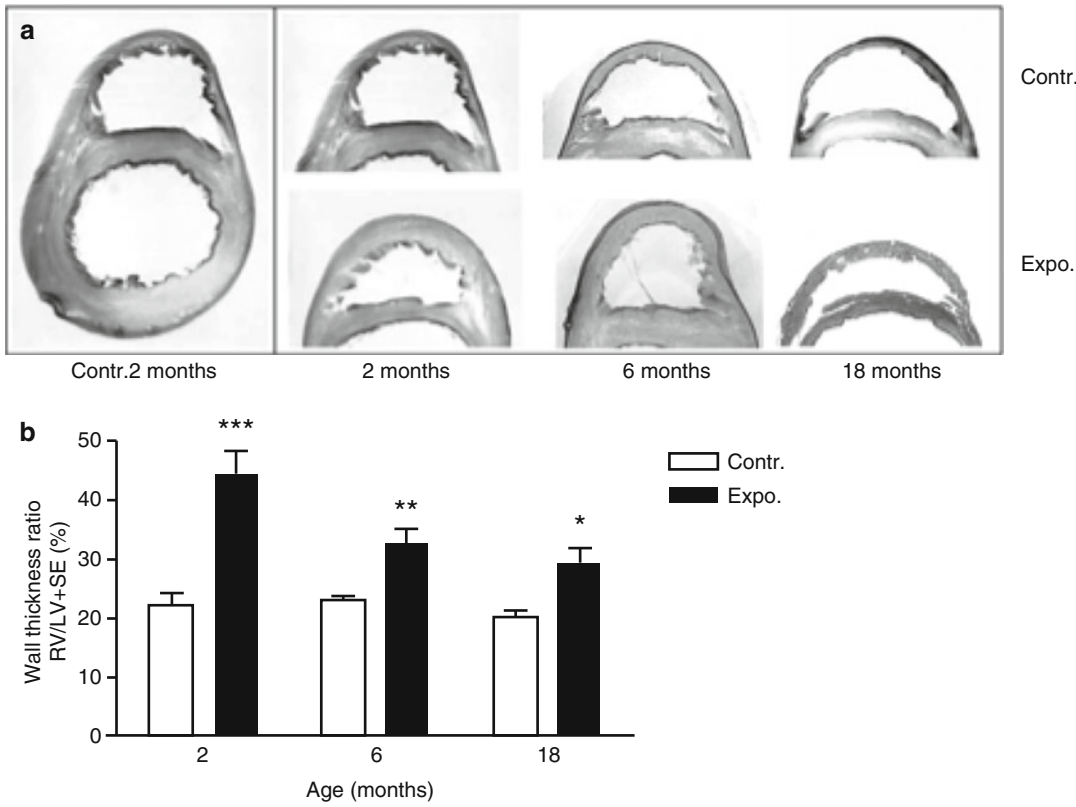

Fig. 9.1 Effect of ageing on the development of RV hypertrophy (Reprinted from Chouabe et al. [16]. With permission from the American Physiological Society). (**a**) total transversal ventricular slice of a 2-mo-old control rat (*left*) and RV transversal slices (*right*) in control (*top*) or exposed (*bottom*) rats. In each age group, picture enlargements are identical to emphasize the difference in wall thickness between them. (**b**) evolution of the wall thickness ratio

dysfunction, as the echographic E wave remained close to that of normoxic controls, whereas it was diminished in the recovery group after hypoxia without DHEA. DHEA also abolished RV systolic dysfunction, as shown by the inhibition of the increase in the slope of the pressure-volume curve in isolated heart. DHEA has been shown to act as an anti-remodeling and vasorelaxant drug [19, 20].

Right Ventricle in Humans at High Altitude

Exploration of cardiac function, especially of the right heart in humans in high altitude conditions have developed recently with the use of portable echocardiographic devices, knowing that right heart catheterisation, as the reference technique, is rarely available in field conditions. Acute exposure of sea level natives to hypoxia may induce pulmonary hypertension through hypoxic pulmonary vasoconstriction that may create a rapid increase in the afterload of RV. However, RV seems to adapt to this constraint since no observation of RV failure has been mentioned in the literature in those conditions. Conversely, chronic exposure to hypoxia in high-altitude natives may lead to important RV hypertrophy, RV failure and overall cardiac (bi-ventricular) failure.

Acute Exposure of Sea Level (SL) Natives

Normal Subjects

In subjects without severe sign of acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE)

during acute exposure to high altitude, no signs of heart dysfunction (neither RV nor LV) have been measured, using either electrocardiographic recordings or Doppler echocardiography. However, it has been suspected that some extent of cardiac insufficiency may favour the development of HAPE. The Tei index of RV function measured by Doppler echocardiography before and after 30 min of hypoxic breathing in 11 HAPE-susceptible subjects compared to nine HAPE-resistant subjects evidenced an enhanced left ventricular myocardial performance but an impaired right ventricular performance in HAPE-susceptible subjects [21].

Elite swimmers following a "Living High Training Low" procedure during 13 days between 2,500 and 300 simulated altitude showed a slight increase in the RV/LV diameters ratio at echocardiography, suggesting a slight dilatation of the right ventricle without alteration of contractile function [22].

Patients with Pre-existing Diseases: COPD, Myocardial Infarction

An increase in mean pulmonary artery pressure (PAPm) and RV dimensions were observed in 40 chronic obstructive pulmonary disease (COPD) patients living at moderate altitude (1,768 m) when compared with COPD patients living at sea level. Despite this increase, systolic and diastolic functions of the RV, as well as global RV performance were similar in COPD patients living at high altitude and sea level, suggesting an adaptation to chronic hypoxia in those patients [23].

Eight patients with a history of acute myocardial infarction and a low risk score were compared at 4,200 m with seven healthy controls during an expedition to the Aconcagua. An increase in RV diameter was observed in the patients at 4,200 m compared with sea level and a trend towards the same result in the control group. A decrease in tricuspid annular plane systolic excursion (TAPSE) was also observed. Measurements of the peak tissue velocity during early diastole (E′) showed a significant decrease in the LV septum and lateral wall at high altitude compared with sea level in both groups. Patients and healthy controls showed comparable changes at high altitude compared with sea level with an increase in RV diameter, a decrease in TAPSE, and decreased E′ as early signs of pulmonary hypertension and LV diastolic dysfunction. These changes can be considered as physiological adaptations to high altitude [24].

Altogether, patients with mild forms of pulmonary or cardiac diseases may adapt to moderate altitude in a similar manner to healthy subjects.

Chronic Exposure of SL Natives

In most studies performed on normal SL natives chronically or intermittently exposed for long periods to high altitudes, slight RV hypertrophy is found with no clear sign of heart dysfunction. An interaction between the left and right ventricle has been observed.

Healthy volunteers (n = 14) were studied immediately before, and within 4 days of return from a 17-day trek to Mt. Everest Base Camp (5,300 m). Immediately after returning from Mt. Everest, left ventricular mass, corrected for body surface area, had decreased by 11 %, but returned to pre trek levels by 6 months. LV and RV stroke volumes were 11 and 12 % lower, respectively, but had returned to normal by 6 months. At no time were there significant changes in ejection fraction or end-systolic or end-diastolic volumes [25].

In 29 miners exposed to chronic intermittent hypoxia (working 7 days at 3,800–4,600 m, resting 7 days at sea level for 2.5 years), systemic and pulmonary arterial pressures measured at sea level did not change with chronic exposure, but were higher in hypoxia. RV showed a slight dilatation but no clear hypertrophy [26]. Similarly, in a cross-sectional study of 50 healthy army men weekly commuting between sea level and 3,550-m altitude for at least 12 years, pulmonary hypertension (PAPm > 25 mmHg, RV and RA enlargement) was found in two subjects (4 %), a PAPm > 20 mmHg in 14 %, and a right ventricle thickness >40 mm in 12 % [27].

During Operation Everest III, echocardiography was performed in 8 healthy sea-level natives at simulated altitudes as high as 8,000 m [28, 29].

Mitral peak E velocity decreased, peak A velocity increased, and E/A ratio decreased. Pulmonary venous flow velocities showed a decreased peak D velocity, a decreased peak S velocity, and a reduction of the D/S ratio, suggesting that the contribution of the atrial contraction to LV filling became more important at high altitude. Systolic Pap increased, as seen on the elevation of the right ventricular/right atrial gradient pressure from 19.0±2.4 at sea level up to 40.1±3.3 mmHg at 8,000 m, and remained elevated 2 d after recompression to sea level. This study confirmed the preservation of LV contractility in prolonged hypoxia already mentioned in Operation Everest II [30, 31] but demonstrated a modification of the LV filling pattern, with a decreased early filling and a greater contribution of the atrial contraction, without elevation of LV end-diastolic pressure [28].

High Altitude (HA) Natives

RV function in normal HA natives and in patients with Monge's disease has been recently explored by Doppler echocardiography, although RV hypertrophy was described many years ago [32].

Pulmonary hypertension in healthy highlanders is related to a delayed postnatal remodelling of the distal pulmonary arterial branches. The magnitude of pulmonary hypertension increases with the altitude level and the degree of exercise. There is reversal of pulmonary hypertension after prolonged residence at sea level or treatment with vasodilators [33]. Chronic mountain sickness develops when the capacity for altitude adaptation is lost [34, 35]. Right ventricular failure seems to be an uncommon complication of Monge's disease, but the exact prevalence of the condition is not known [36].

Children Living at HA

Infants living at high altitude in La Paz, Bolivia (3,800 m) and infants living at low altitude in Santa Cruz, Bolivia (400 m) were explored by echocardiography. At low altitude, the thickness of the anterior wall of RV decreased during the first month of extrauterine life to a dimension, which remained constant for the rest of infancy. At high altitude, the thickness of the anterior wall of the right ventricle at birth was similar to that found at low altitude but did not decrease in the succeeding 12 months. The ratio of the diameter of the aorta to that of the pulmonary artery was higher at low altitude whatever the age. These observations are consistent with the persistence of a high pulmonary arterial pressure during infancy at high altitude [37].

Conversely, in a population of 321 healthy children ranging from 2 months to 19 years and living at high altitude (Tintaya, Peru, 4,100 m), RV and LV morphologic and functional echocardiographic measurements expressed by age and by body surface area were generally similar to SL reference populations, suggesting that the pattern of cardiovascular development at high altitude in children with some degree of high-altitude genetic background and living in comparatively good nutritional and socioeconomic conditions is similar to that reported for SL children [38].

Structural and functional cardiac changes were explored in infants born and living in the Qinghai-Tibetan Plateau (3,600–4,600 m), with high altitude pulmonary hypertension (HAPH). Ten patients with infantile HAPH (aged 12–24 months) and eight healthy age-matched children (control group) underwent MRI and Echo studies. Right ventricular end-diastolic wall (RVEDT) thickness was significantly higher in the HAPH patients when compared with the control group (4.9±1.1 vs 2.1±0.3 mm). Mean systolic PAP (PAPs) in the HAPH group was higher than in the control group and positively correlated with RVEDT. RV ejection fraction was lower in the HAPH group when compared with the control group (29.8±11.8 vs 55.5±9.9 %) indicating that hypoxia-induced infantile HAPH induces RV hypertrophy that may lead to RV dysfunction and right heart failure, while LV function is preserved [39].

Adult HA Natives

RV and LV function were compared between 15 acclimatized Caucasian lowlanders and 15 native

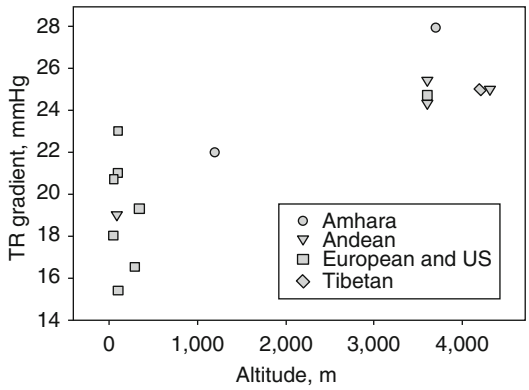

Fig. 9.2 Doppler-estimated average pulmonary artery systolic pressure (TR gradient, mmHg) of populations with low and high residence altitude (Reprinted Hoit et al. [41]. With permission from John Wiley & Sons, Inc)

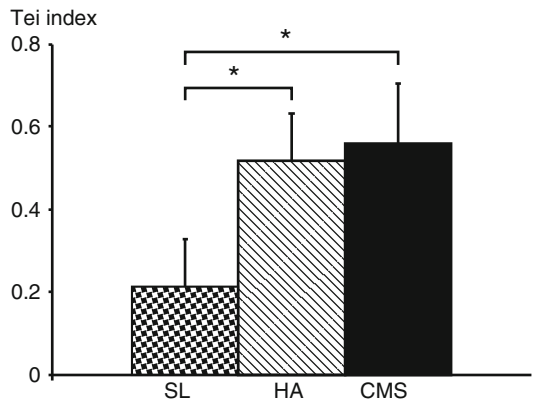

Fig. 9.3 Tei index in Peruvian sea level natives (*SL*), high altitude normal natives (*HA*) and high altitude natives with chronic mountain sickness (*CMS*) *: $p<0.001$ (Adapted from Maignan et al. [42]. With permission from American College of Chest Physicians)

Bolivian highlanders (Oruro, 4,000 m) at high altitudes (La Paz, 3,750 m). Standard echocardiography and tissue Doppler imaging studies were performed. Acute exposure to high altitude in lowlanders caused an increase in mPAP and altered RV and left ventricular diastolic function, with prolonged isovolumic relaxation time, increased RV Tei index, and maintained RV systolic function as estimated by tricuspid annular plane excursion and the tricuspid annular S wave. Native highlanders had a lower mPAP but more pronounced alterations in diastolic function, decreased tricuspid annular plane excursion and tricuspid annular S waves, and increased RV Tei index. Altogether, cardiac adaptation to high altitude appeared qualitatively similar in acclimatized lowlanders and in Bolivian native highlanders [40].

A different pattern of cardiac adaptation was shown in the Amhara population living at 3,700 m in Ethiopia: they had a dilated RV and elevated PAPs (Fig. 9.2), but without elevated pulmonary vascular resistance, as a consequence of high pulmonary blood flow [41].

Cardiac function was explored in 55 CMS patients from Cerro de Pasco (HA, 4,300 m) with hypoxia-induced pulmonary hypertension (PH) compared to 15 healthy men living at SL and 15 healthy men living at HA [42]. None of the subjects had overt cardiac failure symptoms. CMS patients exhibited elevated mPAP as assessed by high-tricuspid pressure gradients (CMS patients, 34 ± 10; HA subjects, 25 ± 4 and SL subjects, 19 ± 3 mm Hg) and RV dilation (mean end-diastolic RV area: CMS patients, 17 ± 2; HA subjects, 13 ± 2; SL subjects, 12 ± 2 cm^2) but did not display impaired systolic RV or LV function, although RV Tei index was increased in CMS and HA subjects (Fig. 9.3). Despite obvious pulmonary arterial hypertension and right heart dilation, CMS patients did not show any clinical or echocardiographic marker of heart failure [42].

The treatment for CMS and associated PH was commonly a move to SL areas (with negative socio-economical consequences) or repetitive blood letting (with a progressive loss of efficiency) [43]. However, recently the use of acetazolamide (Acz) has proved efficient both to reduce polycythemia and pulmonary vascular resistance [44]. A two-phase study was performed in CMS patients (hematocrit ≥ 63 %) from Cerro de Pasco (4,300 m). First phase: a double-blind, placebo-controlled study in 55 patients who received either daily 250 mg Acz ($n=40$) or placebo ($n=15$) for 12 weeks. Second phase: all patients received 250 mg Acz for 12 weeks. During phase 1, mean cardiac output, tricuspid pressure gradient, and pulmonary vascular resistance (PVR) did not change with treatment, although a tendency for ameliorating pulmonary acceleration time was seen in the Acz group.

During phase 2, cardiac output increased and PVR decreased in both groups, whereas pulmonary acceleration time increased only in the group treated by Acz for 24 weeks (Acz- Acz). At the end of phase 2, RV was significantly enlarged in the group treated by placebo then Acz (Pla-Acz) when compared with the Acz-Acz group. There was no difference in RV and LV systolic function indexes (LVEF and RVSF). Therefore, the efficacy of Acz was essentially shown in decreasing PVR and increasing cardiac output, probably partly by reducing blood viscosity [44]. To test this last hypothesis, we evaluated in rats the effect of Acz on blood mechanical properties and PVR during chronic hypoxia. Six groups of rats were either treated or not treated with Acz (curative: treated after 10 days of hypoxic exposure; preventive: treated before hypoxic exposure and exposed to 3 weeks of hypoxia (5,500 m)). Acz treatment in hypoxic rats decreased haematocrit (curative by −10 % and preventive by −11 %), PVR (curative by −36 % and preventive by −49 %) and RV hypertrophy (preventive −20 %), and increased cardiac output (curative by +60 % and preventive by +115 %). Blood viscosity decreased after curative Acz (−16 %) and was correlated with PVR, suggesting that blood viscosity could influence pulmonary hemodynamics. The fall in pulmonary vascular hindrance (curative by −27 % and preventive by −45 %) suggests that Acz could decrease pulmonary vessels remodelling under chronic hypoxia. The effect of Acz appears multifactorial, acting on erythropoiesis, pulmonary circulation, hemorheological properties and cardiac output [45].

Role of RV Dysfunction in Limiting Aerobic Performance at HA?

Altitude exposure is associated with decreased exercise capacity and increased pulmonary vascular resistance (PVR). There has been recent suggestion that 10–25 % of the loss in aerobic exercise capacity at high altitudes can be restored by specific pulmonary vasodilating interventions. Echocardiographic measurements of pulmonary hemodynamics and a cardiopulmonary exercise test were performed in 13 healthy subjects in normoxia and during acute hypoxic breathing (1 h, 12 % oxygen in nitrogen), and in 22 healthy subjects after acclimatisation to an altitude of 5,050 m. Sitaxsentan (a selective endothelin A receptor blocker) decreased PVR in acute and chronic hypoxia, and partly restored maximal oxygen uptake (VO_2max), by 30 % in acute hypoxia and 10 % in chronic hypoxia, without adverse effects on renal function [46]. Whether this is explained by an improved maximum flow output by an unloaded RV remains to be confirmed. Similarly, sildenafil, a PDE5 inhibitor, has been suggested to increase RV contractility in hypoxic exercise, in parallel with a reduced increase in PVR and RV systolic pressure (RVSP). Tricuspid annular isovolumic acceleration (IVA) and annular velocities were measured in 14 subjects at rest and after maximal exercise in normoxia, normobaric hypoxia with or without the administration of 100 mg sildenafil. RVSP during rest increased from 26.9 ± 2.3 in normoxia to 37.8 ± 6.9 mmHg in hypoxia; sildenafil administration reduced RVSP in hypoxia to 30.5 ± 5.6. Compared to normoxia at rest, IVA increased similarly with peak exercise in normoxia and hypoxia with sildenafil, but the increase in IVA during exercise was smaller in hypoxia with placebo. RV contractility, estimated by IVA at peak exercise, was increased with sildenafil as compared to placebo, and was not different from the values seen during exercise in normoxia [47].

The Right Ventricle in Animals at High Altitude

Sea level animals generally suffer from HAPH with large brand and species differences and for example lower response in mice as compared to rats or calf [48]. Therefore large differences also occur in RV response to hypoxia. In rats some strains such as Hilltop, Wistar-Kyoto or Fown-Hooded rats develop larger HAPH or pulmonary arteries muscularization as compared to Madison, Fischer 344 or Sprague Dawley rats [49–51]. HIF-1beta, HIF-1-DNA binding, and iNOS and

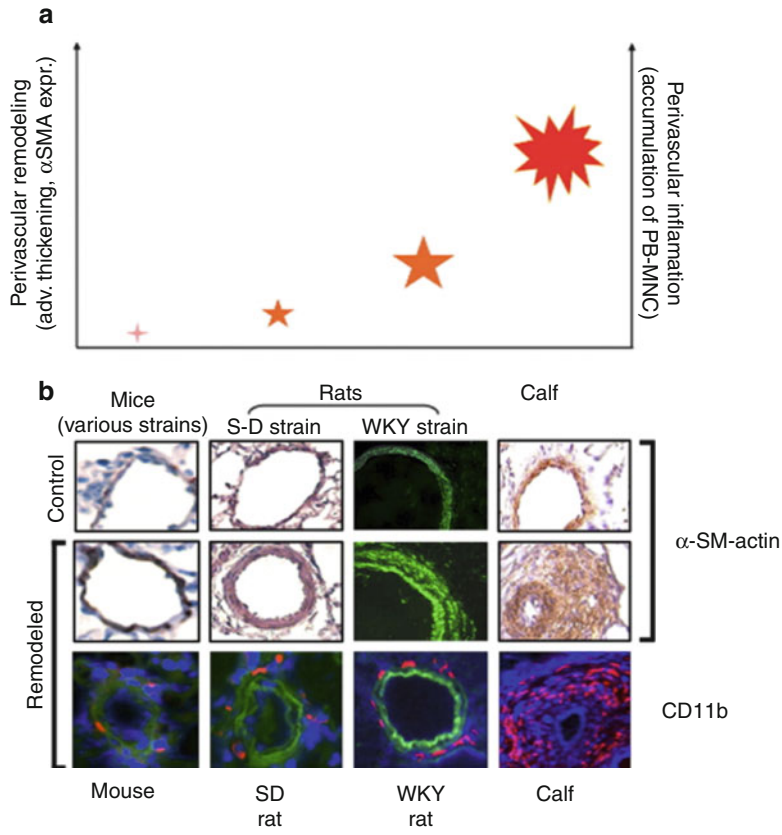

Fig. 9.4 Hypoxia-induced vascular and perivascular remodelling varies significantly among species, ranging from minimal perivascular changes in mice to marked changes in neonatal calves (*upper figur*e: schematic representation of perivascular remodelling and inflammation). Note the strong correlation between remodelling and inflammation. *αSMA and* α-*SM-actin* α-smooth muscle actin, *S-D strain* Sprague-Dawley rat strain, *WKY strain* Wistar-Kyoto rat strain, *expr.* expression, *PB-MNC* peripheral blood mononuclear cell (Reprinted from Stenmark et al. [56]. With permission from the American Physiological Society)

VEGF expression were greater in the Hilltop rats as compared to the Madison rats. With transgenic mice it could be possible to induce a larger RV effect of hypoxia as compared to wild type mice but mainly through alteration of pulmonary vasculature [52, 53].

Thanks to RV pressure-volume measurements obtained in mice during hypoxia, some authors recently reported that hypoxic exposure induced RV hypertrophy, ventricular-vascular decoupling, and a mild decrease in RV contractile reserve assessed by dobutamine stimulation [54].

In conscious dogs, Setty et al. [55] have studied the effect of hypoxia on coronary circulation and observed a restriction of the right coronary flow during hypoxia, which was probably restrained by an adrenergic-mediated increase in right coronary vasomotor tone.

However, as for humans it remains difficult to isolate the direct effect of hypoxia on RV from the indirect effect through HAPH (Fig. 9.4) [56].

Interestingly, Fischer 344 rats were also relatively resistant to hypoxia-induced RV hypertrophy compared to the Wistar-Kyoto rats due to different genetic profile and independently of PAP [57]. More recently, Baandrup et al. [58] showed that the expression in the RV of the same 172 genes participating in fatty acid oxidation and the glycerol channel was altered in the chronic hypoxia or rats with banding of the pulmonary trunk (PTB). Only 11 genes (e.g. insulin-like growth factor binding protein) were upregulated

in the PTB rats and downregulated in the hypoxic rats, and 3 genes (e.g. c-kit tyrosine kinase) were downregulated in the PTB and upregulated in the hypoxic rats. These results associated to a strong positive correlation between the log ratios of gene expression in the hypoxic and the PTB rats ($R^2=0.69$, $P<0.05$, $n=288$) suggest a major role of the pressure load of the RV on hypoxic RV adaptations (83 % of the variance). However, some genes change in opposite directions during hypoxic/PTB challenge, suggesting that hypoxia alone has also an impact and can directly affect gene expression in the RV.

In mice exposed to 10 % O_2 from 1 to 4 weeks, Larsen et al. [59] used Doppler echocardiography and cardiac catheterization to characterize a mouse model of alveolar hypoxia and reported RV hypertrophy, RV dilatation, and RV and LV diastolic dysfunction. Reduced Ser16 phosphorylation of phospholamban in both the RV and LV was suggested being a possible mechanism for the diastolic dysfunction observed in both ventricles. The hypophosphorylation of phospholamban and increased expression of sodium-calcium exchanger occur both in the pressure-overloaded RV and the normally loaded LV free wall, suggesting that other mechanisms than mechanical load might alter the levels of proteins governing removal of cytosolic Ca^{2+} and thereby be involved in the development of cardiac dysfunction due to alveolar hypoxia.

Brisket Disease

Brisket disease is an economically costly disease of cattle raised at elevations greater than 1,500 m. It is a naturally occurring animal model of hypoxic pulmonary hypertension. It appears that no one breed is resistant to the effects of high-altitude hypoxia. Some breeds, and pedigrees within breeds, appear to be more naturally resistant to the effects of high altitude. Multiple factors contribute to the variance in pulmonary arterial pressure in cattle, including breed, gender, body condition, concurrent illness, environmental conditions, elevation, and genetics [60].

Genetically susceptible cattle develop severe pulmonary hypertension and right heart failure at altitudes >7,000 ft (2,134 m) causing the development of fluid in the Brisket. No information currently exists regarding the identity of the pathways and gene(s) responsible for HAPH or influencing severity. Forty-six genes were overexpressed in the affected and 14 genes were downregulated in the affected cattle by at least 20 %. GSEA and Ingenuity analysis identified respiratory diseases, inflammatory diseases and pathways as the top diseases and disorders, cell development and cell signalling as the top cellular functions, and IL6, TREM, PPAR, NFkB cell signalling as the top canonical pathways associated with this gene signature. Therefore, differences in RNA expression may exist in HAPH at a molecular level, and four functional gene candidates were eliminated. Further studies are needed to determine the role of transcribed genes in the development of HAPH [61].

A syndrome of progressive right-sided heart failure also occurred among yearling Holsteins at a heifer-raising facility and 2 dairies on the Colorado Front Range between 2007 and 2011. The disease resulted in the death or premature sale of 55 animals over the 5-year period. Affected heifers developed dyspnea, tachycardia, distension and pulsation of jugular veins, lethargy, and weight loss. Ten cattle with typical clinical signs were examined post-mortem. Seven developed clinical signs after transportation 57–238 days earlier from low altitude. At necropsy, they had marked hypertrophy of RV myocardium, dilated right atria, right ventricles, and pulmonary trunks, as well as hepatomegaly, ascites, and serous atrophy of fat. Hepatic changes were typical of chronic passive congestion. Ultrastructural changes in heart were consistent with uncomplicated hypertrophy of cardiocytes with no evidence of primary cardiomyopathy. The syndrome most likely represents brisket disease due to pulmonary hypertension at the modest elevation of 1,600 m [62].

Animals Genetically Adapted to HA

Animals well adapted to life at high altitude do not show pulmonary hypertension or RV hypertrophy, such as Tibetan Antelope [63].

The blue-sheep, pika, and yak live in the Tibetan highlands at an altitude up to 6,100 m and are typical mammals adapted to high-altitudes. To evaluate the physiological characteristics of high-altitude adaptation in the blue-sheep, changes in the pulmonary hemodynamics during exposure to simulated-altitudes at 0, 2,300, and 4,500 m were examined by means of a climatic chamber in Qinghai Province, China (altitude 2,300 m). Seven blue-sheep inhabiting the mountains (3,000 m) of Qinghai Province, China, were compared with five pigs raised in the same area as controls. Ht, an index of right ventricular hypertrophy (RVW/LVW), and oxygen consumption (VO_2) were significantly lower in the blue sheep compared with the pigs. When the animals were exposed to simulated-altitudes at 0, 2,300, and 4,500 m, Ppa increased significantly in tandem with altitude elevation in both species, but the increases were significantly smaller in the blue-sheep. Ppa/Psa, an index of the right ventricular load, increased with the altitude in both species, but the increases were smaller in the blue sheep [64].

Conclusion

The main question that arises from studies looking at RV in hypoxic conditions of high altitude can be summarized as: is the RV really hypoxic at high altitude or is its (dys)function dependent only on changes in pulmonary circulation? It seems reasonable to say, from both animal and human studies, that moderate or transient hypoxia result in adaptive changes in RV that are reversible with re-exposure to normoxic conditions and RV dysfunction is mainly due to mechanical overload from the pulmonary circulation. When hypoxia is more severe or more prolonged, it may directly impact ventricular diastolic or systolic function through mechanisms that remain to be unravelled. The adrenergic system may be involved, as well as HIF, PKC or phospholamban. More studies should be encouraged to use recent Doppler techniques for a better understanding of RV systolic and diastolic function in humans exposed to altitude hypoxia including acute, chronic or chronic intermittent hypoxia.

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The Right Ventricle in Congenital Heart Diseases

10

Beatrijs Bartelds and Rolf M.F. Berger

Abstract

Right ventricular function is an important determinant of prognosis and outcome in congenital heart diseases. Right ventricular (RV) adaptation to congenital heart diseases (CHD) has many faces as there is a wide variety in defects involving the right ventricle as well as in treatment strategies. This variety induces differences in loading conditions and also changes over time as a result of surgical interventions. Also, treatment practice has evolved changing the nature and outcome of survivors of CHD. Lastly, several lesions also affect the left ventricle (LV) that may interact with RV function and thereby change the RV function.

Although in practice sometimes artificially, for educational and conceptual purposes the effects on the RV can be divided into three types of abnormal loading conditions, i.e. increased preload (e.g. shunts or valvular insufficiency), increased afterload (e.g. stenosis or connection to systemic circulation), or a mixture of both. During the process of maturation and ageing and as a result of interventions loading conditions can shift from increased afterload to increased preload. In this chapter we will describe the different faces of the RV with a focus on the functional capacity. We will differentiate between lesions affecting preload, afterload and a mixture of those. Special attention is given to the RV in corrected tetralogy of Fallot and the systemic RV in congenitally corrected transposition of the great arteries or after the atrial switch procedure for transposition of the great arteries.

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Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
ASD	Atrial septal defect
ccTGA	Congenitally corrected transposition of the great arteries
CHD	Congenital heart diseases
CMR	Cardiac magnetic resonance imaging
EF	Ejection fraction
FAC	Fractional area change
LV	Left ventricle
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
RV	Right ventricle
RVOT	Right ventricular outflow tract
TAPSE	Tricuspid annular plane systolic excursion
TGA-as	Transposition of the great arteries with atrial switch procedure
TOF	Tetralogy of fallot
TI	Tricuspid insufficiency
VSD	Ventricular septal defect

Introduction

Right ventricular function is an important determinant of prognosis and outcome in congenital heart diseases [1]. Right ventricular adaptation to congenital heart diseases (CHD) has many faces as there is a wide variety in defects involving the right ventricle as well as in treatment strategies. This variety induces differences in loading conditions and also changes over time as a result of surgical interventions. Also, treatment practice has evolved changing the nature and outcome of survivors of CHD. Lastly, several lesions also affect the left ventricle (LV) that may interact with RV function and thereby change the RV function.

Although in practice sometimes artificially, for educational and conceptual purposes the effects on the RV can be divided into three types of abnormal loading conditions, i.e. increased preload (e.g. shunts or valvular insufficiency), increased afterload (e.g. stenosis or connection to systemic circulation), or a mixture of both. During the process of maturation and ageing and as a result of interventions loading conditions can shift from increased afterload to increased preload (Table 10.1). A detailed description of cardiac morphology in CHD has been described in the several textbooks of CHD [2, 3]. In this chapter we will describe the different faces of the RV with a focus on the functional capacity. We will differentiate between lesions affecting preload, afterload and a mixture of those.

Lesions Affecting Preload

Lesions leading to an isolated volume load of the RV can be divided into two major groups, lesions with a pre-tricuspid shunt (i.e. atrial septal defect (ASD)), or lesions with valvular insufficiency (e.g. tricuspid insufficiency, pulmonary insuffi-

Table 10.1 Overview of lesions affecting the right ventricle in congenital heart diseases

Increased preload		Mixed		Increased afterload
Atrial septal defect (ASD)	→	ASD + PS	←	Pulmonary stenosis (PS)
	↘	ASD + Pulmonary Hypertension	←	Pulmonary Hypertension
Pulmonary Insufficiency (PI)		PI and PS after correction of TOF	←	Tetralogy of Fallot (TOF)
Tricuspid Insufficiency (TI)		ccTGA + TI	←	Congenitally corrected transposition of the great arteries (ccTGA)
		TGA-as + TI	←	Transposition of the great arteries after atrial switch procedure (TGA-as)
		HLHS + BT shunt HLHS + TI	←	Hypoplastic left heart syndrome (HLHS)

ciency, Table 10.1). Pulmonary insufficiency as a result of treatment in patients with repaired tetralogy of Fallot will be discussed separately. The major difference between the two groups is the increased pulmonary blood flow in shunt-lesions, which may induce increased pulmonary vascular resistance leading to pulmonary hypertension, thus inducing a shift from increased preload to increased afterload.

Atrial Septal Defect

Atrial septal defect (ASD) is a quite common lesion in CHD, with a female dominance [4]. There are several morphological variants depending upon the position of the ASD (Fig. 10.1a). The most common form is ASD II, rare variants are sinus venosus defects. The latter differ in that they are frequently associated with a partially abnormal pulmonary venous return leading to an obligatory left-to-right shunt at the atrial level. Furthermore, sinus venosus defects induce a higher risk for the development of PAH than other types of atrial shunts.

Without association of other defects, an ASD will lead to a left-to-right shunt at atrial level, inducing an increased preload of the RV (Fig. 10.1b). The degree of shunting depends on

(i) the size of the defect,
(ii) presence of partially abnormal pulmonary venous return,
(iii) the orifice of the tricuspid- and the mitral valve,
(iv) the difference in compliance between the receiving right- and left ventricles, and
(v) pulmonary hypertension or pulmonary stenosis affecting the RV compliance.

Prenatally, the right- and left ventricle together take care of the systemic circulation. A right-to-left flow across the foramen ovale is a natural phenomenon, allowing the passage of higher saturated blood into the left ventricle [5]. Also, pulmonary vascular resistance (PVR) is very high and this decreases rapidly at birth. Consequently, pulmonary blood flow increases, thereby increasing pulmonary venous return. These changes will cause the flap of the foramen to be pressed against the atrial septum and lead to closure of the foramen. In patients with an ASD, a left-to-right shunt will develop, the degree of which is dependent upon the decrease of pulmonary vascular resistance. Usually, no significant shunt develops in the first weeks, although in association of lesions affecting the inflow of the LV, such as a congenital malformation of the mitral valve or hypoplastic left heart, the shunt across the ASD may increase more rapidly. Alternatively, underdevelopment of the tricuspid valve will induce a right-to-left shunt across an ASD. Similarly, a restrictive RV in patients with corrected Fallot's tetralogy can lead to a right-to-left shunt, whereas diastolic failure of the LV, often observed in elder patients, may increase pre-existing left-to-right shunt.

Since a volume load of the RV is usually well tolerated in childhood, children with an isolated ASD rarely present with symptoms. However, in association with other cardiac or pulmonary conditions, or in case of a very large ASD, clinical symptoms of left-to-right shunt may occur already early in life. In adult patients, in whom left ventricular diastolic properties change, e.g. in developing heart failure with preserved ejection fraction (EF) due to ischemic heart disease, the left-to-right shunt across the defect will increase. Indeed LV diastolic function should be assessed in every adult patient presenting with an ASD.

When left untreated, 10–20 % of the patients with an ASD will develop pulmonary hypertension (PH). Patients with ASD-PH have less left-to-right shunt due to decreased right ventricular compliance, depending on the degree of PH, which increases the afterload of the RV. Adult patients with Eisenmenger syndrome have been reported to fare better than patients with other types of PAH, however these results may be due to a survival bias, as the survival in children with PAH-CHD is not better. Indeed, studies in animal models with a mixture of preload and afterload showed further deterioration of RV function as compared with isolated afterload only [6].

The RV adaptation to volume load in ASD is dilatation, which leads to increased strain and strain rates especially in the apical segments [7–9]. Also longitudinal motion is increased. Interestingly, in animal models of increased preload, no changes in

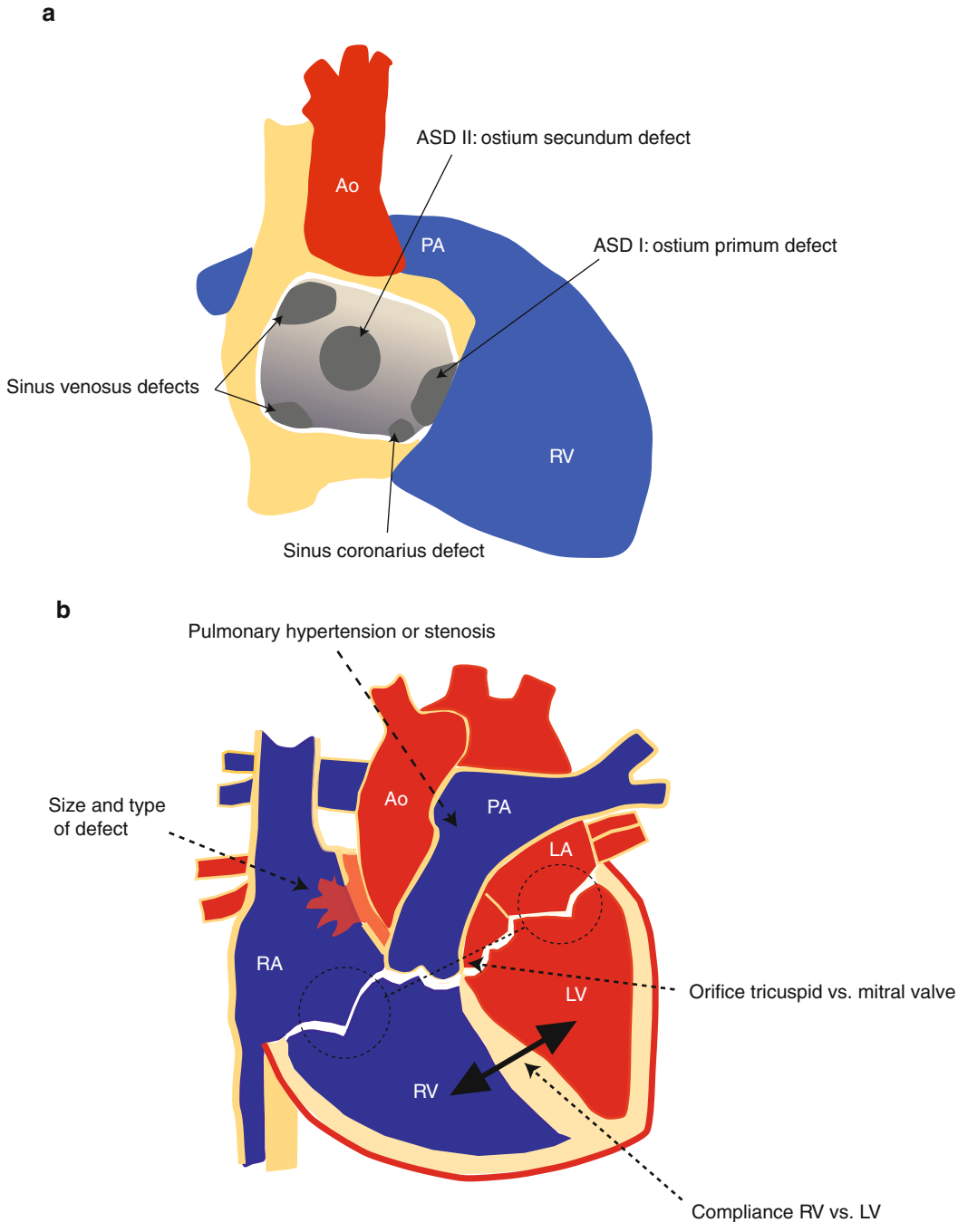

Fig. 10.1 (**a**) Different locations of atrial septal defects. (**b**) Factors influencing degree of shunting in atrial septal defect. *Ao* Aorta, *PA* pulmonary artery, *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

elastance, hence contractility was noted, suggesting that only Frank-Starling mechanisms are responsible for the increased RV output [6]. After closure of the defects, strain and strain rates decrease [7], maybe to even lower than normal values [8]. In a long term follow up study of patients with repaired ASD's, mild RV dysfunction was found in 25 % of patients with secundum ASD and 50 % of patients

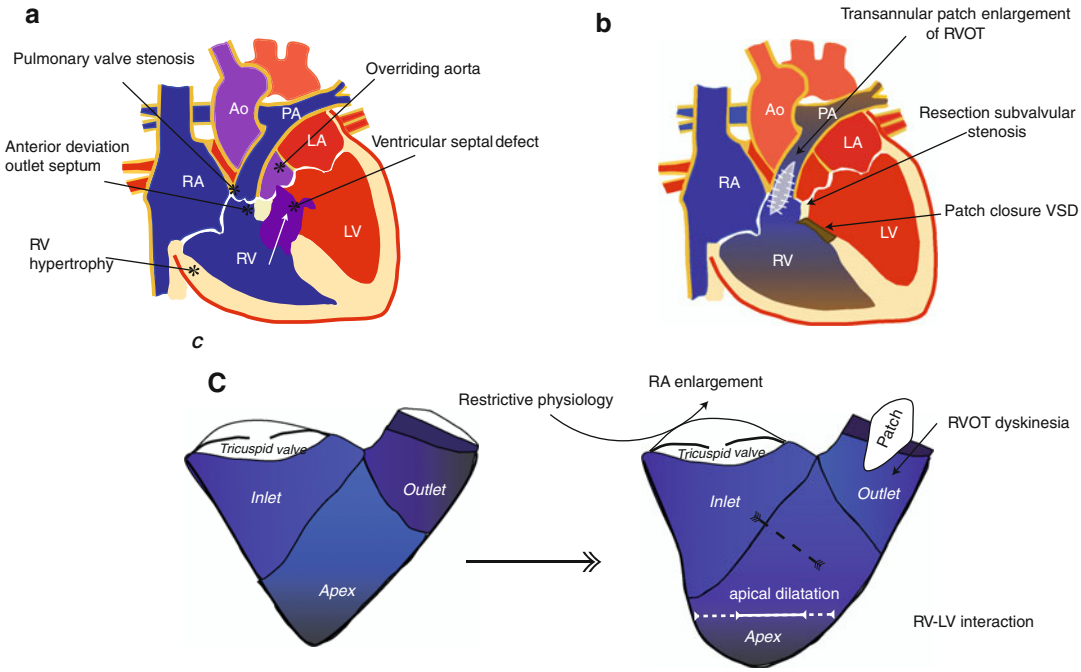

Fig. 10.2 (**a**) Characteristics of the tetralogy of Fallot. (**b**) Schematic representation of correction surgery leading to PI due to patch enlargement of the RV outflow tract. (**c**) Features of RV dysfunction in patients with corrected Fallot. *Ao* Aorta, *PA* pulmonary artery, *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

with sinus venosus ASD [10]. Also tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC) were decreased in 22 and 10 % of the patients. These data indicate long-term effects of increased preload on the RV despite normalization of the loading conditions.

In summary, increased preload of the RV due to a shunt or valvular insufficiency induces RV dilatation that is usually well-tolerated for a long time. Increased pulmonary blood flow in cardiac shunts may change the phenotype to increased afterload. RV dilatation is associated with increased apical deformation during volume loading which decreases after unloading. RV function remains mildly impaired even years after closure of the defect.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is one of the most common forms of cyanotic CHD, accounting for 3.5 % of infants born with CHD. TOF has first been described by Niels Stenson in 1661, but was recognized as it's tetrad by Etienne-Louis Fallot in 1888 [11]. The tetrad consists of a pulmonary stenosis, ventricular septal defect, overriding of the aorta over the ventricular septal defect and due to the increased afterload of the RV, RV hypertrophy (Fig. 10.2a). Although this description is straightforward, it should be recognized that the degree of pulmonary stenosis and subsequent development of the pulmonary artery varies widely, leading to a continuum of this disease with pulmonary atresia with VSD. The tetrad is a result of an anterior deviation of the outlet septum leading almost always to a combination of subvalvular muscular obstruction as well as underdeveloped pulmonary valve area. The morphological aspect of the RV outflow tract is being recognized increasingly as an important determinant of residual lesions after surgical correction. TOF may be associated with peripheral pulmonary stenosis of the PA branches.

Historical Perspective

The majority of the current age survivors were treated at later age as open heart surgery was

only available since the 50s. Since then, with the improvement of perioperative cardiopulmonary bypass techniques and intensive care treatment, survival in the newborn period has increased to 98 %. Also, the timing of surgery has shifted from 2 to 5 years of age in the 80s, to 3–9 months of age at present. With the growing numbers of adult survivors of TOF it became obvious that residual lesions with clinical relevance were associated predominantly with the right ventricular outflow tract (RVOT) reconstruction. The adult population should be divided according to the treatment era and age of surgical correction. The residual lesions and long-term follow up are characterized by:

(i) Pulmonary incompetence
(ii) RVOT dyskinesia
(iii) Restrictive RV
(iv) RV/LV interaction
(v) Arrhythmias and risk of sudden death

Pulmonary Incompetence

Pulmonary regurgitation is a result of the need for relief of outflow tract obstruction caused by the subvalvular muscular obstruction, the stenosed pulmonary valve, and the supravalvular stenosis. To relief these obstructions a so-called transannular patch is used which immediately results in incompetence of the pulmonary valve. (Fig. 10.2b). At first, the residual pulmonary regurgitation was thought to be innocent but long term survival has shown that pulmonary regurgitation is not a benign lesion [12].

The response of the RV to the additional volume load is RV dilatation, which in itself is an adaptation rather than a sign of failure (Table 10.2). RV dilatation is usually associated with increased trabeculation, which may complicate reliable determination of RV volumes with CMR. Therefore, recently quantifications using a semi-automatic threshold-based algorithm excluding the trabeculae have been developed. These algorithms are quick and reliable in tracing RV volumes in corrected Fallot patients [13–15]. RV dilatation is invariably associated with worse outcome [16], reduced exercise performance [17–19], and arrhythmias [16]. Pulmonary regurgitation reduces power efficiency of the RV. The RV power loss increases with increasing RV end diastolic volume [20].

Surprisingly, strategies to prevent RV dilatation using either volume reducing surgery [21] or valve replacement have provided disappointing results in improving outcome [22]. Also, treatment with angiotensin converting enzyme-antagonists did not change RV dilatation or outcome [23]. Timing of volume-reduction is thought to be an important factor in the potential to normalize RV-function or outcome [22].

Table 10.2 CMR-derived RV volumes in patients with corrected tetralogy of Fallot

Author	N	Age at study	Age at surgery	RV EDVi	RV ESVi	RV SVi	RVEF (%)
Roest et al. [19]	15	17 ± 3	2 ± 2	132 ± 36	62 ± 26	69 ± 16	54 ± 9
van den Berg et al. [41]	36	17 (7–23)	0.9 ± 0.5	138 ± 40	64 (36–145)	66 ± 15	49 ± 7
Fernandes et al. [29]	33	12 ± 3	17 ± 16	157 ± 39	–	–	49 ± 9
Frigiola et al. [96]	60	22 ± 11	3 ± 5	142 ± 43	73 ± 33	40 ± 10	51 ± 10
Knauth et al. [97]	88	24 (10–57)	3 (0–30)	z-score 3.9 (3.2)	66 ± 33	–	48 ± 12
Babu- Narayan et al. [23]	32	29 ± 9	5 ± 6	123 ± 30	58 ± 21	65 ± 16	53 ± 9
Bonello et al. [35]	154	31 (22–40)	4.5 (2–8)	127 (102–148)	58 (45–75)	66 (55–76)	53 (47–58)
Greutmann et al. [98]	101	33 ± 12	5 (0.5–36)	158 ± 51	–	–	41 ± 8
Davlouros et al. [32]	85	33 ± 15	9 (0.5–50)	116 ± 33	56 ± 24	60 ± 18	52 ± 9
Kempney et al. [99]	21	36 (29–46)	7 (4–8)	140 ± 36	77 ± 26	42 ± 9	45 ± 10

Data are mean ± standard deviation or median and (range). Age is in years. Volumes are in ml/m^2
EDV end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *EF* ejection fraction

Alternatively, volume loading per se may not be the only aspect of the RV dysfunction in corrected Fallot. Other factors affecting RV dysfunction are: RV deformation, dyssynchrony or chronotropic incompetence, restrictive physiology and RV-LV interaction [24, 25] (Fig. 10.2c).

RV Motion: A Gradient from Base to Apex

The wall motion of the RV can be described by echocardiography using longitudinal displacement and transversal displacement. Longitudinal displacement is reduced [26] already in childhood. Global longitudinal strain is also reduced and reduces further despite stable ejection fraction (EF) suggesting this may be a marker for timing of interventions [27]. Apart from a global decrease in longitudinal motion, there is also a gradient in transversal motion from base to apex. The RV can be divided into segments ranging from base to apex. Regional deformation imaging has shown reduced strain rates in all segments, in patients with Fallot as compared with controls or with e.g. ASD [28–30]. However, in patients with Fallot, strain rates in the apex are more affected than those at base [31]. The apex of the RV contributes to more than half of the stroke volume and possibly failure of the apical region may contribute to RV failure.

RVOT Akinesia and Dyskinesia

Due to the extensive surgery the motion of the RVOT may be disturbed, leading to either RV akinesia or RV dyskinesia. RVOT akinesia is defined as the lack of thickening during systole, whereas dyskinesia ("aneurysm") is defined as an outward movement of the RVOT during systole. In a study of patients with "late repairs" (age of repair median 9 year), Davlouros et al. showed that RV akinesia/dyskinesia was present in ~55 % of the patients and was an independent predictor for increased RV end-diastolic volume apart from pulmonary regurgitation [32]. RVOT dyskinesia may hamper proper interpretation of RV function [33]. The reduced performance of the RVOT may be the result of the reduced RV EF measured in many Fallot patients [34]. RV EF however, is a poor prognosticator as it is the ratio of RV end-diastolic volume and stroke volume, hence even when SV is maintained or enhanced EF may be lower. RVOT dyskinesia does not only hamper interpretation and volumetric assessment but also predicts risk for ventricular arrhythmias [35], maybe due to scar tissue from surgery.

Dyssynchrony

RV dyssynchrony is almost always present after TOF correction due to the right bundle branch block related to VSD closure. The QRS duration prolongation caused by this block as well as residual volume loading has been shown to be an independent risk factor for the development of arrhythmias [36], although it should be noted that these patients were corrected at older age (mean 5 years). It is unknown if these relations will hold in the cohort of patients corrected <1 year of age.

The QRS prolongation induces *inter*ventricular RV dyssynchrony although this effect may be limited. TOF is also invariably associated with *intra*ventricular dyssynchrony, of which as yet no uniform definition is given. However, so far studies looking a the contribution of *intra*ventricular dyssynchrony to RV dysfunction have yielded conflicting results [37–39]. Hence, although dyssynchrony is described in corrected Fallot's, it's relation with RV adaptation and failure is yet unclear.

Restrictive RV Physiology

One of the hallmarks of the RV in patients after correction of TOF is the so-called restrictive physiology, first described by Gatzoulis [40]. A restrictive RV is defined as antegrade flow in the pulmonary artery during diastole throughout the cardiac cycle. In the first description it was associated with less RV dilatation and improved exercise performance, although this view has been corrected by later research. Recently, long-term follow up from the same group did not show an advantage of restrictive RV on prevention of

RV dilatation or exercise performance. Indeed, using dobutamine-stress it has been shown that a restrictive RV leads to worsening of RV filling during cardiac stress [41]. The mechanisms of the diastolic dysfunction are unknown. It is suggested to be related to cardiac fibrosis, which is increased in patients with TOF [42]. Alternatively, it may be related to RV dilatation itself as dilated chambers operate at a steeper part of the pressure-volume relation leading to increased stiffness [43]. Restrictive RV physiology has recently also been associated with worse LV function, another component of patients with TOF [44]. It is speculated that it may interfere with LV filling, but further studies are necessary to elucidate the mechanisms of the restrictive RV.

LV Function and Arrhythmias

LV dysfunction is an integral part of patients with TOF. It has been associated with more RV dilatation and possibly interference of LV filling. Also, so far the LV is the only ventricle that has been amenable to medical therapy, as ACE inhibitors only mildly improved LV movement [23]. LV dysfunction may also be a predictor of adverse outcome, albeit a late one [29, 45, 46]. Similarly, the outcome of TOF is greatly determined by the occurrence of late arrhythmias [16, 47], which has also been attributed to RV dilatation and fibrosis [42].

In summary, Tetralogy of Fallot before correction imposes an increased afterload on the RV, but the majority of problems of RV dysfunction arise years after correction and are mainly associated with additional volume loading to the pulmonary regurgitation. Specific features adding to RV dysfunction in this lesion are RVOT dyskinesia, reduced apical deformation, dyssynchrony, and restrictive physiology.

The Systemic RV

In specific congenital heart diseases, the RV supports the systemic circulation rather than the low-resistance pulmonary circulation, phrased as a systemic RV. As the systemic circulation has a higher resistance, the RV has to increase it's power in order to maintain cardiac output. Congenital heart defects associated with a systemic RV can be distinguished into two major phenotypes, i.e. the systemic RV in a biventricular circulation vs. the systemic RV in a univentricular circulation.

A systemic RV in a *biventricular* circulation either occurs naturally in the congenitally corrected transposition of the great arteries (ccTGA), or is a result of treatment in patients with a transposition of the great arteries after the atrial switch procedure (TGA-as) (Fig. 10.3a, b). Before the 90s, palliation in TGA was achieved by rerouting the venous circulations using the procedure described by Senning or that by Mustard [3], leaving the RV coupled to the systemic circulation. In the 90s, the *atrial* switch operation has been replaced by the *arterial* switch operation, which switches the pulmonary artery back to the RV and the aorta to the LV. The arterial switch operation creates a more physiological solution, as the LV is now again coupled to the systemic artery. However, at present there are still many adult survivors of the atrial switch procedure with a systemic RV.

A systemic RV in a *univentricular* circulation occurs in the growing group of survivors with a hypoplastic left heart syndrome, or other univentricular malformations with a dominant RV.

The Systemic RV in a Biventricular Circulation; ccTGA and TGA-Senning/Mustard

ccTGA is frequently complicated by associated lesions, which profoundly affect clinical course. The most prevalent are pulmonary stenosis and/or a ventricular septal defect. Whereas a pulmonary stenosis (which in this situation forms an increased afterload for the LV) is generally well tolerated by the LV, a VSD leads to a volume load of the subaortic ventricle, which is the RV, and may cause signs and symptoms of congestive heart disease. Also, patients with ccTGA are prone to develop

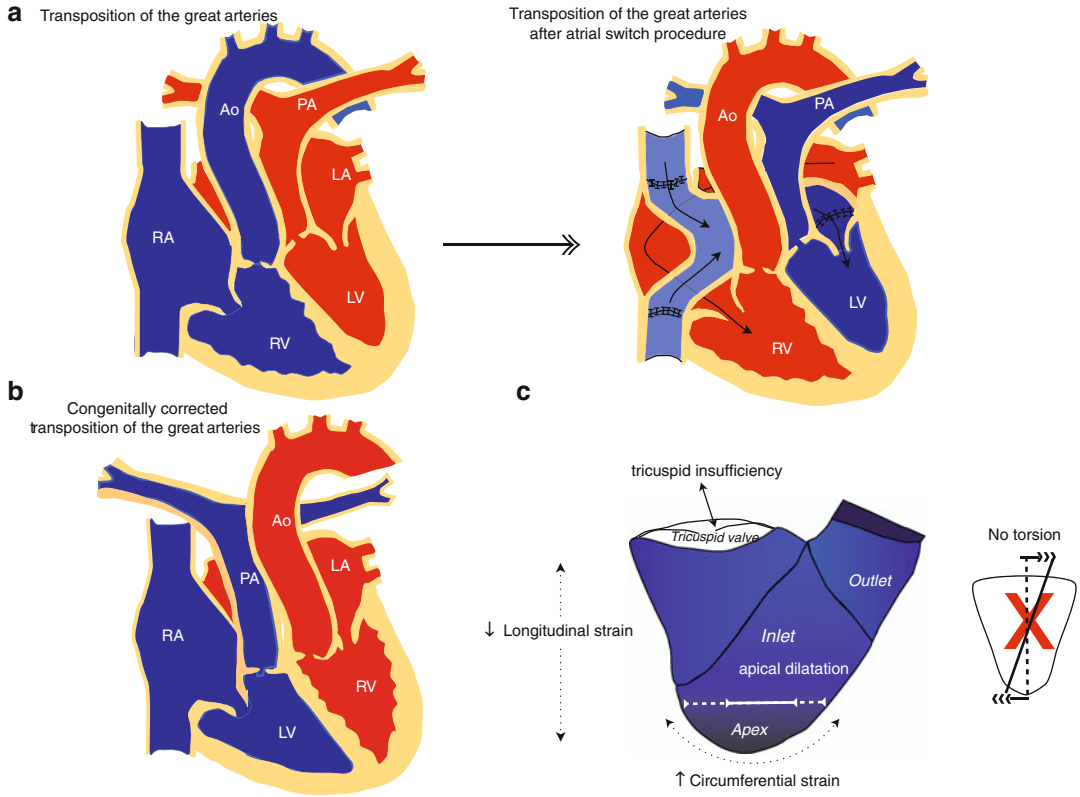

Fig. 10.3 (**a**) Transposition of the great arteries with subsequent atrial switch procedure leading to a systemic RV. (**b**) Congenitally corrected transposition of the great arteries. (**c**) Features of RV dysfunction in patients with a systemic RV. *Ao* Aorta, *PA* pulmonary artery, *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

AV-block, due to the anterior deviation of the atrio-ventricular node [2]. Atrio-ventricular block is prevalent without surgery and is a common complication of surgical procedures in patients with ccTGA [48, 49].

The natural history of ccTGA is characterized by a relatively long period of RV adaptation to the increased afterload which is present from birth, but eventually RV dysfunction appears in all patients [48]. However, RV dysfunction occurs earlier in patients with associated lesions. In the largest cohort series described so far, at the age of 45 years 67 % of the patients with complex ccTGA vs. 25 % of the patients with simple ccTGA had signs of RV dysfunction [48]. In other cohorts, primarily determined by surgical patients, the overall picture is similar [49]. It is yet unknown why patients with associated lesions have a worse prognosis but suggestions are: chronotropic incompetence due to damage of AV node and myocardial damage during cardiac surgery. It should be noted though that patients with a systemic RV, hence an RV that has not been unloaded after birth, generally tolerate this pressure load quite long, while patients with idiopathic pulmonary hypertension, hence an acquired loading condition, develop RV failure in a much shorter time interval.

TGA and Atrial Switch

The natural history of TGA after atrial switch procedure (TGA-as) either via a Mustard or a Senning operation, is like that of the ccTGA determined by RV dysfunction, albeit that it usually arises earlier than in ccTGA [50]. Long term follow up studies show that after 25 years

61 % of the patients had RV dysfunction shown by echocardiography [51]. Outcome may improve with improved surgical protection of the myocardium as a more recent study found RV EF >40 % was found in 98 % of survivors with simple TGA-as. However, in complex TGA-as, RV EF >40 % was found in only 58 % of the survivors. Complicating factors are loss of sinus rhythm in >60 % of the patients and the development of supraventricular arrhythmias [49, 52].

In ccTGA and TGA-as alike, RV dysfunction is a final common pathway of the RV coupled to the systemic circulation. Factors associated with RV dysfunction are:

(i) Tricuspid insufficiency,
(ii) RV dyssynchrony,
(iii) Response to exercise.

RV Dysfunction in Systemic RV

Evaluation of RV failure is via clinical assessment of signs and symptoms. In adults with ischemic heart disease, the NYHA classification of heart failure has been invaluable in analyzing and stratifying patients at risk. However, in adults with CHD there is dissociation between complaints and functional values measured with CMR or exercise testing [53]. In adults with CHD, 15 % of the patients in NYHA class I fulfill HF criteria defined as increased NT-proBNP and peak exercise capacity <25 ml/kg/min [53].

Apart from perceived status of heart failure, RV function can be serially assessed by echocardiography and CMR. CMR is regarded the gold standard for evaluation of RV function in patients with CHD [54], as it is best suited to quantify RV volume. As in patients with Fallot, exclusion of trabeculae yields the most reliable and reproducible RV volumes [55]. Care should be taken when comparing volumes between studies since scanning tools and protocols differ between centers.

A wide range of RV volumes and EF is reported when studying patients with systemic RVs (Table 10.3). The question is whether RV dilatation is an adaptive strategy, as is frequently described in animal models of increased pressure load [6, 9] or a sign of decompensation? At present there is no answer to that question, but in general severe RV dilatation is regarded as a sign of failure. Indeed, recently an RV end-diastolic volume of >150 ml/m^2 has been suggested to be a predictor for adverse events in a follow up study of patients with both ccTGA and TGA-as [56]. The use of RV EF as predictor may be less accurate as it is influenced by tricuspid insufficiency and tricuspid insufficiency is invariable present in patients with systemic RVs [48].

Apart from CMR, 2D echocardiography of RV dimensions and wall motion has been used, reviewed in [27]. However, traditional measurements of RV motion, as TAPSE and FAC, correlate poorly with RV function in systemic RV as assessed by CMR [57].

Valuable insight in mechanisms of RV adaptation to increased afterload comes from studies combining both tissue Doppler imaging measurements by echocardiography with 3D volume measurements by CMR [58]. The contraction

Table 10.3 RV volumes in systemic RVs

Author	N	Cohort	Age at study	RV EDVi	RV ESVi	RV SVi	RV EF (%)
van der Bom et al. [56]	88	All	33 ± 10	133 ± 35	86 ± 31	–	36 ± 7
Fratz et al. [68]	11	ccTGA	37 (6–59)	91 (60–208)	51 (14–96)	41 (28–59)	44 (20–75)
Grothoff et al. [50]	19	ccTGA	35 (19–49)	99 (65–134)	51 (37–56)	47 (36–65)	47 (43–55)
Fratz et al. [68]	12	TGA-as	20 (15–28)	98 (59–198)	54 (21–159)	45 (34–58)	47 (24–78)
Grothoff et al. [50]	31	TGA-as	22 (18–27)	95 (79–118)	49 (45–76)	36 (31–45)	41 (31–49)
Roest et al. [54]	27	TGA-as	26 ± 5	155 ± 55	70 ± 34	85 ± 26	56 ± 7
Pettersen et al. [58]	14	TGA-as	18 ± 1	119 ± 39	63 ± 26	–	47 ± 8

Data are mean ± standard deviation or median and (range). Age is in years. Volumes are in ml/m^2
EDV end-diastolic volume, *ESV* end-systolic volume, *SV* stroke volume, *EF* ejection fraction

pattern in a normal RV shows a peristaltic wave beginning in the inflow region and moving toward the infundibulum [59, 60]. There are two major movements in a normal RV, an inward movement of the RV free wall, leading to a bellows effect, and a longitudinal movement from apex to base [61]. In the normal RV the longitudinal movement and strain exceeds that of the circumferential fibers. In the systemic RV, this pattern is reversed, i.e. circumferential strain exceeds longitudinal strain, resembling normal LV movements (Fig. 10.3c). However, both strain and strain rates were lower than in the LV. The reversal of strain patterns in the systemic RV vs. the normal RV has been confirmed by several echocardiographic studies [62]. Recently, a decrease in global RV strain by 10 % has been shown to predict adverse events in adults with TGA-as [63].

Also, in contrast with the LV, the systemic RV does not develop torsion. Torsion, the angle between the rotation at the base vs. apex contributes to LV emptying by producing a wringing motion as well as to LV filling during elastic recoil. The functional significance of these findings is not yet completely understood, since these observations were made in a population with relatively normal CMR measurements [58]. It is unclear whether these adaptation patterns are due to chronic abnormal loading or to myocardial perfusion defects. In the normal RV myocardial perfusion via the right coronary artery occurs both during systole and diastole. However, in the systemic RV, myocardial perfusion is substantially changed which may affect function or induce fibrosis or scarring. Perfusion defects have been shown by several studies [64, 65] Also, coronary flow reserve was reduced [66, 67]. The increased perfusion defects were associated with worse RV function [65], although these results are debated in recent years [68].

It has been postulated that impaired perfusion together with increased demand may lead to ischemic events and subsequently scar forming and/or cardiac fibrosis. Cardiac fibrosis has been extensively shown in patients with systemic RVs [42, 69], and is related with decreasing RV function. Fibrosis may also be the results of increased RV wall stress [65]. Whether these factors are amenable for therapeutic strategies remains to be determined.

Tricuspid Insufficiency

Tricuspid insufficiency (TI) is almost invariable present in late survivors with a systemic RV. The question is whether TI is either *a result of* RV dysfunction, due to annular dilatation, or *the cause for* RV dysfunction, leading to an additional volume load in an already pressure loaded RV [6]. TI is influenced by the morphology of the valve, the annular dilatation and the septal movement. In a systemic RV, where the septum bulges to the LV, the TI may increase. Indeed, patients with a subpulmonary stenosis have less TI. In ccTGA, the tricuspid valve is often dysplastic and in this setting TI precedes the development of RV dysfunction [70]. In TGA-as the relation between TI and RV dysfunction is less clear. Tricuspid valve surgery does not prevent RV failure, but outcome of this surgery appears to be better when performed with good RV function [71].

Dyssynchrony

Deformation imaging has suggested that RV dysfunction is associated with RV dyssynchrony [72, 73]. Moreover, patients with dyssynchrony had more RV dilatation and reduced RVEF and exercise capacity. Increased dyssynchrony may provide treatment opportuniteis, such as resynchronization. Since dyssynchrony is an important component of RV dysfunction, cardiac resynchronization therapy has been postulated.

Response to Exercise/Stress

More information may be derived from the RV response to stress such as exercise or dobutamine stress. Exercise capacity is generally lower in patients with CHD as compared with age matched controls [25]. Likewise, in systemic RVs, though a wide range of peak VO2 is reported, the average

is about 66 % of expected normal values [74]. There may be several reasons for the impaired exercise tolerance:

(i) Impaired increase in contractility
(ii) Impaired RV filling
(iii) Chronotropic incompetence
(iv) Lung function

Several studies reported that patients with a systemic RV can increase cardiac output during exercise or dobutamine stress [54, 68, 75, 76]. The ability to increase contractility, measured by ESPVR, in the systemic RV appears to be normal. In contrast, the ventricular filling rate decreases in patients with TGA-as, whereas it increases in normal individuals [54, 75]. The reduced atrial filling rate during exercise/stress is more prominent in TGA-as than in ccTGA and is attributed to the extensive atrial surgery. During follow-up a mild baffle obstruction is frequently encountered [52], which may have profound effects on ventricular filling especially when heart rate increases.

Besides a reduced atrial filling, also chronotropic incompetence may play a role in reduced exercise capacity. Few patients with ccTGA or TGA-as are in normal sinus rhythm, there is a high rate of atrioventricular block and many patients are chronotropic incompetent. Although these issues all may add, increasing chronotropic response via advanced pacing strategies did not improve exercise capacity [77]. In contrast, in a trial study using beta blocker therapy, a lower heart rate during exercise was associated with better filling properties and improved exercise capacity [78], suggesting reverse relation between heart rate and output in systemic RVs. These observations underline the importance of abnormal filling patterns during stress in systemic RV, most prominent in TGA-as. The response to stress can be predictive for outcome in the systemic RV [56, 78]. Hence, exercise capacity is reduced and may reflect outcome though not directly related to intrinsic myocardial dysfunction.

Treatment Options

In the patient with heart failure due to ischemic heart disease, the cornerstones of treatment are angiotensin converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARB), beta blockers and diuretics. In patients with heart failure due to systemic RV failure these therapies appear to be less effective.

Small series testing ACE inhibitors did not find any effects on RV EF, exercise capacity or quality of life [79–81] (Table 10.4). The lack of

Table 10.4 Effects of medical treatment in systemic RV

	Agent	ccTGA/TGA-as	Pro/retro	N	Follow-up (months)	RVEF	VO_2 peak	NYHA
Beta blockers								
Lindenfeld	Carvedilol	ccTGA	Pro	1	7	↑	NA	NA
Giardini	Carvedilol	Both	Pro	8	12	↑	=	↑
Josephson	Various	TGA-as	Retro	8	36	NA	NA	↑
Doughan	Various	TGA-as	Retro	31	4	NA	NA	↑
ACE inhibitor								
Robinson	Enalapril	TGA-as	Pro	9	12	=[a]	=	NA
Therrien	Ramipril	TGA-as	Pro	17	12	=	=	NA
Hechter	Various	TGA-as	Retro	14	24	=	=	NA
ATII antagonist								
Dore	Losartan	Both	Pro	29	4	=[a]	=	NA
Lester	Losartan	TGA-as	Pro	7	2	↑	NA[b]	NA
Vd Bom	Valsartan	both	Pro	88	36	=	=	=

Adapted and updated from Winter et al. [100]. With permission from BMJ Publishing Group Ltd
Pro/retro prospective or retrospective study design
[a]EF determined by echocardiography instead of CMR
[b]Positive effect on exercise duration

effect was supposedly due to the relative lack of heart failure in these subject and low levels of neurohormonal activation. Two small trials of angiotensin receptor blockade showed different results [82, 83]. However, in a recent large randomized trial, comprising 88 patients with ccTGA or TGA-as no significant effect was found on RVEF, the primary endpoint, after 3 years of follow-up [84]. Neither was there an effect on peakVO2 or quality of life. The authors found a significant difference in the change of RV volumes, although RV volumes at the end of the study were not different between the groups (270 ± 77 ml in Valsartan vs. 259 ± 85 ml in placebo group). Hence there appears to be no benefit of ARB or ACE, findings that were recently also confirmed in an animal model of increased RV afterload [85].

Beta blocker therapy has not yet been evaluated in a large randomized trial. Beta blocker therapy has been shown to be successful in rats with increased afterload [86]. In a small non-randomized study in eight patients with systemic RVs, that were concomitantly treated with ACE inhibitors, Giardini et al found an increase in exercise duration and RV EF and a decrease in RV volumes [87]. Possibly, lower heart rates improved RV filling thereby accounting for the improvements. It should be noted though that all patients also received ACE, and that two patients did not tolerate the adequate dosage. One other small study also reported positive effects in prevention of RV remodeling [88]. Further studies into the efficacy of beta blockade in systemic RVs are warranted.

Pulmonary Artery Banding and Double Switch

Historically it was recognized that patients with a pulmonary stenosis in the setting of ccTGA faired better, maybe due to less TI or to better RV performance when increasing septal pressure. Hence, pulmonary artery banding has been used as a strategy to support a failing circulation. Originally with the idea that after retraining the LV, the atrial switch procedure could be combined with an arterial switch procedure (double switch) so that the LV is again connected to the systemic circulation. However, many adult patients with heart failure did not reach the double switch procedure, but were adequately supported by pulmonary artery banding. Indeed, in an animal model of increased RV afterload, additional aortic constriction also improved RV function [89]. The reason for this increase is incompletely understood, but the interaction of the ventricular septum with RV contraction appears to play a role.

The RV in Eisenmenger Syndrome

The RV in Eisenmenger syndrome poses an additional challenge and puzzle to the cardiologist. PAH quite frequently develops in CHD [90], but the term "Eisenmenger syndrome" was originally used only for PAH in patients with a non-restrictive ventricular septal defect (or other post-tricupid shunts), hence a volume load of the LV (due to the VSD) and a pressure load of the RV (due to the non-restrictive VSD). Nowadays, the Eisenmenger syndrome is also used in PAH-CHD with pre-tricuspid shunts, although that may be misleading since in these lesions the RV is originally volume loaded (due to the ASD), but as PAH progresses becomes more pressure loaded. Also, PAH develops more rapidly in post-tricuspid shunts than in pre-tricupid shunts. These differences should be taken into account when comparing PAH-CHD cohorts.

The increased afterload to the RV is generally well tolerated for many years in a subset of patients. Indeed, these survivors reaching adulthood have lead to the impression that an Eisenmenger syndrome is less severe of a loading condition than isolated pulmonary hypertension itself [91]. However, this observation is skewed by the survival bias, as in childhood 5-year survival of patients with PAH due to CHD does not differ much from iPAH [92, 93]. Other differences between PAH-CHD in pediatric versus adult cohorts are the better preserved RV function at diagnosis and less syncope at presentation [93, 94]. Again, the observation is that a RV that is not unloaded at birth (due to a congenital heart

defect) may be better able to tolerate pressure and/or volume load than an unloaded RV that is suddenly confronted with increased afterload as iPAH. This suggest that the RV has a regenerative capacity that so far is unexplored.

Also, it should be noted that patients with the Eisenmenger syndrome have a natural ability to unload the RV via the shunt, in contrast to patients in which PAH develops later in life. In that regard these patients behave as patients palliated with a Potts-shunt in end-stage PAH with RV dysfunction.

A major difference between Eisenmenger syndrome and all other forms of RV in CHD is the long lasting hypoxemia due to the right-to-left shunt. The hypoxemia induces polycythemia and hyperviscosity, an increased risk for thrombosis which in presence of the shunt can give rise to arterial emboli and can induce systemic organ dysfunction [90, 95].

Summary

The RV in CHD poses a challenge for the cardiologist to evaluate and dissect the mechanism of RV adaptation and (dys)function as well as to treat RV failure. Many CHD lead to abnormal loading conditions of the RV, i.e. increased preload, increased afterload or a mixture of both. Moreover, every lesion has specific features leading to RV dysfunction, which is a main predictor of adverse outcome. Lesions with increased preload of the RV due to a shunt or valvular insufficiency induces RV dilatation that is usually well-tolerated for a long time. Increased pulmonary blood flow in cardiac shunts may change the phenotype to increased afterload. RV dilatation is associated with increased apical deformation during volume loading which decreases after unloading. RV function remains mildly impaired even years after closure of the defect.

Tetralogy of Fallot before correction imposes an increased afterload on the RV, but the majority of the problems of RV dysfunction arise years after correction and are mainly associated with additional volume loading to the pulmonary regurgitation. Specific features adding to RV dysfunction in this lesion are RVOT dyskinesia, reduced apical deformation, dyssynchrony, and restrictive physiology.

Lesions leading to increased afterload such as the systemic RV induce a switch to "LV-like" contraction pattern. However, the RV has no capability to develop torsion to support the adaptation. Although with a considerable "lag-time", RV failure eventually ensues and is associated with additional volume load via tricuspid insufficiency, remodeling associated with perfusion defects and fibrosis, reduced filling especially at higher heart rates, and dyssynchrony.

Current treatment strategies have not been effective in preventing or reducing RV failure in the RV in CHD. New developments to support the RV maybe resynchronization, supporting septal motion via pulmonary artery banding and exploring the effects of beta blocker therapy.

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Pulmonary Embolism

11

Angel López-Candales

Abstract

Acute pulmonary embolism (aPE) is one of the great masqueraders in medicine. Therefore, a high index of clinical suspicion coupled with a detailed history and physical examination are invaluable when evaluating patients. Acute venous thromboembolism (VTE) that usually originates from the lower extremity deep veins (DVT) is clearly recognized a significant health care problem. In the United States an estimated 900,000 cases of DVT and PE occur per year, causing approximately 300,000 deaths. Clinically, aPE is defined as massive, sub-massive or non-massive. In the assessment and management of patients presenting with suspected aPE, clinical information not only is critical to the initial assessment of prognosis; but also to guide therapeutic decision making. Hemodynamic stability and right ventricular (RV) function are found to be critically important in determining morbidity and mortality. Thus, risk stratification algorithms have been proposed to help physicians identify high versus low-risk patients aPE in order to expedite diagnosis and treatment. Computed tomographic pulmonary angiography (CTPA) has been the imaging of choice in aPE patients not only for its higher sensitivity and specificity; but also for providing alternate diagnosis in patients with non-specific signs and symptoms of aPE. More recently, echocardiography has been able to provide anatomical, functional as well as mechanical information regarding RV function and RV-pulmonary unit interaction. This chapter not only intents to summarize the most important pathophysiological processes involved from clot formation to distal pulmonary embolization; but also to describe potential hemodynamic implications and associated clinical manifestations. Current diagnostic and therapeutic algorithms are reviewed; available imaging modalities with most typically diagnostic aPE features

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are described; and mechanical characterization of the anatomical and functional abnormalities with regards to RV function are examined in terms of the hemodynamic derangement caused by acute obstruction to pulmonary flow.

Abbreviations

aPE	Acute pulmonary embolism
CDMT	Catheter-directed mechanical thrombectomy
CTPA	Computed tomographic pulmonary angiography
DVT	Deep venous thrombosis
IVS	Interventricular septum
LV	Left ventricle
PA	Pulmonary artery
PH	Pulmonary hypertension
PIOPED	Prospective investigation of pulmonary embolism diagnosis
PVR	Pulmonary vascular resistance
RV	Right ventricle
RVOT	RV outflow tract
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiogram
V/Q scan	Ventilation-perfusion scintigraphy
VTE	Venous thromboembolism
VTI	Velocity time integral

Introduction

Acute pulmonary embolism (aPE) has perennially being considered one of the great masqueraders in medicine. Even though PE might be considered both a common and ubiquitous disorder, presenting symptoms and signs are often nonspecific; therefore, a high index of clinical suspicion coupled with a detailed history and physical examination are invaluable when evaluating patients.

A wealth of clinical and laboratory data has linked the development of deep venous thrombosis (DVT) with thromboembolic potential that may result in aPE [1–11]. Representative Duplex images of a normal popliteal vein (Fig. 11.1a, b) and acute DVT (Fig. 11.1c, d) as well as a chronic DVT (Fig. 11.2a, b) are shown for comparison. Even though DVT is the most common source of embolization resulting in aPE; additional sources for potential embolization are shown in Fig. 11.3. A more complete list of potential recognized sources of thromboembolism is listed in Table 11.1.

It is important to remember that most patients with acute venous thromboembolism (VTE) describe patients having thrombosis in the legs as well as pulmonary symptoms at the time of diagnosis [12]. Hence, a high index of suspicion is required to recognize which patients are at risk of this otherwise deadly clinical entity. VTE is clearly recognized as a significant health care problem in the United States. It is estimated that 900,000 cases of DVT and PE occur per year and approximately 300,000 deaths are attributed to VTE [13]. Therefore, better understanding of the mechanisms regulating venous thrombosis and clot resolution is critical.

Although thrombophlebitis or DVT of the lower limbs was first reported in the ancient Hindu Medicine writings of Susruta around the year 800 BCE [14] subsequent descriptions of venous thrombogenesis are less clear. We currently relate to Virchow's triad of stasis, changes in the vessel wall, and thrombogenic changes in the blood as the principal concept regarding the pathogenesis of VTE. Yet, revision of previous literature accounts cast doubts on the existence of the so called Virchow's triad as currently quoted [15]. Despite some inconsistencies, Virchow coined the terms venous thrombosis and PE; nevertheless, the triad of factors relating to the development of venous thrombosis is somewhat elusive [15].

It is estimated that the incidence of VTE in industrialized countries is 1–3 individuals per 1,000 per year [8, 16–20]. Most importantly, a dramatic increase in the risk of VTE occurs over

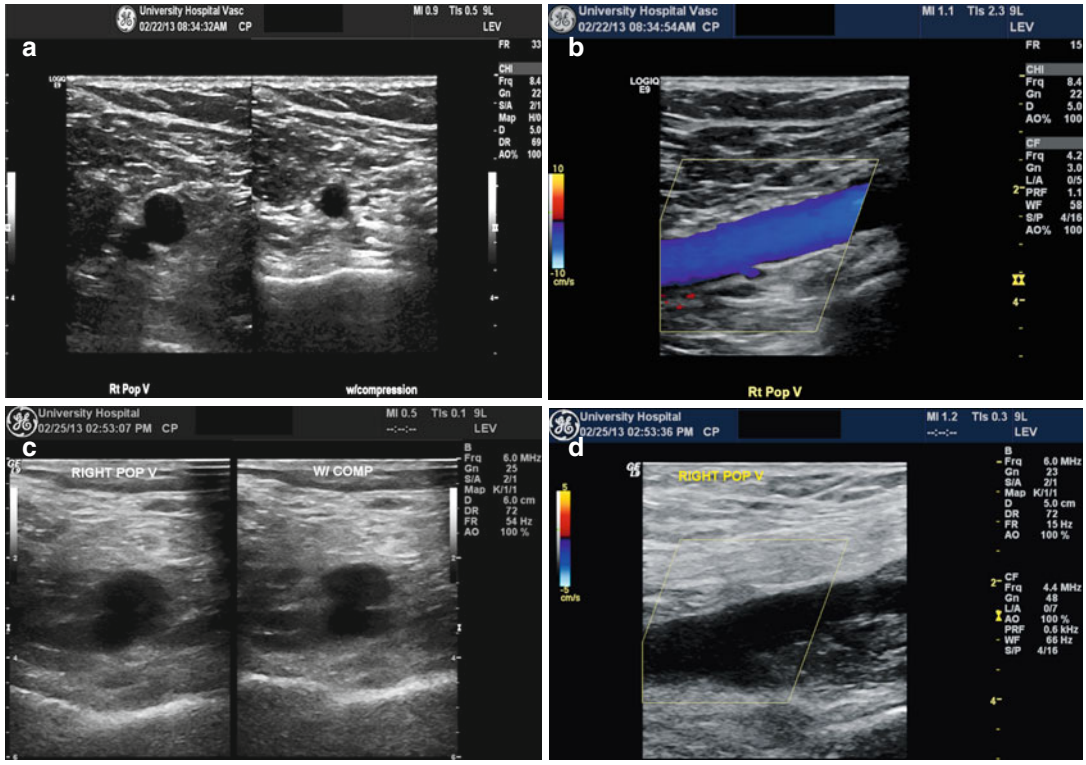


Fig. 11.1 (**a**) A representative Duplex images showing a normal popliteal vein before and after manual compression. (**b**) Normal color Duplex signal in a normal popliteal vein filling the whole vein contour. (**c**) Case of an acute DVT showing a dilated popliteal vein that lacks compressibility. (**d**) Color is not found due to the proximal acute DVT that impedes flow

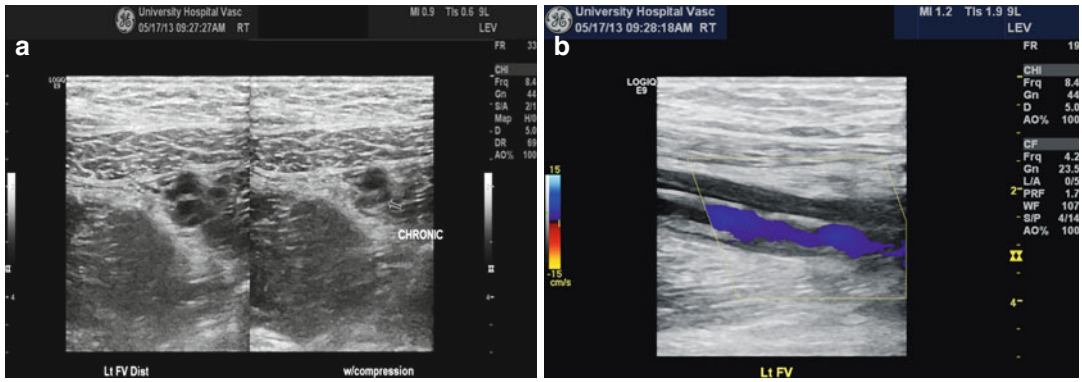


Fig. 11.2 (**a**) In sharp contrast, a chronic case of DVT is showing a visible organized clot (*arrow*). Please note that in most instances of a fresh clot as seen in Fig. 11.1c, in acute DVT, the clot was not well visualized. (**b**) Color flow Duplex signal within a popliteal vein with a partially filling clot that has distorted the main lumen

the age of 50 reaching as high as 1 in every 100 individuals annually [8]. These alarming statistics have led the United States Senate in 2005 to designate March as "DVT Awareness Month" followed by the Surgeon General's call to action in 2008 to prevent DVT and PE.

Anticoagulation is the mainstay of treatment of symptomatic VTE. Anticoagulation prevents

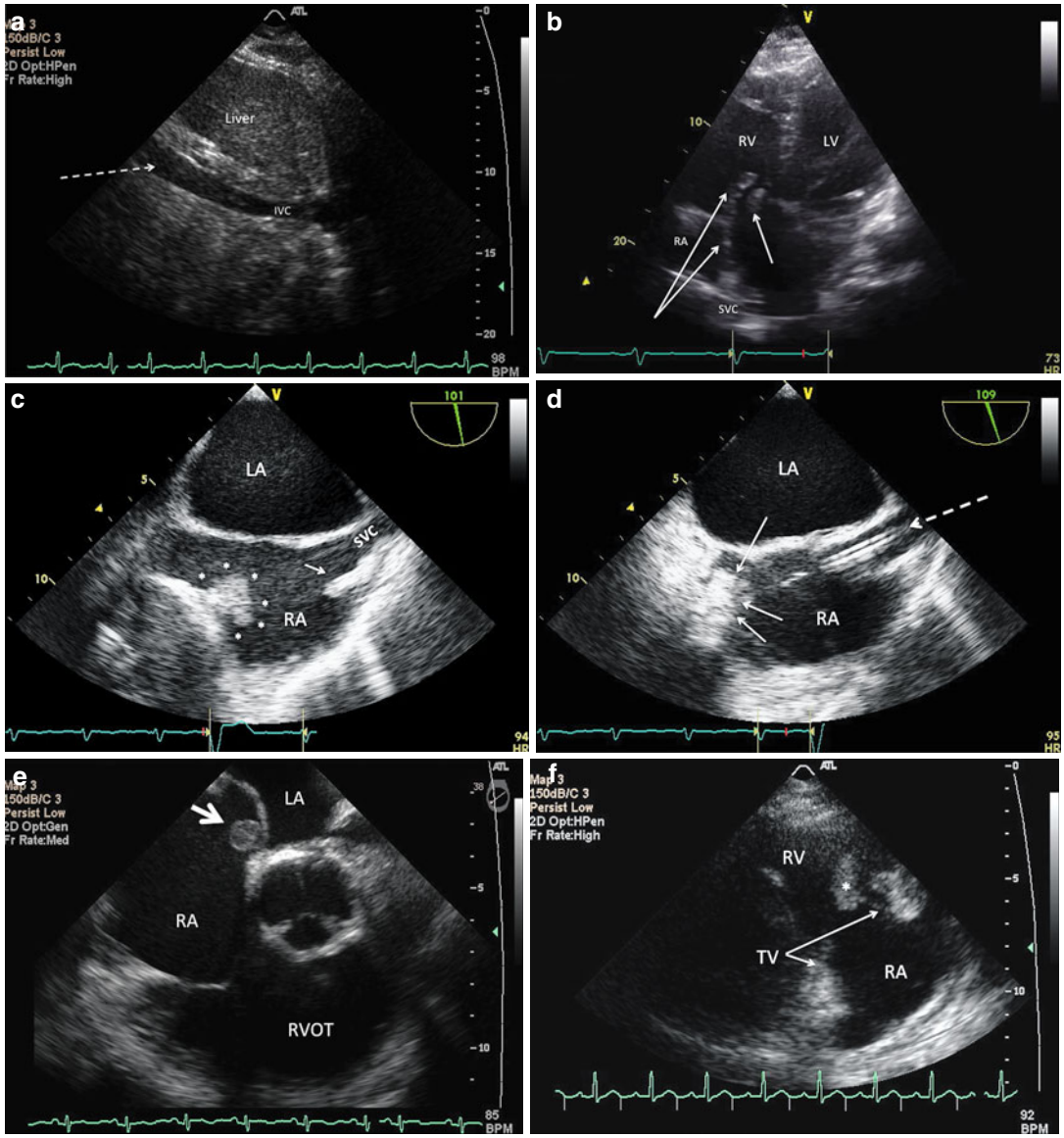


Fig. 11.3 (**a**) Representative subcostal echocardiographic image showing a homogeneous density filling the inferior vena cava (*IVC*) denoted by the *white arrow*. (**b**) Four-chamber apical echocardiographic image showing a rather large tubular thrombus cast within the right atrium (*RA*, *arrow*), crossing the tricuspid valve and into the right ventricle (*RV*), superior vena cava (*SVC*), left ventricle (*LV*). (**c**) Transesophageal view from the bi-caval view at 90° showing the right atrium (*RA*) and catheter (*arrow*) in the superior vena cava and a thrombus mass due to catheter-related trauma encircled by (*). (**d**) Improved visualization of the catheter seen in the SVC and the mural thrombus seen in the right atrium (*RA*, *broken arrow*). (**e**) Transesophageal view from 45° showing the right atrium (*RA*), RV outflow tract (*RVOT*), left atrium (*LA*) as well as a globular homogeneous mass (*arrow*) attached to the interatarial septum that was resected and found to be a myxoma. (**f**) Trans thoracic view from the RV inflow, during diastole while the tricuspid valve is open, showing the right atrium (*RA*), right ventricle (*RV*), and tricuspid valve (*TV*) as well as a homogeneous mass found to be a vegetation (*). (**g**) Additional view, during systole resulting in closing of the tricuspid valve, showing the same tricuspid valve vegetation (*) involving the whole leaflet, as seen in (**f**) with the same labeling annotations

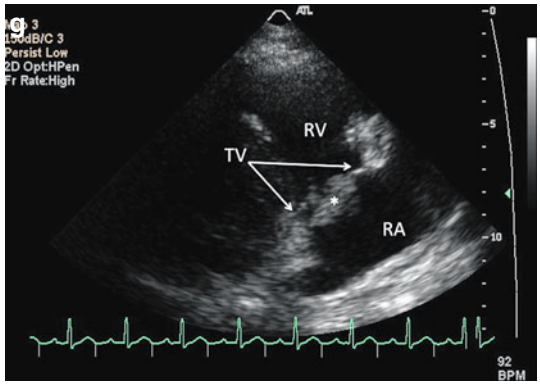


Fig. 11.3 (continued)

Table 11.1 Potential mechanisms of thromboembolism

Venous clots originating from lower extremities (DVT)
Paget-Schroetter syndrome (Spontaneous upper extremity venous thrombosis due to a compressive anomaly of the thoracic outlet)
May-Thurner syndrome (compression left common iliac vein)
Inferior vena cava abnormalities (Agenesis, hypoplasia or malformation that will cause DVT)
Massive micro embolism during surgery
Air embolism
Carcinomatous tumor embolism
Cavitoatrial embolization of a renal carcinoma
Bone fat embolism after long bone skeletal fracture
Body sculpting fat embolism
Iatrogenic injections of various cements and coagulation materials
Embolization of a right-sided heart valve (tricuspid and pulmonic valves) vegetation

further thrombus deposition, allows established thrombus to undergo stabilization and/or endogenous lysis, and reduces the risk of interval recurrent thrombosis [12]. This chapter not only focuses on the pathophysiological and hemodynamic alterations that occur with aPE; but also on the mechanical abnormalities that these processes have on the right ventricle (RV). This review intends to highlight the importance of the pulmonary-circulation-ventricular circuit in mediating cardiac performance and how the later is the most critical factor determining both morbidity and mortality.

Table 11.2 Mechanisms responsible to maintain non-thrombogenic state of endothelial surfaces

Endothelial production of thrombomodulin
Activation of protein C
Endothelial expression of heparan sulfate
Endothelial expression of dermatan sulfate
Constitutive expression of tissue factor pathway inhibitor
Local production of tissue plasminogen and urokinase-type plasminogen activators
Endothelium production of nitric oxide
Endothelium production of prostacyclin
Endothelium production of interleukin-10

Mechanisms Regulating Thrombosis

Even though the molecular and translational pathways that regulate the dynamic balance between clot formation and lysis are well beyond the scope of this chapter; it is important to have a basic understanding of the individual elements responsible for these processes.

A healthy vascular endothelium is critical in maintaining adequate hemostasis. Under normal conditions, intact endothelial cells promote vasodilatation and local fibrinolysis. Hence, blood coagulation, platelet adhesion and activation, as well as inflammation and leukocyte activation are suppressed resulting in normal blood fluidity. A list of specific elements that maintain the natural nonthrombogenic state of the endothelial surface can be found in Table 11.2 [21, 22].

In contrast, during periods of direct vascular trauma or as a result of activation of the coagulation cascade, a prothrombotic and proinflammatory state ensues [22]. The latter is mainly characterized by an enhanced production of von Willebrand factor, tissue factor, plasminogen activator inhibitor-1, and Factor V that augment thrombosis [22]. In addition, release of substances such as platelet activating factor and endothelin-1 promote vasoconstriction [23]. Finally, an exposed endothelial surface increases the expression of cell adhesion molecule, promoting accumulation and activation of leukocytes that further amplifies inflammation and thrombosis as shown in Fig. 11.4 [21, 24].

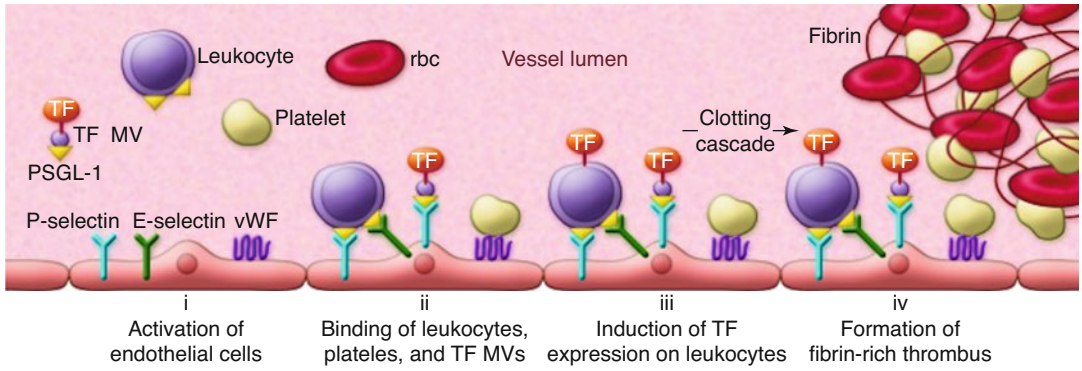


Fig. 11.4 Proposed mechanisms for venous thrombosis. My group proposed that formation of a venous thrombosis can be divided into distinct steps. First, the endothelium is activated by hypoxia and/or inflammatory mediators and expresses the adhesion proteins P-selectin, E-selectin, and vWF. Second, circulating leukocytes, platelets, and TF+MVs bind to the activated endothelium. Third, the bound leukocytes become activated and express TF. The local activation of the coagulation cascade overwhelms the protective anticoagulant pathways and triggers thrombosis. The fibrin-rich clot also contains platelets and red blood cells (Reprinted from Mackman [24]. With permission from American Society for Clinical Investigation)

Table 11.3 Risk factors predisposing to deep venous thrombosis

Increasing age
Surgery (abdomen, pelvis, lower extremities)
Trauma (fractures of pelvis, hip or lower extremities)
Obesity
Cancer and its treatment
Pregnancy and puerperium
Hormone-based contraceptives/hormone replacement therapy
Acute infection
Prolonged immobilization
Paralysis
Long-haul travel
Smoking
Prolonged hospitalization
Previous DVT
Congestive heart failure
Myocardial infarction
Indwelling central venous catheters
Inflammatory bowel syndrome
Nephrotic syndrome
Heparin-induced thrombocytopenia
Disseminated intravascular coagulation
Paroxysmal nocturnal hemoglobinuria
Thromboangiitis obliterans
Thrombotic thrombocytopenia purpura
Behçet's syndrome
Lupus anticoagulant (anti-phospholipid antibody)
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden mutation
Prothrombin gene mutation
Dysfrinoginemia
Factor XII deficiency

Blood clots contains a mixture of platelets, fibrin and in some cases red blood cells [25, 26]. Arterial clots are formed under high shear stress, typically after rupture of an atherosclerotic plaque or other damage to the blood vessel wall, largely platelet-rich (white clots) and thus generally treated with antiplatelet drugs [22, 27, 28]. Venous clots form under lower shear stress and are mostly rich in fibrin (red clots); hence treated with anticoagulant drugs [12, 22, 29–31].

The coagulation cascade is regulated at several levels. Interaction of tissue factor exposed by vascular injury with plasma factor VIIa results in the formation of small amounts of thrombin. This thrombin production is then amplified through the intrinsic pathway, resulting in the formation of the fibrin clot. These reactions take place on phospholipid surfaces, usually the activated platelet surface [32]. In case of venous thrombosis, changes in blood flow and in the endothelial cell lining of blood vessels, as initially proposed by Virchow, increases the risk of VTE [33]. A series of well-recognized risk factors, as shown in Table 11.3, have been associated with an

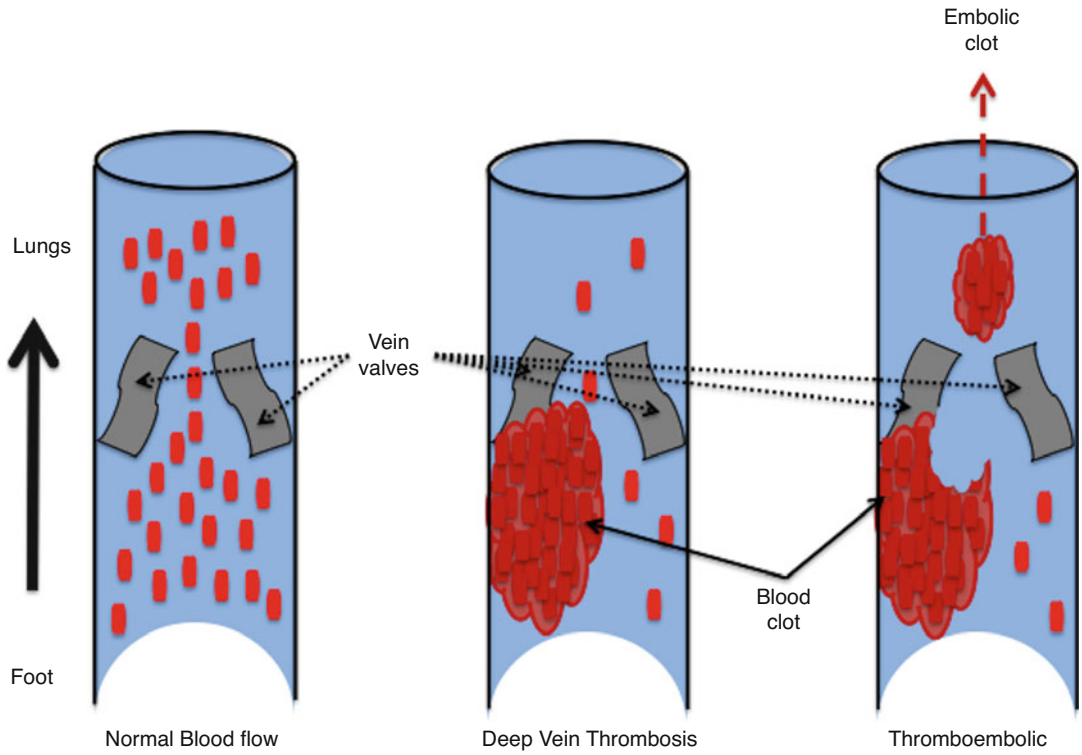


Fig. 11.5 Diagrammatic representation of a deep vein during normal flow, during acute thrombus formation (DVT) and during potential embolization (VTE). During normal flow blood cells are freely moving across vein valves. In the event of DVT, a clot forms on the underside of the vein valves. Ion the case of VTE, potential dislodgement of part of the clot material can be released into the venous circulation. Thrombosis is thought to be enhanced by a significant decline in oxygen tension in the region of the valve pocket sinus resulting in clot formation and the potential for VTE

increased risk of DVT and the potential for VTE [34–53]. Patients with significant liver disease as a result of prolonged clotting times, reduced clearance of fibrin degradation products, and thrombocytopenia have a very low risk of developing VTE [53].

With the exception of compression of the left common iliac vein either by the presence of the fetus during pregnancy or in patients with May-Thurner syndrome [54, 55]; the most likely site of thrombus formation in DVT is the valve pocket sinus [56–60]. These sites are particularly prone to thrombosis because of the disrupted and irregular blood flow patterns [56]. Initial formation of thrombus within the venous valve pocket disrupts the architecture of these valve pockets, disrupting pulsatility of venous flow and favoring local stasis of cellular elements [61]. Formation of a semi-solidified mass causes further activation of circulating platelets and leukocytes inducing additional fibrinogenesis favoring the growth of the thrombus beyond the confines of the valve pocket [61]. Amplification of this process causes further alteration of luminal flow dynamics resulting in progressive occlusion of the vein lumen [61]. Intraluminal growth of the thrombus has also been shown to lower local oxygen tension, as oxygen is being consumed by trapped cells resulting in luminal hypoxemia favoring cell death and contributing to thrombus growth [61]. Notwithstanding as the luminal linear velocity of the blood continues to decline and further oxygen is being locally consumed, passing blood stream tugs additional layers of cells to the growing thrombus [63]. A graphic representation of this process is illustrated in Fig. 11.5 [56, 61–63].

Two simple anatomical considerations are important for when understanding DVT and the

potential for VTE. First, as the number of these vein valves increase within any given vein segment; thus the risk of DVT increases. Second, it is during the stage of thrombus thrombus formation that not all portions of the thrombus anchor to the necrotic parietalis endothelium, but in fact some portions of the growing thrombus become less strongly attached and hence at risk for distal embolization. Development of local symptoms not only depends on the extent of thrombosis and adequacy of collateral vessels; but also on the severity of associated vascular occlusion and inflammation. In addition, embolic symptoms largely depend on the capacity of the patient to tolerate thrombosis given by the underlying cardiopulmonary reserve [57–59].

The early post venous thrombosis stage is characterized by recruitments of neutrophils that are essential for early thrombus resolution by promoting fibrinolysis and collagenolysis [64, 65]. This process then transitions over the course of a few days, peaking at approximately day 8, to a monocyte predominant venous thrombus milieu that is then associated with plasmin and matrix metalloproteinase mediated thrombus breakdown [66, 67].

Epidemiology of Venous Thromboembolism

It is important to realize that current estimates clearly underestimate the true incidence rate of DVT and VTE; particularly since most patients with fatal or non-diagnosed events are never identified. Furthermore, the number of thrombosis cases treated outside the hospital setting is rarely recorded. In addition, since many studies have used stringent validation criteria patients with typical clinical findings but non-diagnostic radiologic studies and not reported. Finally, patients treated in long-term care facilities and those cancer patients in hospice settings are usually not enrolled in clinical studies. It is also important to keep in mind that studies that include a large number of VTE cases diagnosed by autopsy has generally reported a higher proportion of PE than DVT cases likely due to overestimation of the incidence of PE by detecting asymptomatic cases.

Despite these limitations, the reported incidence of first time diagnosis of VTE has been estimated to be approximately 100 persons per 100,000 each year in the United States. Even though review of the literature suggests that in up to 50 % of patients with first-time VTE diagnosis, no identifiable risk factor can be found; a number of risk factors can be clearly demonstrated. Age has been recognized as a very important risk factor for VTE. Of the reported cases of VTE, approximately less than 5 cases per 100,000 persons are reported in individuals less than 15 years old compared to approximately 500 cases per 100,000 persons in older individuals up to the age of 80 years [68]. Ethnicity is another major risk factor identified for VTE. Specifically, incidence of VTE is significantly higher incidence among Caucasians and African Americans than among Hispanic persons and Asian-Pacific Islanders. Treatment at a hospital, nursing home, or other chronic care facility confinement is another independent risk factor for VTE likely due to immobilization, acuity and severity of illness [69]. VTE risk is highest among hospitalized patients with previous surgery conferring a nearly 22-fold increased risk [69]. This risk has been linked surgery and recent trauma [69]. Obesity in patients undergoing total hip arthroplasty is a recognized combo at significant risk for VTE [70]. Presence of a malignant neoplasm has been associated with a fourfold increased risk of VTE. Patients with cancer receiving immunosuppressive or cytotoxic chemotherapy are at an even higher risk for VTE [69, 71, 72]. Patients with neurologic disease and extremity paresis or plegia had a threefold increased risk for VTE that was independent of hospital confinement [69]. Finally, VTE, has been shown to occur with a higher incidence in the winter than in the summer [68].

Despite anticoagulant therapy, VTE recurs frequently in the first few months after the initial event, with a documented recurrence rate of approximately 7 %; particularly in cancer patients [68]. In cases of recurrent VTE, these episodes most likely occur in the weeks after initial hospitalization for DVT [68].

Accurate assessments of case fatality rates after initial VTE are hindered by the nature of the analysis. First, retrospective data analysis is difficult to interpret, particularly when autopsy data was used to identify patients with PE. Second, prospective data collection is also difficult to interpret if autopsies were not performed to confirm aPE diagnosis in patients dying unexpectedly. Despite these limitations, it is believed that in up to two-thirds of patients simply manifest DVT alone and death occurs in approximately 6 % of these patients within a month of diagnosis, whereas a third of patients with symptomatic VTE develop PE and may experience up to a 12 % mortality during the same time period [68]. Finally, it is certain to conclude that early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease [68, 69].

The risk imparted by gender remains uncertain; however, in women, pregnancy, the postpartum period, use of oral contraceptives, hormone replacement therapy, tamoxifen and treatment with the selective estrogen receptor modulator raloxifene have been shown to confer an increased risk for VTE [53, 73–78].

In conclusion, based on available data, VTE not only is a chronic disease with episodic recurrence; but also is influenced by multiples clinical factors and disease processes with genetic-environmental interactions. Most importantly, there are some individuals at greater risk for incident and recurrent VTE and potential aPE that need special attention and appropriate prophylaxis.

Pulmonary Vasculature

The pulmonary vasculature consists of the arterial, venous, bronchial arteries and to some extent albeit not a robust system the microvascular collateral circulation [79–82]. Obviously, with regards to pulmonary embolism, the pulmonary arterial (PA) system network is the most important and closely follows the bronchial pathways. From an anatomical perspective the main PA connects the RV outflow tract (RVOT) to the left and right pulmonary arteries. The left PA appears to be a continuation of the main PA as it arches over the left main stem bronchus and begins branching to supply the left upper and lower lobes. A representative view of the main PA with its main bifurcations is seen in Fig. 11.6. Typically, the right PA not only is longer and gives rise to the right upper lobe artery as it arches over the right main stem bronchus; but also normally courses more caudal than the left, and its length is better visualized in chest radiography. The normal main PA caliber is less than 3 cm while both left and right PAs are usually 1.5 cm [83].

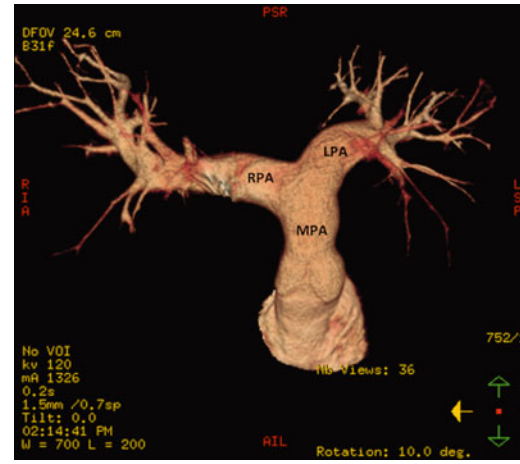


Fig. 11.6 Volume-rendered reconstructions of a multidetector-row computed tomographic scan elegantly showing the main pulmonary artery (*MPA*), *LPA* left pulmonary artery, and *RPA* right pulmonary artery with proximal bifurcations (Image provided by Amy L. Smith, RT (R) (CT) and Dr. Robert O'Donnell, MD, University of Cincinnati Medical Center)

The right PA gives rise to an upper lobe artery, which then divides into an apical, a posterior, and an anterior segmental artery. The next right lobar artery branch is the middle lobe artery, which divides into a lateral and a medial lobe segmental artery. The right lower lobe artery divides into an apical, an anterior, a posterior, a medial, and a lateral segmental artery. Although this major branching pattern is typical and related to lobar and segmental lung development, other arterial branches may arise directly from the right and left PA [83]. In contrast, a typical left PA gives

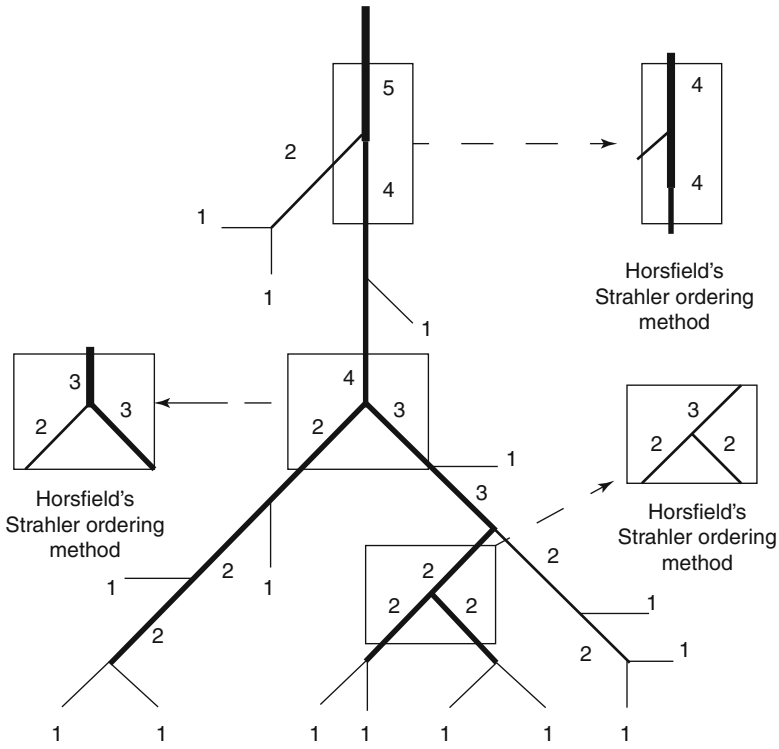


Fig. 11.7 Illustration of diameter-defined Strahler ordering system. Vessel order numbers are determined by their connection and diameters. Arteries with smallest diameters are of order 1. A segment is a vessel between two successive points of bifurcation. When two segments meet, order number of confluent vessel is increased by 1. Horsfield and diameter-defined systems apply to arterial and venous trees only. They are not applicable to capillary network, topology of which is not treelike. Each group of segments of the same order connected in series is lumped together and called an element. *1–5* represent size of the vessels in increasing order from 1 to 5 (Reprinted from Huang et al. [330]. With permission from The American Physiological Society)

rise to an upper and a lower lobe artery. The left upper lobe artery gives off the apicoposterior, anterior, and lingular arteries that further divide into a superior and an inferior segmental arteries. The left lower lobe artery divides into a superior, an anteromedial, a lateral, and a posterior basal segmental artery [83].

Final diagnostic documentation of the involved segment is based on the highest branching order resolved by the imaging technique. Therefore, main PA arising from the RVOT is recognized as the first order. The right and left PA are considered as second order. Visualization of lobar artery segments is considered third order. Finally, segmental arteries as recognized as fourth order, subsegmental arteries as fifth order and the first branches of subsegmental arteries are described as sixth order [83]. Figure 11.7 demonstrates the proposed diameter-defined Strahler ordering system with regards to the PA system. Representative tomographic images of aPE cases are shown with a typical proximal saddle embolus shown in Fig. 11.8 and a subsegmental aPE shown in Fig. 11.9.

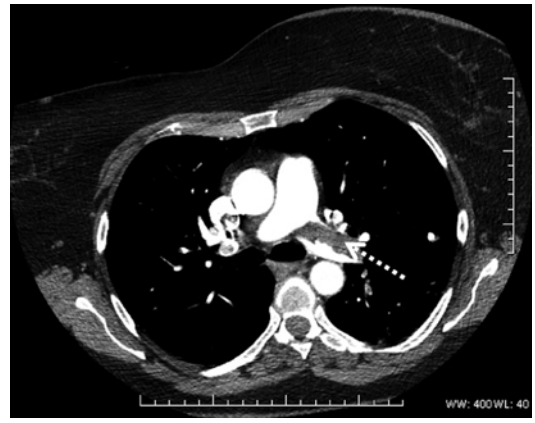


Fig. 11.8 Chest tomographic image showing a large filling defect suggestive of a large saddle embolus seen (*broken arrow*) (Image provided by Amy L. Smith, RT (R) (CT) and Dr. Robert O'Donnell, MD, University of Cincinnati Medical Center)

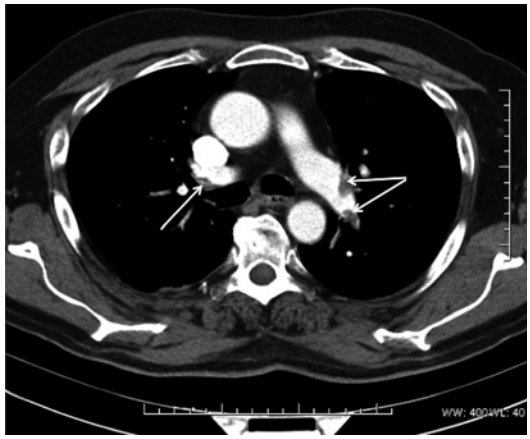


Fig. 11.9 Chest tomographic image showing two filling defects (shown by the *arrows*) on the left side and a defect on the right side representative of subsegmental regions of the PA vasculature (Image provided by Amy L. Smith, RT (R) (CT) and Dr. Robert O'Donnell, MD, University of Cincinnati Medical Center)

Pulmonary Arterial System Network and the Right Ventricle

In the normal state, while the pulmonary artery vasculature acts as an elastic reservoir for the stroke volume ejected from the RV, minimal resistance is provided from the main PA all the way down to subsegmental arteries of approximately 0.5-mm diameter. Furthermore, this PA system network is important for the dynamic regulation of circulation matching perfusion and ventilation needs. Exquisite flow resistance regulation takes place at the level of the muscular arteriole capillaries, which exert the greatest arterial flow and pressure control [84–86]. In the normal state, this dynamic process is instrumental in matching perfusion to ventilation in real time. The diameter of these artery segments closely parallels that of the accompanying bronchi [86–90].

This intricate PA system network is critically important in regulating RV systolic function. Specifically, RV cardiac output depends on proper calibration between RV myocardial contractility and impedance to blood flow through the lungs. It has been well described that the RV can accommodate large volumes without significant compromise in RV systolic performance; however, the RV has a limited contractile reserve to match even minor increases in impedance to ejection. Hence, the degree of hemodynamic compromise will certainly depend on the magnitude and timing of pulmonary vascular obstruction [91–98]. Clinical aPE presentation may range from vague symptoms that include mild dyspnea, to shock with sustained hypotension to death. Most importantly, depending on its clinical presentation, case fatality rate for aPE ranges from <1 % to about 60 % [99].

Even though the proposed pathways leading to RV injury are intrinsically different between chronic and acute pulmonary hypertension (PH); [100] RV dilatation and systolic dysfunction are common abnormalities shared by both clinical entities. These abnormalities in RV size and systolic performance are mainly explained by the LaPlace relationship [101]. Specifically, an increased ratio between cavity radius to thickness will increases wall stress while a decrease in this ratio will decrease wall stress [102]. This principle is illustrated in Fig. 11.10 showing the relationship between RV wall dilatation and increase thickness and its effect on the left ventricle (LV).

In the case of the LV, wall thickness is greater than the RV and a series of compensatory patterns of hypertrophy have been noted to occur as a result of specific valvular lesions [102]. In terms of the RV, under normal conditions the thin walls of this chamber allows the RV to be more compliant. Thus, the RV not only is able to accommodate larger volumes without hemodynamic stress, but also allow the RV to eject blood against approximately 25 % of the afterload of the LV [103]. In sharp contrast, these same characteristics do not allow the RV to tolerate acute increases in afterload, such as it occurs in aPE [101]. In cases of gradual increase in RV afterload, such as occurs in chronic PH, the RV is equipped to handle these circumstances much better, as there is time to assemble new sarcomeres in parallel in order to increase wall thickness and compensate for the hemodynamic stress [101]. However, in cases of

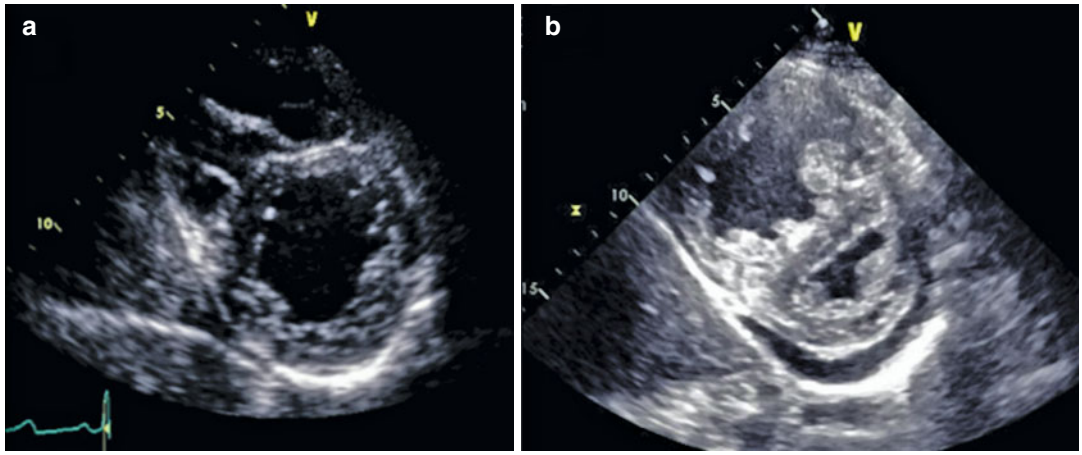


Fig. 11.10 (**a**) Echocardiographic short axis view of the left ventricle at the papillary muscle level showing a normal curvature of the left ventricle in relationship to a normal sized RV with normal wall thickness. (**b**) In contrast, a dilated and hypertrophied RV not only requires more energy to pump the same amount of blood as compared to the normal sized-RV; but also the resultant higher wall tension and thus RV peak systolic pressure results in bowing of the interventricular septum causing systolic flattening during ventricular contraction

aPE, direct mechanical obstruction of the PA by thromboembolic material, hypoxemia and contribution from potent pulmonary arterial vasoconstrictors causes a rapid increase in pulmonary vascular resistance (PVR) that compromises RV performance and results in hemodynamic collapse [104–115].

Transthoracic echocardiographic (TTE) estimation of PVR utilizes the maximum tricuspid regurgitation (TR) jet velocity using continuous wave Doppler and the velocity time integral (VTI) of the pulsed Doppler signal across the RVOT. Thus, TTE calculation uses the following formula: PVR (Woods unit [WU]) = (TR Velocity max/RVOT VTI) × 10 + 0.16 to approximate values that are obtained during invasive right heart catheterization. Representative TTE Doppler signals are shown in Fig. 11.11 [116].

Thus, a rise in PVR not only depends on the location and extent of the acute thromboembolic occlusion as well as the generation of local vasoconstrictive mediators along the PA system network; but also is a major determinant of prognosis in conjunction with the functional state of the myocardium. Data from the International Cooperative Pulmonary Embolism Registry (ICOPER) of 2,454 prospectively enrolled patients from 52 hospitals in seven countries provided a unique opportunity to study further this clinical problem [117].

In this study, not only almost half of the enrolled patients had a baseline TTE; but also follow-up data was collected in 98 % of patients three months' post enrollment [117]. Using a simple approach, these investigators included information on the history and clinical presentation at the time of aPE diagnosis and the only TTE variables studied were the presence of RV dysfunction or intra-cardiac thrombi. Using this analysis, from a total of 1,113 patients, only 42 patients had evidence of a right heart thrombus; while 1,071 patients had none [117]. However, patients with a demonstrable intracardiac thrombus at the time of the TTE were more hemodynamically compromised as suggested by lower systemic arterial pressure, higher prevalence of hypotension, faster heart rates, and frequent hypokinesis of the RV as determined by TTE than patients without a demonstrable intracardiac thrombus at the time of diagnosis [117].

Clinically, aPE is defined as massive, submassive or non-massive. This definition not only allows determination of the clinical magnitude of the thrombotic occlusion and its hemodynamic consequence; but also helps to expedite therapeutic strategies [118]. A massive aPE is

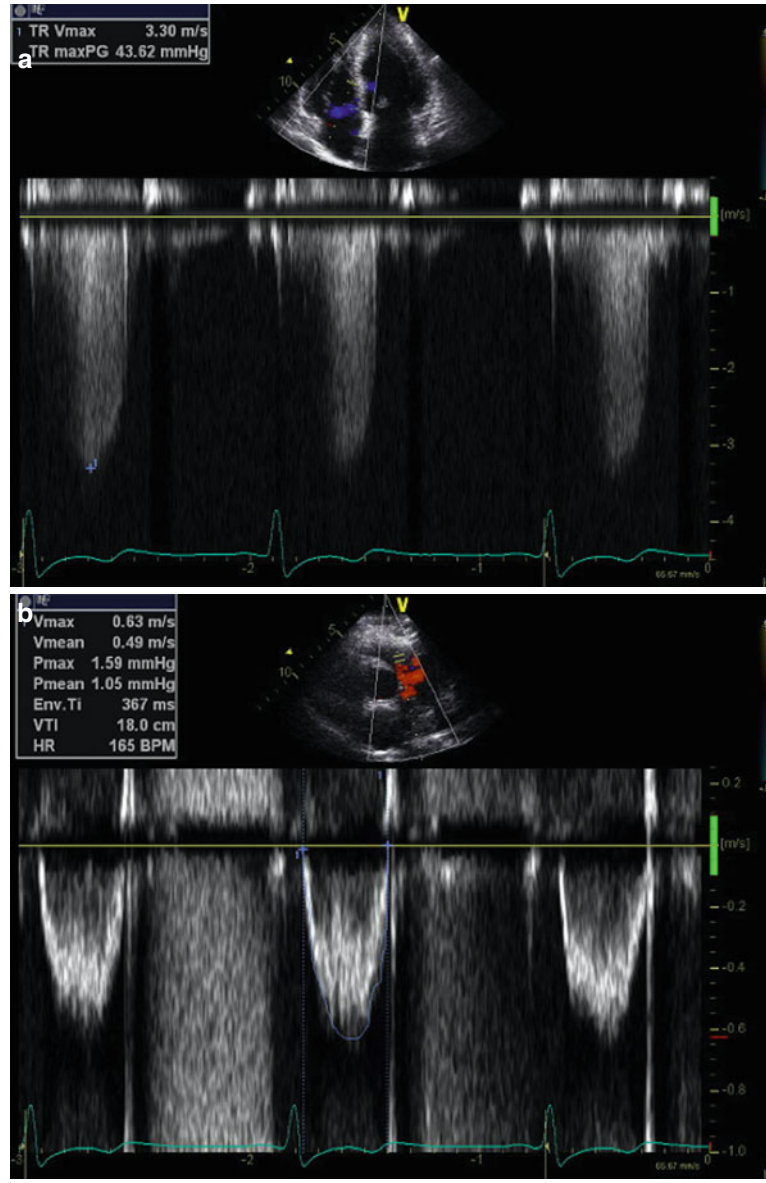


Fig. 11.11 Representative Doppler tracings used for PVR calculation using echocardiography. (**a**) Maximal TR velocity jet signal obtained from the apical four-chamber view measuring 3.3 m/s. (**b**) Pulsed Doppler signal across the RVOT showing a velocity time integral (VTI) of 18 cm resulting in a PVR of 2.0 WU. Echocardiographic estimation of PVR uses the following formula: PVR (Woods unit [WU]) = (TR Velocity max/RVOT VTI) × 10 + 0.16

further categorized as saddle, main branch, or ≥2 lobar pulmonary emboli, with associated cardiogenic shock carrying an estimated 60 % mortality, two-thirds of which occur within the first hour after onset [16, 99, 119]. In contrast, submassive aPE occurs in hemodynamically stable patients who demonstrate evidence of right heart strain, which is most commonly identified by TTE or elevation of cardiac enzymes [99, 119]. Furthermore, submassive aPE not only carries an estimated 15–20 % 30-day mortality rate; but also has been associated with chronic thromboembolic pulmonary hypertension and subsequent development of cor-pulmonale [120]. Finally, a non-massive aPE is characterized by a normotensive patient with no evidence of RV dysfunction. A diagrammatic representation of this interrelationship is seen in Fig. 11.12. In summary, a high index of clinical suspicion is required to identify patients at risk as subtle findings can make the difference between life and death as shown in Fig. 11.13.

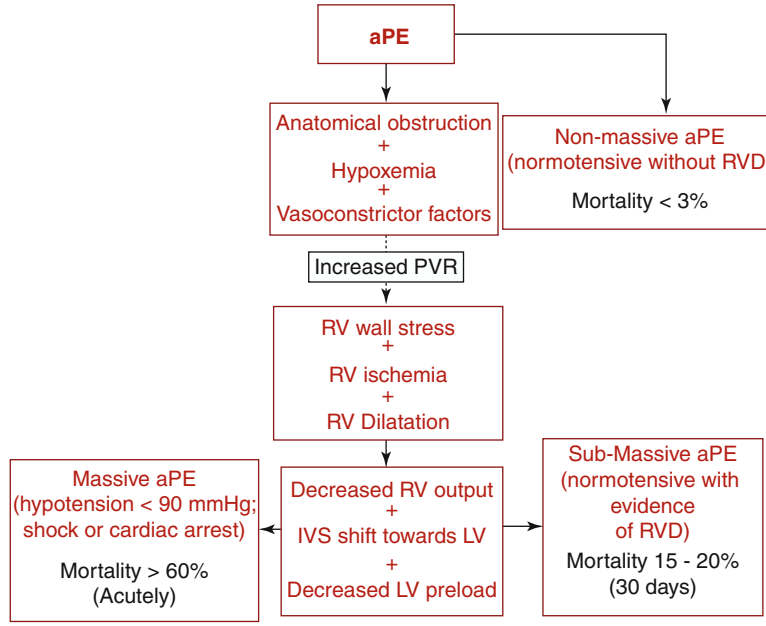


Fig. 11.12 Diagrammatic representation of the sequence of events during aPE and the potential clinical implications of the thrombotic occlusion and resultant hemodynamic implications with associated mortality rates

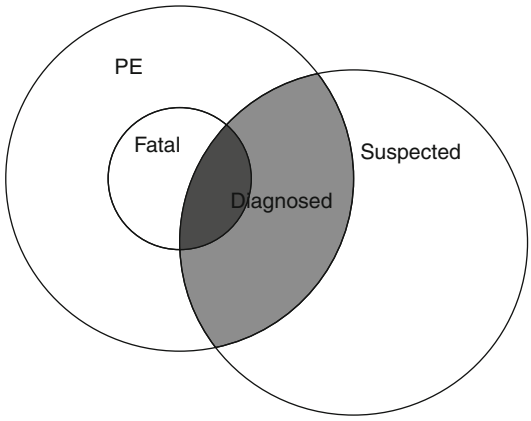


Fig. 11.13 Schema of relationship between suspected and actual cases of pulmonary embolism (*PE*) (Reprinted from Ryu et al. [331]; with permission from Elsevier)

Acute Pulmonary Embolism, Right Ventricular Architecture and Myocardial Mechanics

Despite the obvious, an acute occlusive thrombus not only causes a sudden increase in PVR disrupting normal RV ejection; but also has been shown to result in RV myocyte lysis and induce a proinflammatory phenotype [121–123]. Experimental data of aPE in the rat model suggests that neutrophils are present in the RVOT region between 6 and 18 h of the thrombotic insult [124]. Current data seems to indicate that this inflammation not only amplifies the initial thrombotic injury; but also is independent from the damage caused by the obstructive thrombus [124, 125]. In humans, an elevated concentration of circulating myeloperoxidase as well as other inflammatory biomarkers have been demonstrated in the aPE setting [126–128]. Hence, it has been suggested that an inflammatory response might be a primary part of the development of acute RV dysfunction in the setting of aPE in both clinical and experimental models [100]. Finally, new understanding of myocardial fiber orientation has been instrumental to advance our knowledge of how RV responds to an increase in afterload.

It is important to remember that from an architectural perspective, the RV free wall is mainly comprised of transverse fibers while the LV is encircled by oblique fibers [129]. Furthermore, the interventricular septum (IVS) consists primarily of oblique fibers, which also extend into the RVOT [130]. A schematic representation of this fiber orientation is shown in Fig. 11.14. It is now well established that comparison of varying fiber orientations shows marked differences in contractile performance. Specifically, helical or oblique fibers are responsible for twisting and untwisting; while transverse fibers exert rather a compressive bellows-like activity [130]. From a mechanical perspective, helical or oblique fibers

Fig. 11.14 Schematic representation of the myocardial fiber orientation relationship of the IVS, composed of oblique fibers that arise from the descending and ascending segments of the apical loop, surrounded by the transverse muscle orientation of the basal loop that comprises the free RV wall (Reprinted from Buckberg and RESTORE Group [130]. With permission from Oxford University Press)

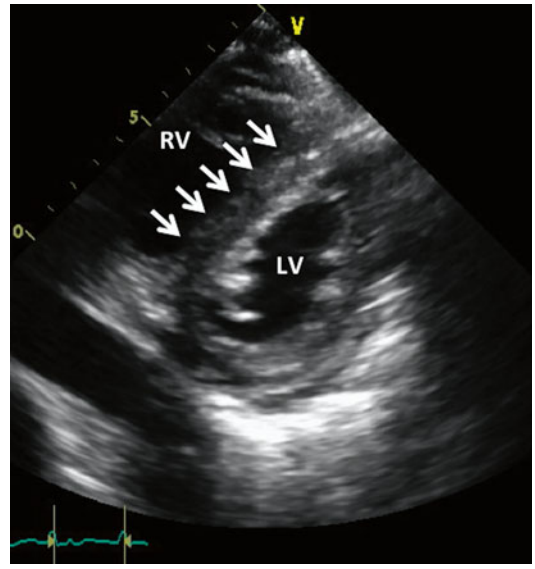


Fig. 11.15 Short axis TTE view of the LV at the level of the papillary muscle showing a dilated RV that is causing significant flattening of the IVS as a result of an acute rise in PVR

are at a considerable mechanical advantage compared with transverse fibers [131].

In this healthy state, although there is a very substantial contribution from helical or oblique fibers to overall contractile performance, transverse fibers are the principal fiber group maintaining RV performance [132, 133]. However, in situations resulting in elevation in PVR, as it occurs in aPE, contribution from the IVS helical or oblique fibers becomes increasingly significant [134]. This contribution is of course in turn dependent on the overall contractile state of the LV. The influence of LV contractile function on RV contractile function via the shared IVS is called ventricular interdependence. In fact, left ventricular activity contributes to about 80 % of the flow and up to two thirds of the pressure generated by the RV during systole [132].

Therefore, it becomes apparent that an acute rise in PVR will undoubtedly result in systolic IVS flattening causing loss of the oblique orientation of the septal fibers as seen in Fig. 11.15. Significant increases in PVR and RV dilatation not only will cause significant shift of the IVS towards the LV; but also will cause LV under filling and impair LV performance, with catastrophic consequences as shown in Fig. 11.16.

Careful analysis of IVS in patients with chronic PH has resulted in the identification of two types

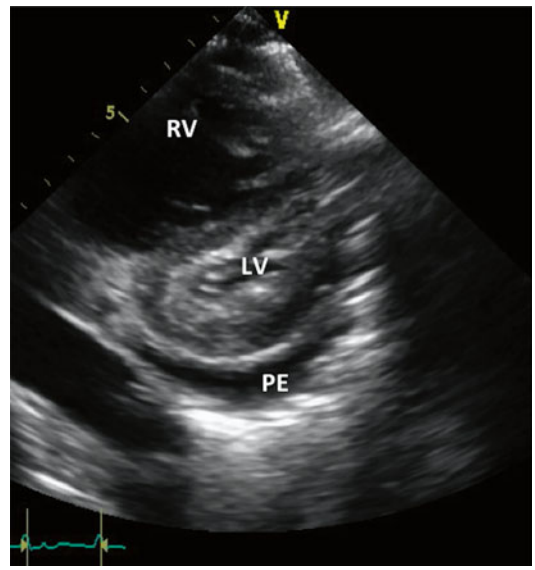


Fig. 11.16 Short axis TTE view of the LV at the level of the papillary muscle showing a markedly dilated RV causing significant flattening of the IVS as a result of an acute rise in PVR resulting in both LV under filling and impairing LV performance associated with hemodynamic compromise in cases of massive aPE. A pericardial effusion (*PE*) is also noted

of septal motions. Type A has been described as marked anterior motion in early systole while Type B shows marked posterior motion in early diastole [135]. More importantly, Type A IVS

motion is mainly seen in patients not only with worse hemodynamic profiles, but also clinical outcomes when compared to patients having Type B IVS motion [135]. Furthermore, deviation of the IVS toward the LV will also compromise LV systolic as well as diastolic function [136–138].

Therefore, IVS motion not only speaks volumes of the intricate hemodynamic and mechanical interdependence of the RV-pulmonary circulation unit, but also highlights the importance of identifying RV dysfunction; particularly when aPE mortality is indisputably dependent on the presence and magnitude of RV strain [93, 99, 136, 139–147].

Assessment of Right Ventricular Function in Acute Pulmonary Embolism

In the assessment and management of patients presenting with suspected aPE, clinical information not only is critical to the initial assessment of prognosis; but also to guide therapeutic decision making. As already established, both hemodynamic stability and RV function appear critical in the initial evaluation of a patient being evaluated with a presumptive diagnosis aPE. Thus, risk stratification algorithms have been proposed to help physicians identify high versus low-risk patients aPE in order to expedite diagnosis and treatment, as shown in Fig. 11.17 [148–152]. Even though current imaging modalities such as computed tomography and TTE might not offer true anatomic approximations of the RV (Fig. 11.18); they provide useful information that can be applicable in day-to-day practice to identify patients at risk of hemodynamic instability in aPE. Since hemodynamic stability is clearly discernible based on clinical examination; identification of high-risk features associated with significant RV strain and impending circulatory collapse can be somewhat challenging. Table 11.4 summarizes the most commonly associated variables currently used in the identification of abnormal RV strain.

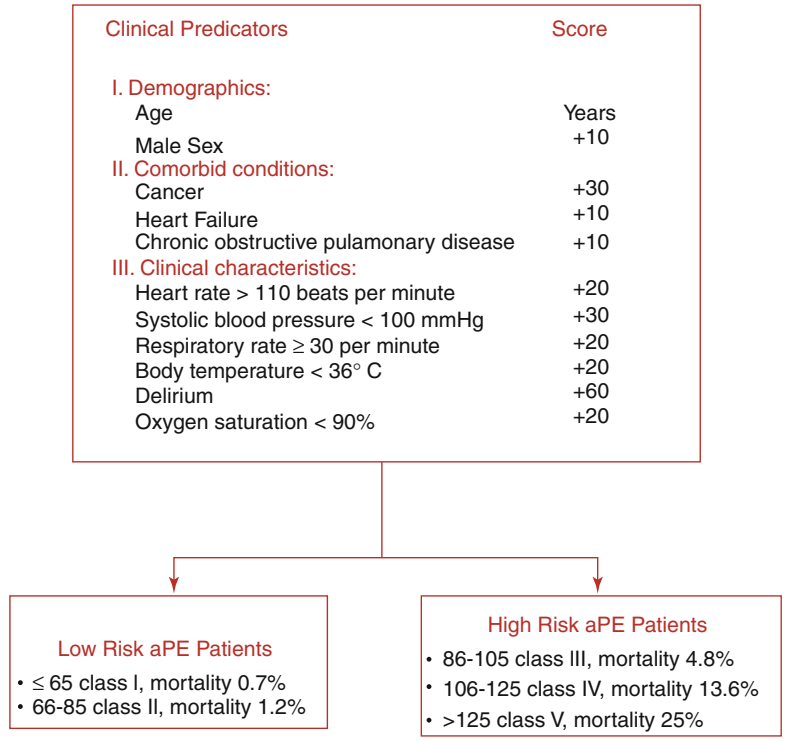


Fig. 11.17 Pulmonary embolism severity index (P.E.S.I) (Based on data from Refs. [148, 213])

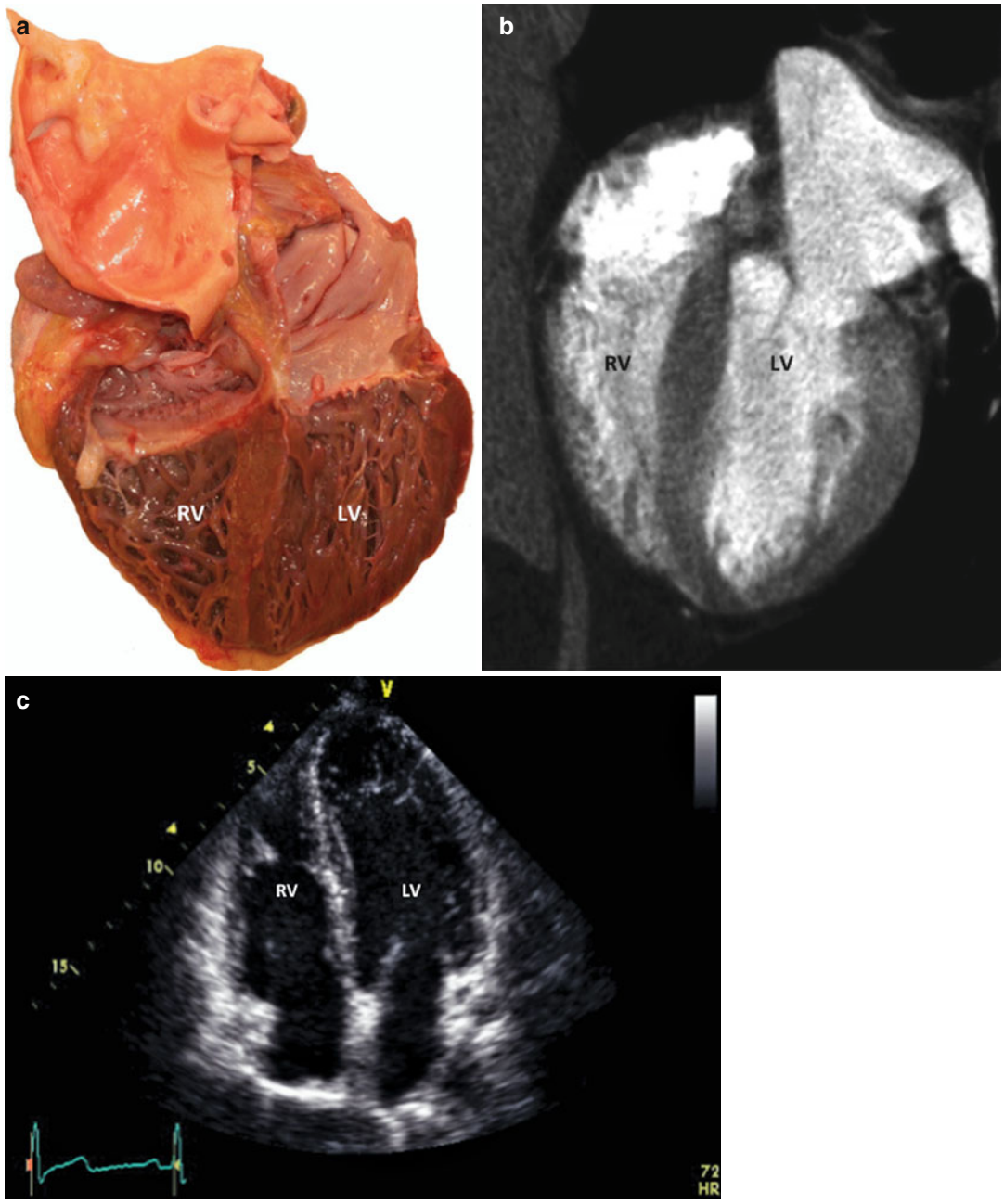


Fig. 11.18 (**a**) Open cut macroscopic view of heart in a four-chamber view depicting the thin-walled RV in relation to the LV. (**b**) Computed tomographic view of a representative four-chamber view showing the same anatomical relationship of the macroscopic specimen. Image shows corresponding reformatted four-chamber contrast-enhanced ECG-gated MDCT scan. (**c**) TTE representation of the RV and LV obtained from the same four-chamber apical view orientation as represented in (**a**) and (**b**) (**a** and **b**: Reprinted from Dupont et al. [155]. With permission from *American Journal of Roentgenology*)

Table 11.4 Common markers of RV strain

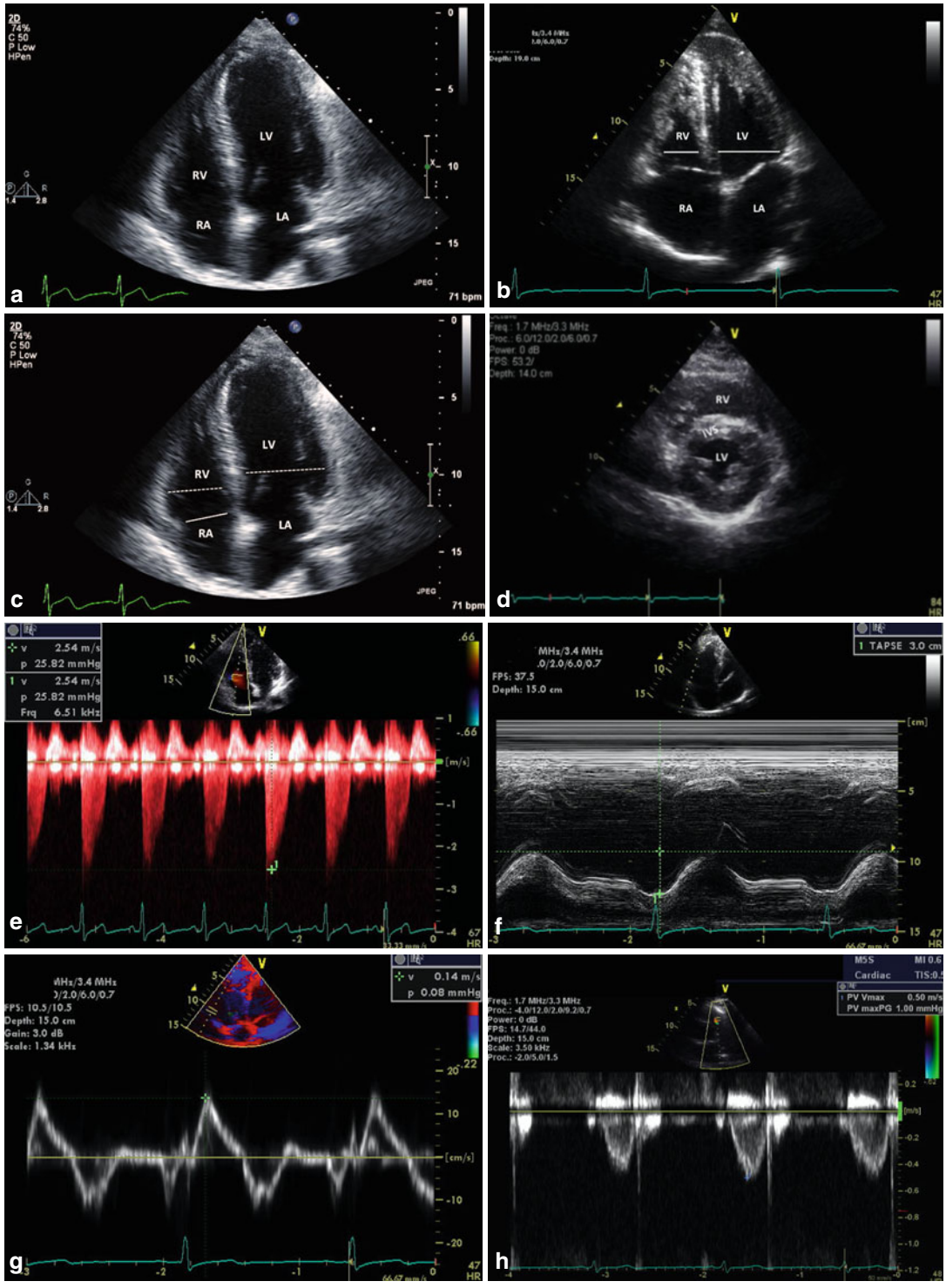
Common markers of RV strain	References
RV end systolic and end diastolic dilatation	[152, 153]
Increased RV to LV maximal diameter cavity ratio	[146, 152–158]
Dilated RV apex	[159]
Dilated tricuspid annulus	[152]
Presence of IVS flattening	[160–167]
Increased pulmonary artery pressures	[152, 168, 169]
Increased PVR	[116, 170–172]
Reduced measures of RV systolic function	[173–178]
Fractional area change	[152, 179]
TAPSE	[152, 180–186]
Tricuspid annular TDI systolic velocity	[152, 187]
Abnormal pulsed Doppler signal across RVOT	[188–191]
Reduced RVOT systolic excursion	[192, 193]
Regional RV wall motion abnormalities	[122, 194–196]
Reduced RV myocardial velocity generation	[152, 197, 198]
Reduced RV strain generation	[152, 199–205]
Presence of RV dyssynchrony	[199, 201–203]
Increased diameter of the superior vena cava	[178, 205, 206]
Reflux of contrast medium or color flow signal into the inferior vena cava	[207, 208]
Increased circulating levels troponin I in the absence of left heart abnormalities	[93, 209–214]
Increased circulating levels of brain natriuretic peptide	[213–219]
Abnormal electrocardiographic changes	[220–228]

Furthermore, Fig. 11.19 shows a pictorial representation of normal TTE RV findings that can be contrasted to abnormal RV strain findings as seen in Fig. 11.20.

For a long time ventilation-perfusion scintigraphy (V/Q scan) used to be the preferred imaging modality in patients suspected of having an aPE [229]. However, results of the prospective investigation of pulmonary embolism diagnosis (PIOPED) study demonstrated that clinical assessments combined with V/Q scans established the diagnosis or exclusion of aPE only for a minority of patients [230]. In addition, limited availability and long acquisition times allowed to the emergence of an alternative imaging technique, namely computed tomographic pulmonary angiography (CTPA) that has become the new standard of care and the imaging of choice in aPE patients [231–233]. CTPA not only has become more popular for its higher sensitivity and specificity; but also has been useful in patients with non-specific signs and symptoms of aPE in which an alternate diagnosis can be then provided [234]. Finally, CTPA was able to provide an unmatched piece of data that V/Q scans were unable to provide, information regarding RV strain or dysfunction.

As previously shown (Figs. 11.8 and 11.9), CTPA not only provides powerful clot burden information; but also RV information as seen in Fig. 11.21. Additional CTPA findings in aPE are shown in Figs. 11.22, 11.23, and 11.24. In contrast, Figs. 11.25 and 11.26 show examples in

Fig. 11.19 Pictorial representation of normal TTE markers of RV size and systolic function. (**a**) Representative end diastolic four-chamber apical frame showing normal relation of RV size when compared to the LV, The right (*RA*) and left (*LA*) atria are also seen. (**b**) End systolic four-chamber apical frame showing a normal size relationship between the RV and LV denoted by *straight white lines*. (**c**) Representative end diastolic four-chamber apical frame showing normal size relationship between RV and LV (*dashed lines*) as well as a normal tricuspid annular size, denoted by the *solid line*. (**d**) Representative short axis view at the level of the papillary muscles showing a normal relationship between RV and LV. Please note the crescent shape of the RV cavity at this level as well as the normal curvature of the IVS. (**e**) Representative tricuspid regurgitation signal that peaks early in systole with a peak velocity of 2.54 m/s. (**f**) Representative tricuspid annular plane systolic excursion from a normal patient with a maximum amplitude of 3 cm. (**g**) Representative tricuspid annular tissue Doppler imaging signal from a normal patient showing a normal systolic velocity of 0.14 m/s or 14 cm/s. (**h**) Representative pulsed Doppler signal across the pulmonic valve showing a normal RVOT envelope


LV
RV
RA
LA
71 bpm
a
b
c
d
e
f
g
h
1 TAPSE 3.0 cm

which CTPA was useful to distinguish acute from chronic PE cases. Finally, Fig. 11.27 lists potential patient- and technique-related artifacts as well as anatomic mimickers that are important to be recognized when using multidetector CT when evaluating patients with a presumptive diagnosis of aPE.

Even though the number of patients presenting with a suspicion of aPE over the last decade has increased; there has been a significant decrease in the incidence of CTPA aPE detected cases. In addition, there has been an increase in the diagnosis of non–thrombotic abnormalities

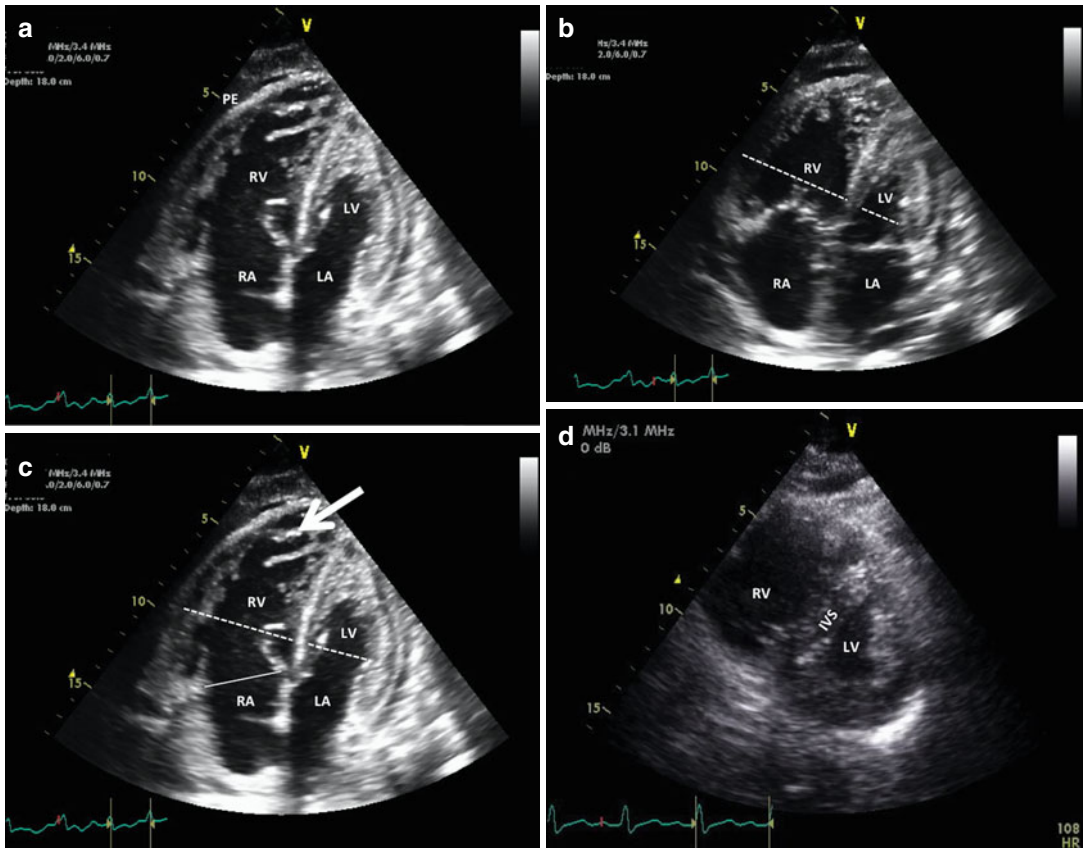


Fig. 11.20 Pictorial representation of abnormal TTE markers of RV strain. (**a**) Representative end diastolic four-chamber apical frame from a patient with a confirmed aPE showing a dilated RV in comparison to the LV, a pericardial effusion (*PE*) is also appreciated. (**b**) End systolic four-chamber apical frame showing a markedly dilated RV when compared to the LV denoted by the *dashed white lines*. (**c**) Representative end diastolic four-chamber apical frame showing a dilated RV when compared to the LV. In addition, a dilated tricuspid annulus is also seen (*solid line*). Furthermore, stretched RV apex is also noted by the *arrow* and can be easily contrasted to the normal RV apex seen in Fig. 11.18c. (**d**) Representative short axis view at the level of the papillary muscles showing a markedly dilated RV and s mall compressed LV. In addition, please note the flattened IVS that bows against the LV. (**e**) Representative tricuspid regurgitation signal that peaks late in systole with a velocity of 2.98 m/s in a patient with aPE. (**f**) Representative tricuspid annular plane systolic excursion from a patient with hemodynamically significant aPE that is hypotensive. Please note the significant reduction in the maximum amplitude of less than 1 cm. (**g**) Representative tricuspid annular tissue Doppler imaging signal from a patient with a hemodynamically significant aPE showing significant reduction in the systolic velocity of 5 cm/s. (**h**) Representative pulsed Doppler signal across the pulmonic valve showing a markedly abnormal RVOT envelope from a hypotensive patient with a confirmed aPE please note the narrow width (*lines*) of the signal and the mid-systolic indentation in the signal (*arrows*)

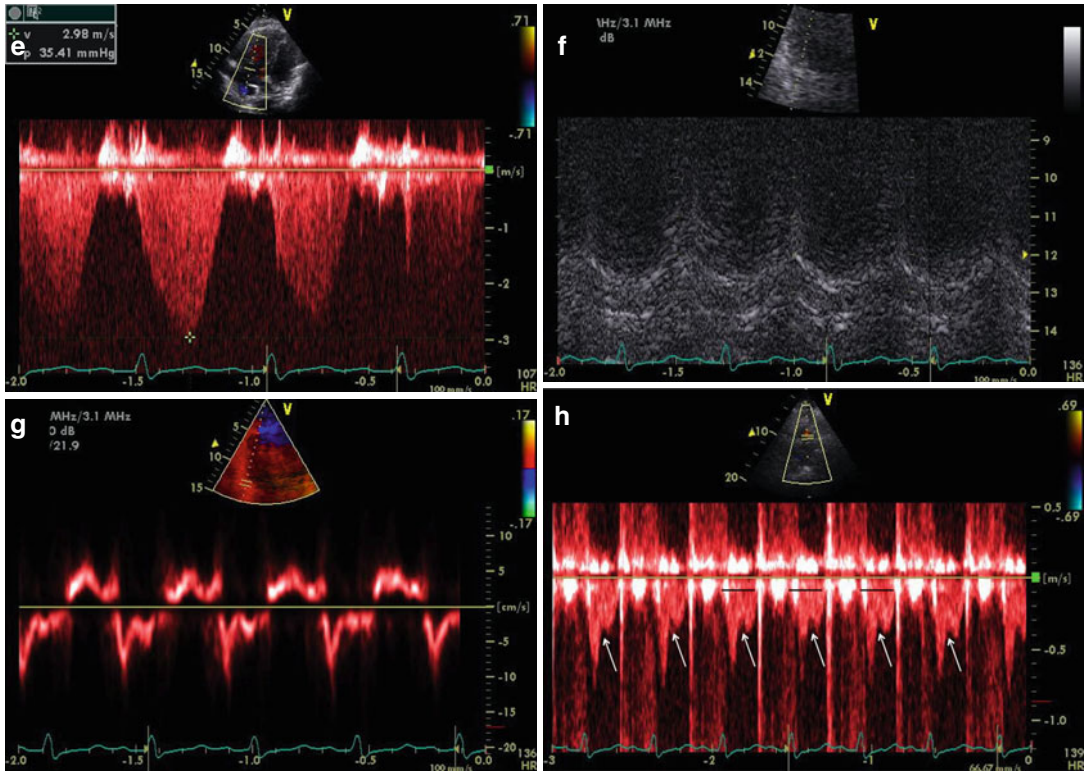


Fig. 11.20 (continued)

[235–238]. Furthermore, newer scanners that use dual energy CT (DECT) or dual-source scanners allow identification of perfusion defects in the adjacent lung parenchyma without the need for direct identification of peripheral endoluminal clots located within subsegmental or more distal branches [233, 239]. However, as with any radiologic imaging modality there are legitimate concerns for substantial radiation exposure, particularly in children, young adults and females requiring appropriate triage to prevent unnecessary radiation exposure.

As a result, there has been a genuine effort to resurrect TTE as a useful imaging modality in the initial evaluation and follow-up of aPE patients; despite past skepticism regarding the predictive value of TTE in assessing RV dysfunction among hemodynamically stable aPE patients [240, 241]. However, the use TTE in aPE is now well validated [145, 242]. Obviously, to become a serious imaging contender, TTE has to offer critical data that surpasses rudimentary information based on subjective interpretation of RV size and wall motions, abnormal IVS motion, presence of tricuspid regurgitation, and lack of collapse of the inferior vena cava during inspiration [241]. Even though not comparable to TTE, it is important to recognize the value that venogram-detected DVT has in the diagnosis and management. For example, the latter modality has been reported to detect DVT in 70–90 % of aPE cases; [243–245] however, documentation of DVT by ultrasonography only occurs in <50 % of aPE patients [243, 246, 247]. Hence, absence of DVT by ultrasound does not preclude aPE diagnosis while the presence of DVT by ultrasound is not confirmatory of aPE [143]. Thus, the use of ultrasound in the aPE setting might be

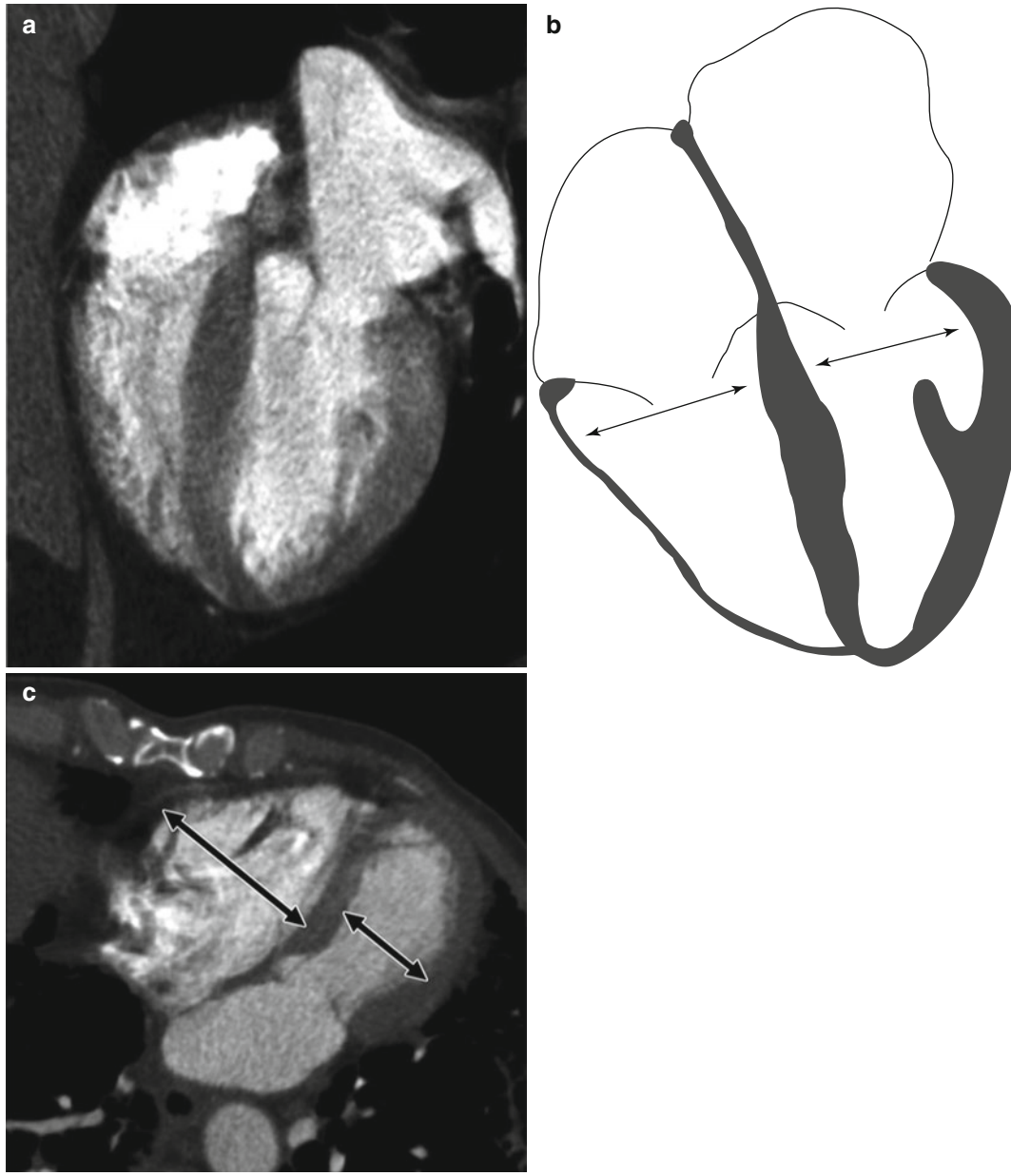


Fig. 11.21 (**a**) CT view showing a reformatted normal four-chamber contrast-enhanced ECG-gated MDCT scan. (**b**) Diagram of four-chamber view shows how to measure ratio of right ventricle (*longer arrow*) to left ventricle (*shorter arrow*): right and left ventricular dimensions are identified as maximal distance between free ventricular wall and interventricular septum, perpendicular to long axis of heart, at level of mitral and tricuspid valves. (**c**) Case of a 76-year-old man with idiopathic pulmonary fibrosis. Reformatted four-chamber non-ECG-gated contrast-enhanced MDCT scan shows right ventricle dilatation, with ratio of right ventricle (*longer arrow*) to left ventricle (*shorter arrow*) measured at 1.5 (Reprinted from Dupont et al. [155]. With permission from *American Journal of Roentgenology*)

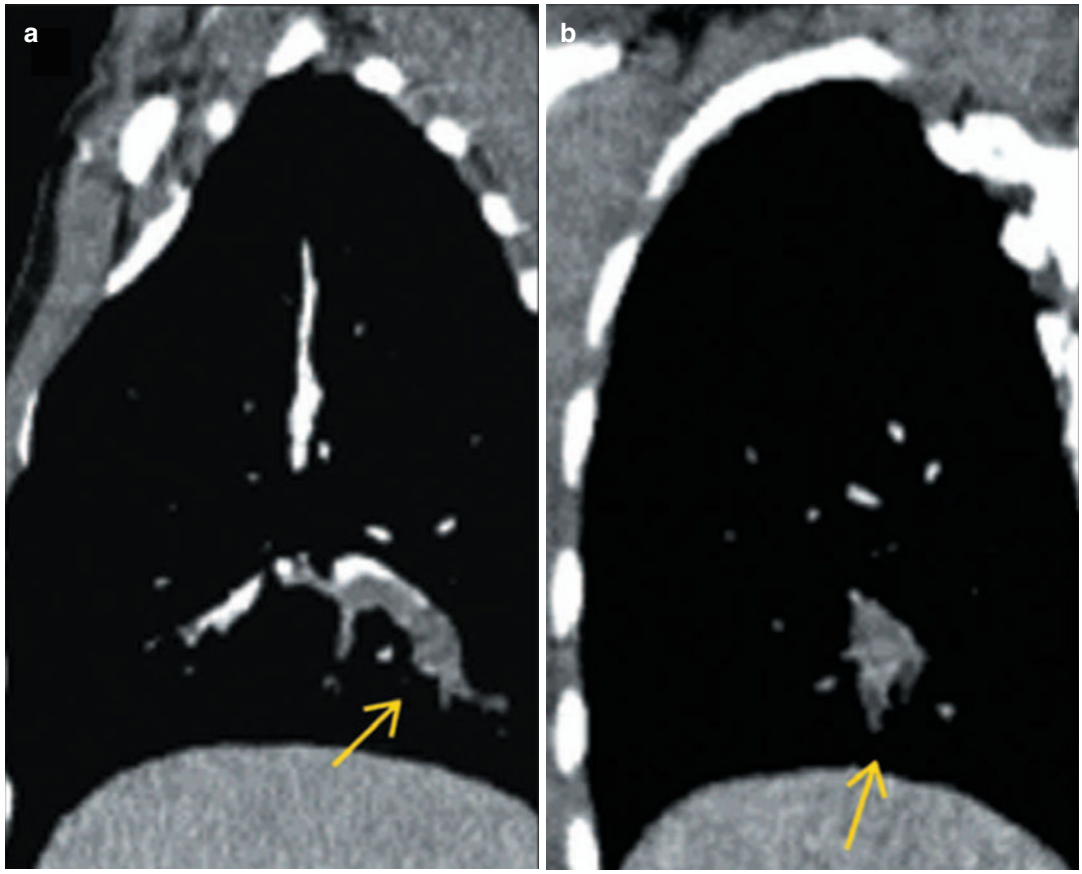


Fig. 11.22 (**a**) Sagittal and (**b**) coronal reformatted images in a 56-year-old man with chest pain and dyspnea reveal thrombosed lower lobe posterior basal segmental artery branches. Notice the relative associated abnormal vascular enlargement (*arrows*) as compared with the adjacent patent vessels (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

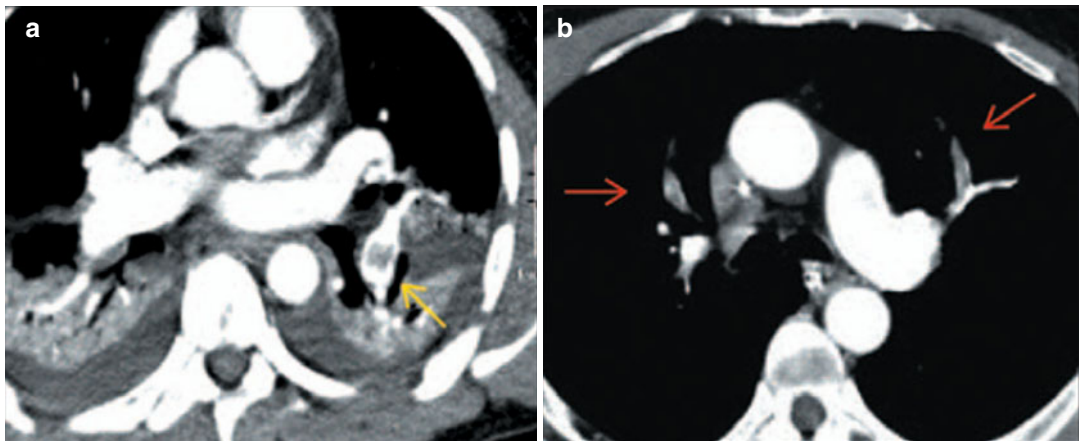


Fig. 11.23 (**a**) The donut sign in the left lower lobe pulmonary artery (*arrow*) and (**b**) tram track sign (*arrows*) in bilateral upper lobe segmental pulmonary arteries in cases of acute pulmonary emboli (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

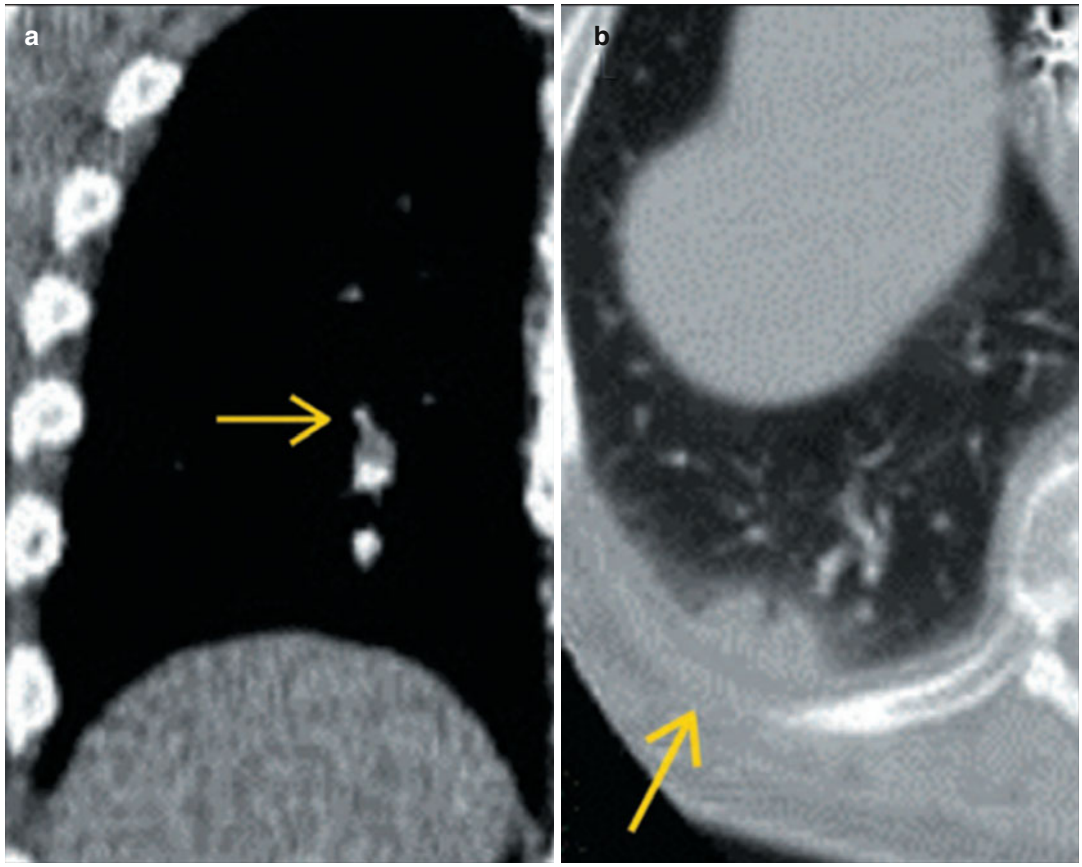


Fig. 11.24 (**a** and **b**) Acute right lower lobe subsegmental pulmonary embolus (*arrows*) in a 60-year-old man with peripheral pulmonary infarct (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

truly limited to assist in the decision of starting anticoagulation or placing an inferior vena cava filter [143].

Even though life-threatening aPE is dependent on clot burden as well as the underlying cardiac reserve; this relationship becomes less transparent as some patients with a massive aPE but excellent cardiac reserve might behave similarly to patients with submassive aPE but compromised cardiac reserve [248, 249]. Nonetheless, untreated aPE is fatal in up to 30 % of patients [140, 250–252]. Since hemodynamic stability appears to be more dependent on RV function than the magnitude of clot burden in aPE, particularly within the first hour; confirmation and assessment of mechanical stability of RV function are promptly required once this diagnosis is entertained (Fig. 11.28) [176, 205, 253–274].

New Frontiers in the Assessment of Right Ventricular Function in Acute Pulmonary Embolism

Although it is clear that the integrity of RV function plays a pivotal role in determining prognosis after aPE; [100, 141, 143, 176, 205, 253–274] experimental data using healthy dogs has revealed that acute embolization using microbead injections induces dramatic stiffening of the

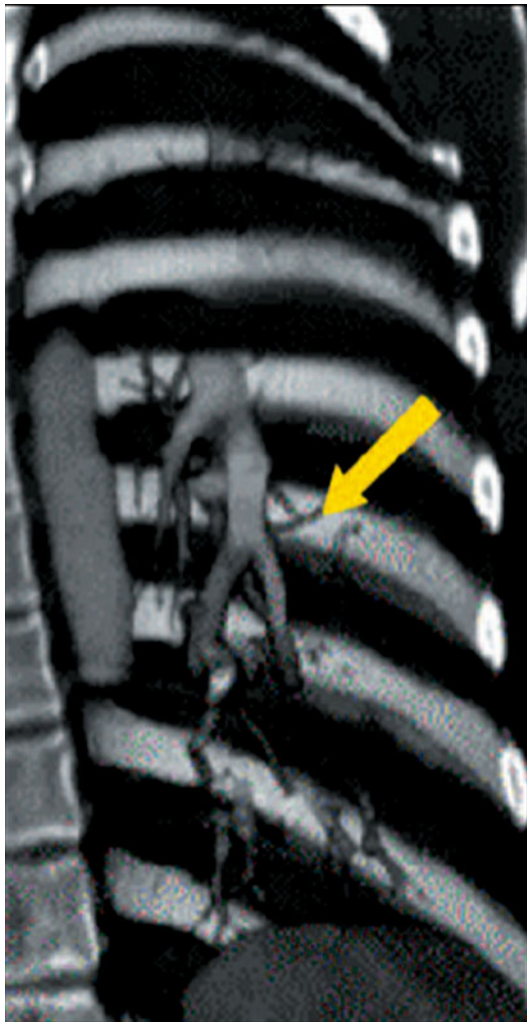


Fig. 11.25 A 56-year-old man with a history of treated pulmonary embolism in the left lower lobe segmental arteries presented with acute chest pain. No evidence of acute embolism was seen. This volume-rendered coronal image reveals an abrupt cutoff in the left lower lobe segmental arteries (*yellow arrow*) with visualization of dilated bronchial collaterals (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

PA leading to increased RV stroke work [275]. In this particular model, the use of both invasive and magnetic resonance imaging measures to assess PA stiffness and RV systolic function revealed that the RV was able to shift its working conditions, preserve function, and maintain hemodynamic coupling with the PA despite the acute insult [275]. Still, the increased RV stroke work occurred at the expense of a reduction in RV efficiency [275]. This interaction between RV and PA has clarified our understanding of RV function and it is now clear that RV systolic function cannot be studied in isolation, as both RV and PA work in series [276]. Therefore, it is clear that the evolution of RV pathology from normal to a decompensated state parallels the evolution of pulmonary vascular pathology; hence studying the RV and the PA as a unit will be critical to understanding the true performance of the RV [276].

RV-PA coupling is critically important and this relationship is best demonstrated by changes in hydraulic load occurring in the setting of PA stiffening as it will occur in aPE. As the RV is met with increased hydraulic wave reflection, its workload is greater to maintain forward flow. It is important to remember that to up one half of the hydraulic power in the main PA is contained in the pulsatile components of flow. Thus, acute changes in PA impedance, a measure of opposition to these pulsatile components of flow, would be crucial; though unrealistic unless they are measured in animal models. Furthermore, elastic properties of the pulmonary vasculature are also vitally important as the heart would not be able to generate forward flow without them [277–279].

From a mechanistic perspective, RV ejection is dependent on PVR as well as on the oscillatory or pulsatile component of flow that is dissipated as wasted energy through the PA system with each RV ejection [279–282]. Hence, PA elasticity is crucial to maintain RV efficiency [279–282]. Since hemodynamic instability unmistakably predicts adverse outcomes and 30-day mortality in aPE patients when RV dysfunction is confirmed; a proposed scheme of high-risk features for the potential development of hemodynamic instability in aPE is listed in Fig. 11.29 [176, 205, 253–274, 283–287].

Identification of the McConnell sign, regional RV dysfunction that spares the apex, was found of having 77 % sensitivity and 94 % specificity

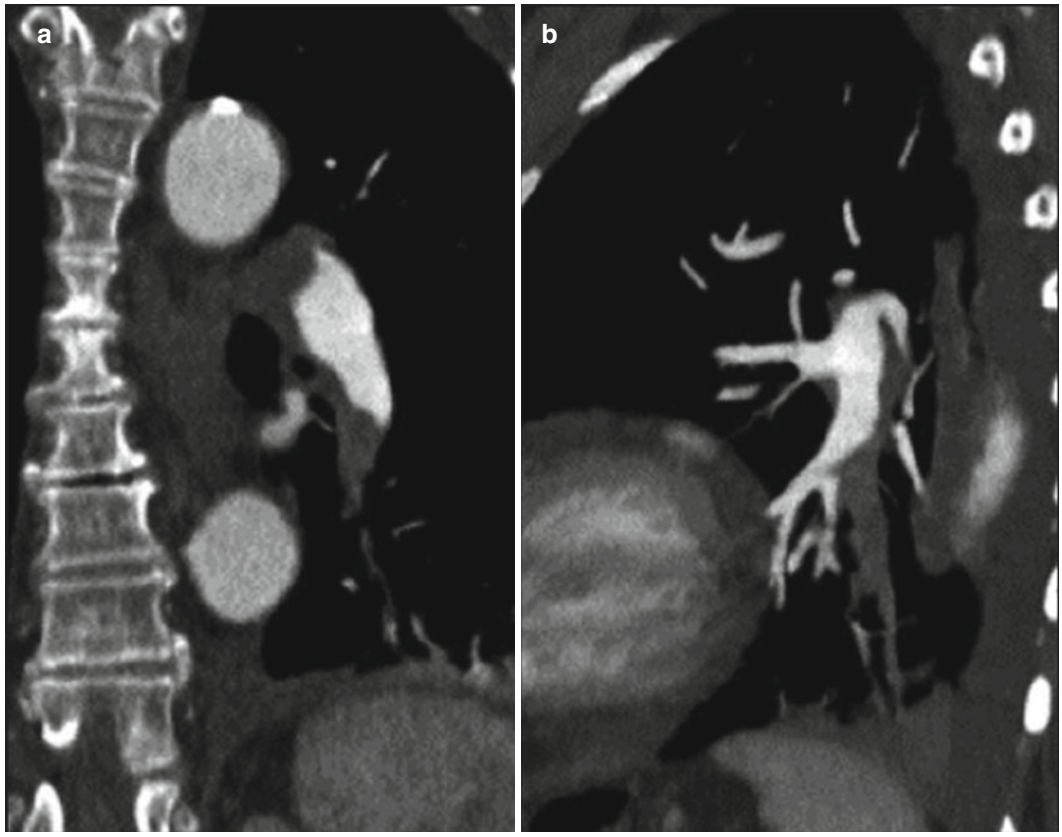


Fig. 11.26 (**a**) Coronal and (**b**) sagittal reconstructions in a 70-year-old man with a history of bilateral acute pulmonary embolism and a 6-month history of warfarin treatment. These scans show chronic pulmonary emboli forming obtuse angles with the vessel wall in the left lower lobe pulmonary artery and its posterior segmental branch (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

Artifacts and Mimics on Multidetector Ct for aPE

- **Patient-related artifacts:**
  - Respiratory motion
  - Body habitus
  - Flow related Vascular resistance
- **Anatomic pathologic mimics:**
  - Peribronchial lymph node
  - Unopacified veins
  - Mucus-filled bronchi
  - Perivascular edema
- **Technique-related artifacts:**
  - Poor timin
  - Window setting
  - Patial voluming
  - staristep

Fig. 11.27 List of potential patient- and technique-related artifacts as well as anatomic mimickers on Multidetector CT for aPE (Reprinted from Chhabra et al. [332], Copyright 2007, With permission from Anderson Publishing Ltd)

for aPE diagnosis with a positive predictive value of 71 % and a negative predictive value of 96 % was initially thought to be a useful TTE marker to diagnose aPE [194]. However, McConnell sign was later found unreliable, as similar abnormalities were also seen in patients with an acute RV infarct [195]. A global rather than a regional RV abnormality in aPE was subsequently challenged when analyzing myocardial deformation with the use of velocity vector imaging. This imaging tool identified a significant reduction in global myocardial strain generation of all main RV chamber segments, including the RV apex [288]. However, involvement of the RV apex during aPE and its role in overall prognosis has not been fully elucidated [204, 288, 289]. A representative velocity

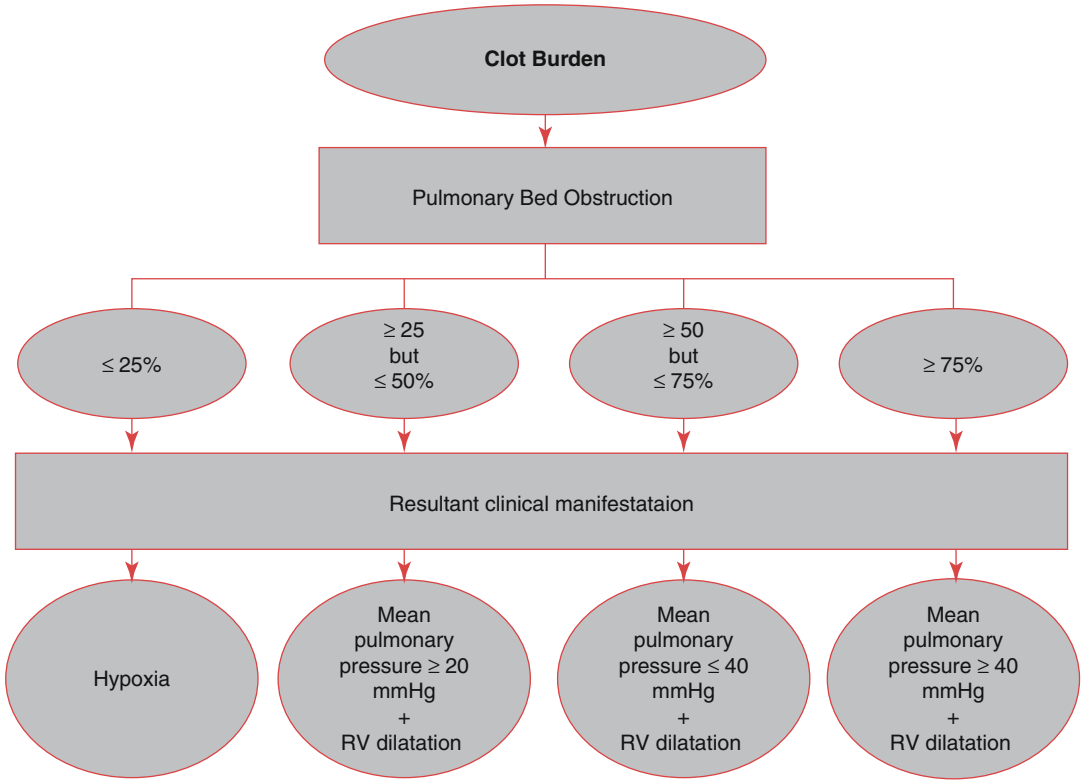


Fig. 11.28 Diagrammatic representation of the relationship between clot burden and approximate degree of pulmonary bed obstruction and corresponding clinical effect in the absence of previous cardiopulmonary history and normal RV reserve

vector imaging sample from a normal RV showing normal longitudinal strain of all segments, including the RV apex is shown in Fig. 11.30. In sharp contrast, a representative velocity vector image is also shown from a patient with confirmed aPE (Fig. 11.31) shows significant reduction in overall systolic deformation from all segments, a very abnormal RV apical segment signature and significant temporal dyssynchrony among all six RV segments when compared to the well-coordinated peaking of all RV segments in Fig. 11.30.

Furthermore, speckle tracking strain imaging not only has been shown to be extremely accurate and reproducible, but also extremely useful in identifying subtle wall motion as well as systolic function abnormalities [290–293]. Tissue Doppler and speckle tracking imaging have been invaluable for assessing myocardial mechanics in chronic pulmonary hypertension; [136, 198, 199, 294–296] especially in quantifying global as well as segmental longitudinal RV peak systolic strain and defining the presence of RV dyssynchrony in aPE patients [203]. Moreover, these abnormalities in RV heterogeneity and dyssynchrony resolve after the acute aPE insult and return to normal values [203]. Thus, speckle tracking as a portable, accurate and reproducible imaging modality holds particular promise in offering prompt and reliable information that not only can be used at the bedside for diagnostic purpose; but also for follow-up of aPE patients once appropriate therapy is instituted. Representative speckle tracking images from a normal individual (Fig. 11.32) and from a patient with confirmed aPE (Fig. 11.33) are shown.

In order to link the RV-PA unit with the LV, it will then be useful to review our current under-

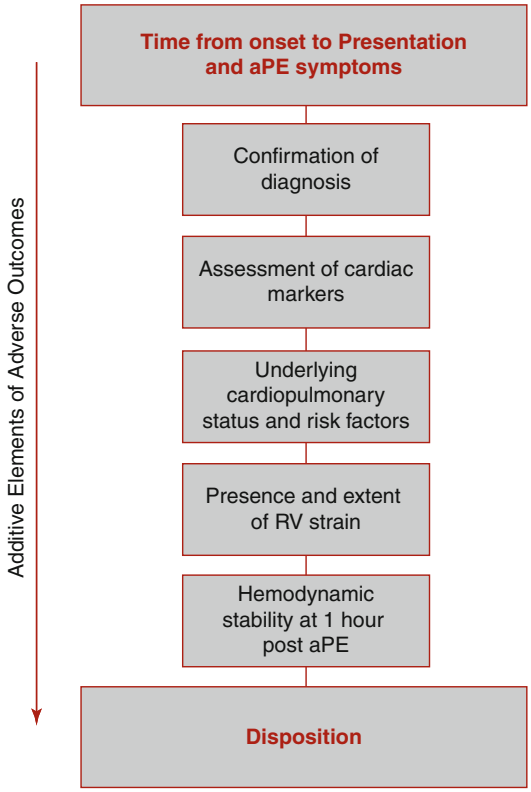


Fig. 11.29 Schematic diagram demonstrating high-risk features on admission that helps in the identification of poor prognosis in aPE

standing of myocardial fiber direction. As proposed by the late Torrent-Guasp, if indeed there is a continuum of subepicardial RV muscle fibers forming a plane along the posterior LV to the region of the left fibrous trigone and these fibers do descend from the left fibrous trigone to the LV apex; [297, 298] then whichever process affects the RV will certainly impact the LV. It has been shown that potential traction on this muscular band by RV dilatation adversely affects basal LV rotation in cases of chronic PH [136]. Whether this represents a functional continuity between the ventricles or is merely a static anatomical entity mediated by the IVS remains largely unknown. Therefore, it is reasonable to believe that similar interactions do occur with sudden increase in RV afterload in aPE. In addition, bowing of the IVS towards the LV has been shown to alter global LV kinetics in the rat model, even if intrinsic LV systolic function is normal [299]. In humans, aPE has shown to induce reversible global LV dysfunction; nonuniformity of LV contractility in the radial, longitudinal, and circumferential directions; and discoordination of radial LV wall motion [203]. Once again, all these abnormalities were found to be reversible and normalized with treatment after patient stabilization [203]. Recent evidence in experimental animal models suggests that aPE mainly impairs LV performance by primarily altering septal strain and apical rotation [300]. Similarly, even though mainly recognized in case of human chronic PH, abnormal LV diastolic function might be likely affected by the similar mechanisms during aPE [136, 137, 201, 301]. Unfortunately, to date none of these mechanisms that directly affect LV diastolic function in cases of aPE have not been yet clinically investigated.

Finally, identification of an altered RVOT Doppler signal has been shown useful not only in characterizing PH severity, but also in overall RV systolic performance [188–191, 302]. RVOT systolic excursion has been useful in estimating global impairment in RV contractility as well as acute hemodynamic derangement [192]. Likewise, the ratio between main chamber RV fractional area change and RVOT systolic excursion appear to be markedly abnormal in patients with CTPA proven bilateral proximal embolus causing aPE and is also found to be the best echocardiographic variable in distinguishing aPE from chronic PH [193]. Representative RVOT images from a normal patient (Fig. 11.34) and a patient with a confirmed aPE (Fig. 11.35) are shown.

After Acute Pulmonary Embolism Diagnosis

It summary, it is clear that certain clinical conditions predispose to the development of DVT and also aPE; however, these conditions are also found in otherwise healthy people, and aggressive investigation for potential pulmonary embolism is likely to find an incidental clot without clinical consequence [303]. In fact, in up to 90 % of autopsy reports an identifiable new or old PE might be found, particularly if microscopic examination on numerous blocks of lung tissue

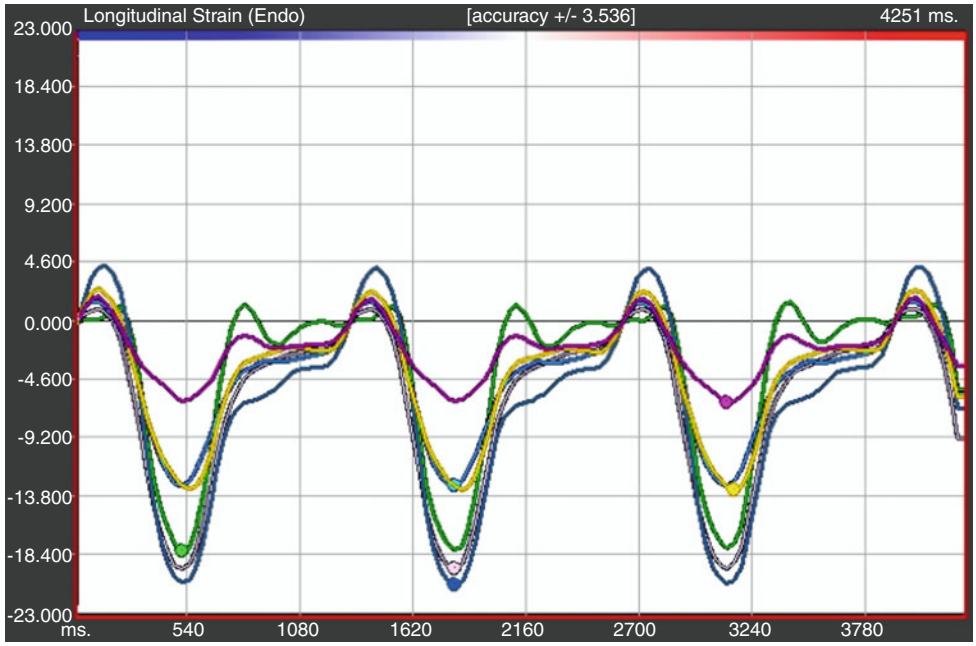


Fig. 11.30 Representative velocity vector imaging from a normal RV showing normal longitudinal strain curves from all six segments. Individual segment recognition is a follows: RV free wall annulus side is *green*; Mid RV free wall is *lilac*; apical side of the RV wall is *light blue*; IVS base is *dark blue*; mid IVS is *yellow* and apical side of the IVS is *purple*. Please note that all six segments have a normal negative deflection in systole with normal peak values of approximately −20 %. Specifically, note the normal movement of the RV apical segment

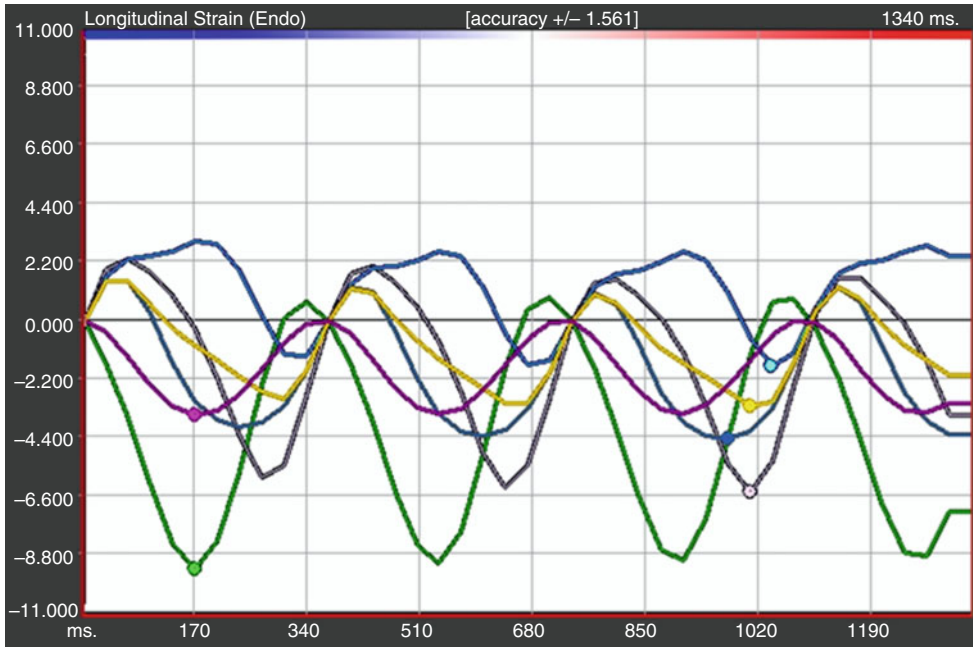


Fig. 11.31 Representative velocity vector imaging from an aPE patients showing abnormal longitudinal strain curves from all six segments. Individual segment recognition is similar as noted for Fig. 11.28. Please note that all six segments have significant reduction in overall systolic deformation. Specifically, note the very abnormal RV apical segment signature. Finally, a significant amount of dyssynchrony is also noted as time to peak of all six-segments is different when compared to the well-coordinated peaking of all segments in Fig. 11.28

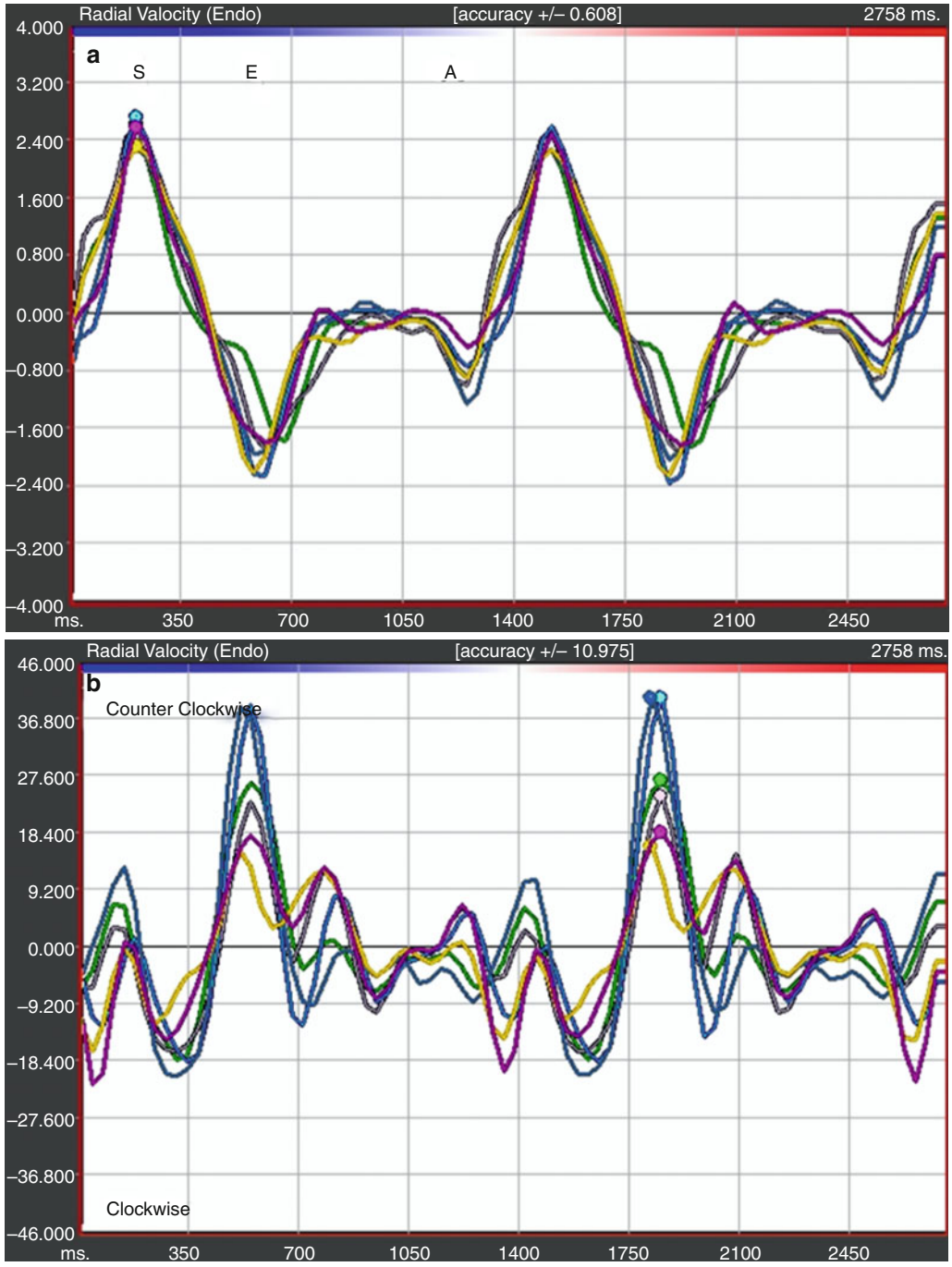
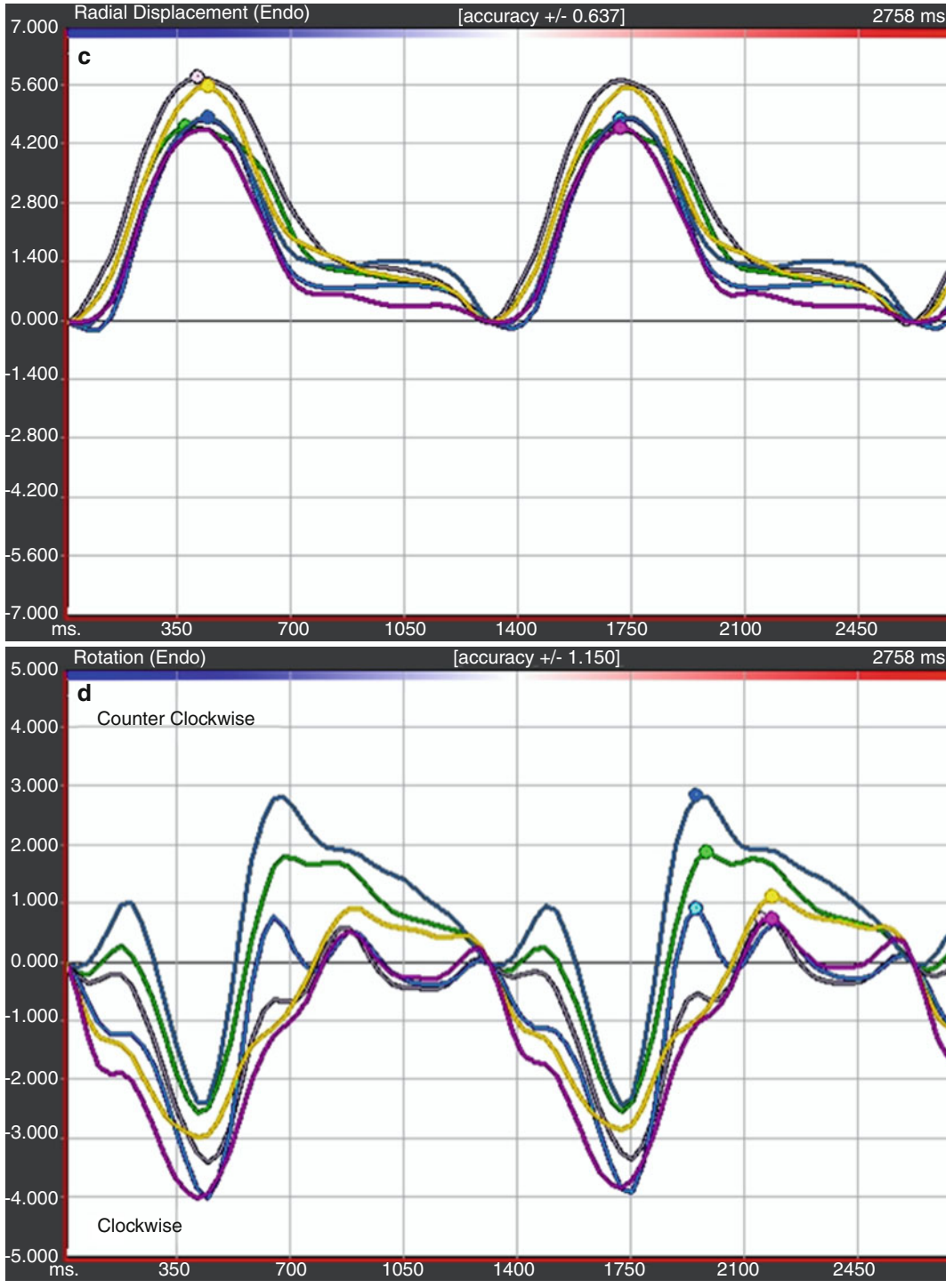


Fig. 11.32 Representative LV speckle tracking imaging signals obtained from the short axis view at the level of the papillary muscles from an individual with normal biventricular systolic function. Color coded representation is similar for all images and the *green* corresponds to the anterior septum; *light purple* to anterior wall; *light blue* to the lateral wall; *dark blue* to the posterior wall; *yellow* to the inferior wall; and the deep purple to the inferior septum. (**a**) Radial velocity is shown for all six segments with the systolic component represented by *S*, early diastole by *E* and late diastole by *A*. (**b**) Representative rotation rate showing normal synchronous counter clockwise as well as clockwise rotation of all segments. (**c**) Normal radial displacement curves of all six LV segments. (**d**) Representative radial rotation displacement curves showing normal synchronous counter clockwise as well as clockwise rotation of all segments. (**e**) Normal radial strain curves for all six LV segments. (**f**) Normal circumferential strain curves for all six LV segments



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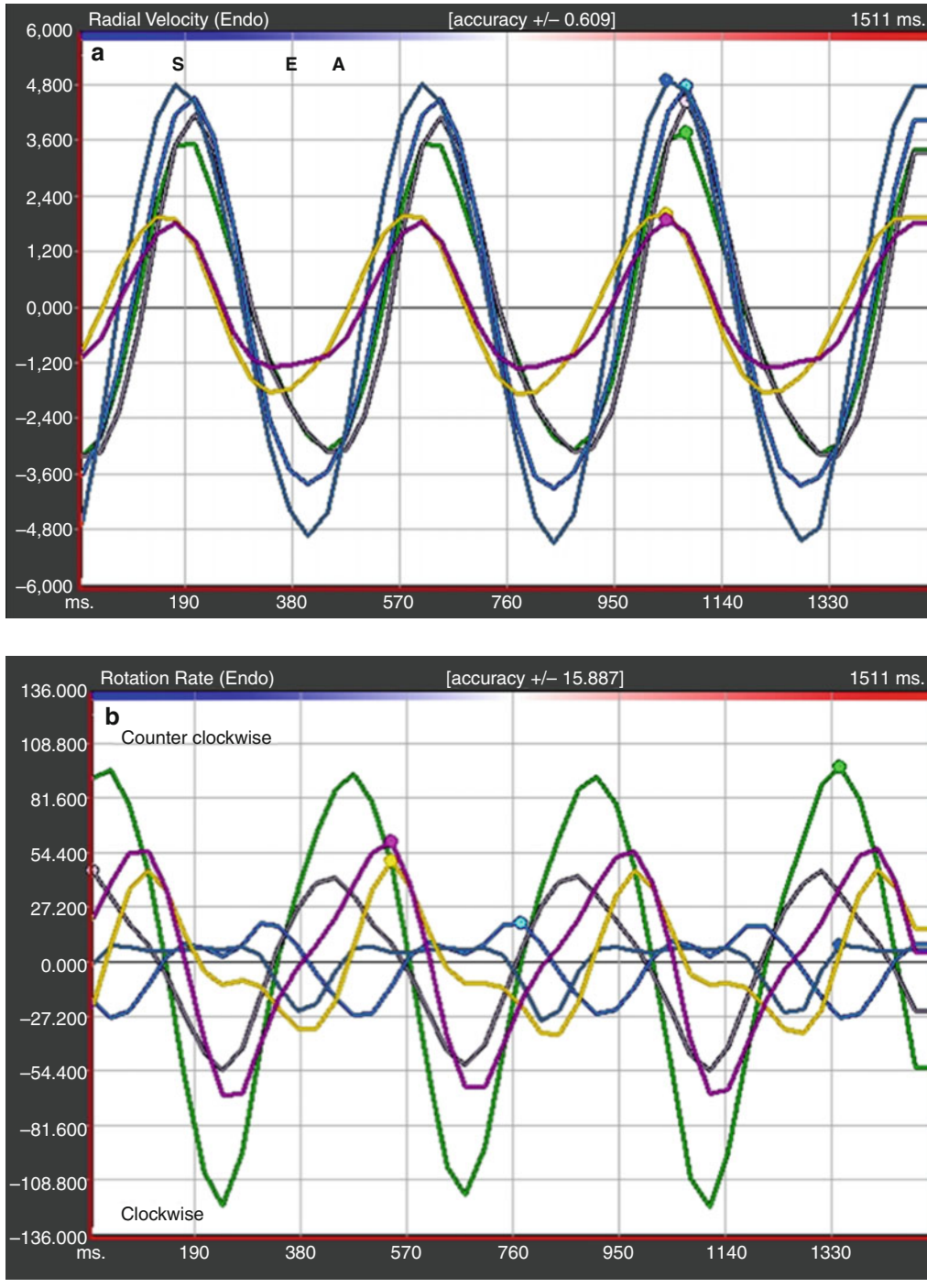
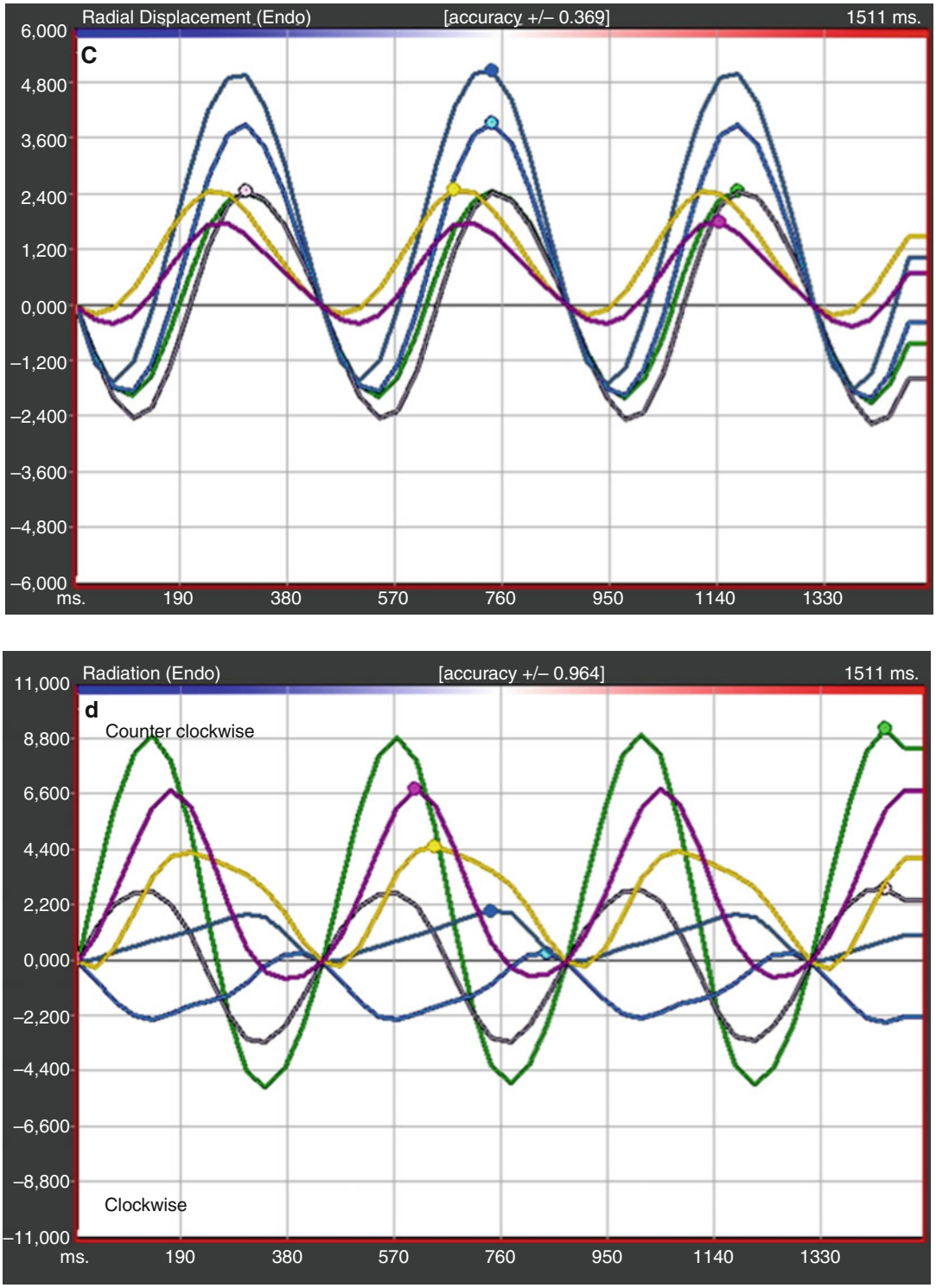


Fig. 11.33 Representative LV speckle tracking imaging signals obtained from the short axis view at the level of the papillary muscles from a patient with confirmed aPE and RV dysfunction and abnormal strain. Color coded representation is similar for all images as listed in Fig. 11.30. *Green* corresponds to the anterior septum; *light purple* to anterior wall; *light blue* to the lateral wall; *dark blue* to the posterior wall; *yellow* to the inferior wall; and the *deep purple* to the inferior septum. (**a**) Radial velocity is shown for all six segments with the systolic component represented by *S*, early diastole by *E* and late diastole by *A*. (**b**) Representative rotation rate showing dyssynchronous counter clockwise and clockwise rotation abnormalities of all segments. (**c**) Abnormal radial displacement curves of all six LV segments. (**d**) Representative radial rotation displacement curves showing dyssynchronous counter clockwise and clockwise rotation abnormalities of all segments. (**e**) Abnormal radial strain curves for all six LV segments. (**f**) Abnormal circumferential strain curves for all six LV segments



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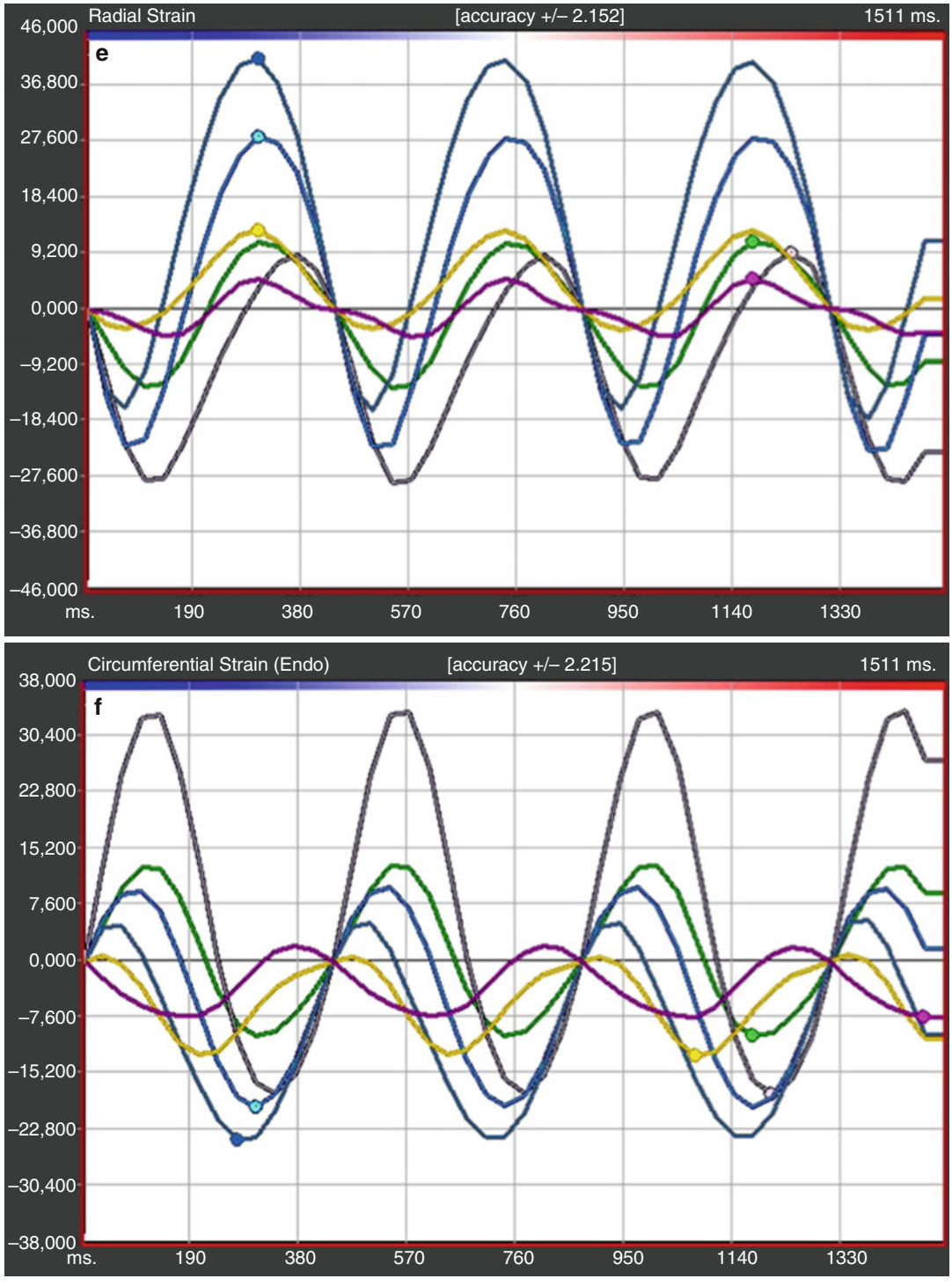

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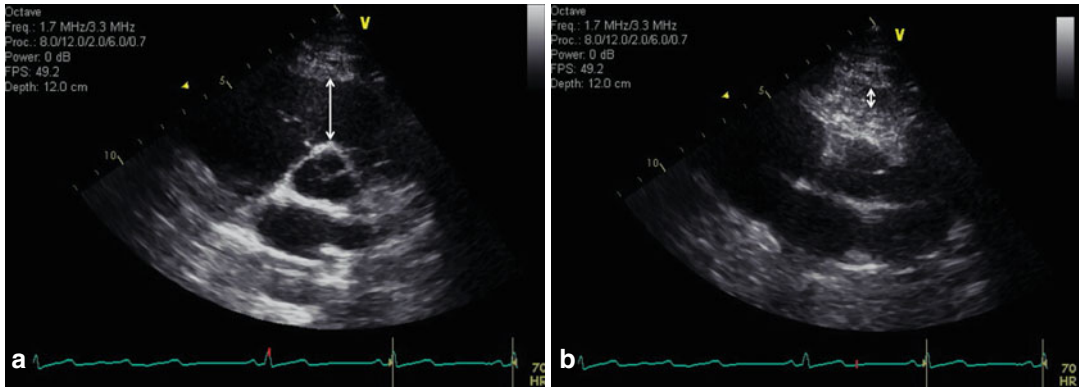

Fig. 11.34 Representative short axis views at the level of the aortic valve demonstrating (**a**) RVOT end diastolic length and (**b**) end systolic length by the *white arrows* from a normal patient demonstrating excellent RVOT systolic function (RVOT end diastolic length − RVOT end systolic length)/RVOT end diastolic length × 100

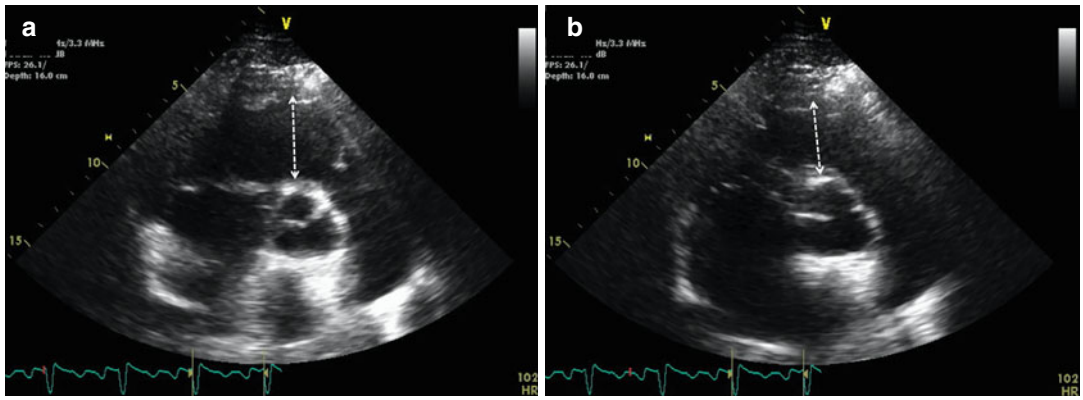

Fig. 11.35 Representative short axis views at the level of the aortic valve demonstrating (**a**) RVOT end diastolic length and (**b**) end systolic length by the *dashed white arrows* from a patient with confirmed aPE. No significant difference between RVOT end diastolic and end systolic lengths corresponding to a reduced RVOT systolic excursion based on the formula listed in the figure legend of Fig. 11.34

[304–306]. Therefore, it becomes sometimes difficult to determine how often any of these clots are clinically significant. Similarly, the advent of advanced diagnostic modalities has allowed detection of very small thrombi of otherwise unknown clinical significance; [303] particularly, when healthy outpatients present with severe pleuritic chest pain. Data has suggested that these patients should not undergo evaluation for aPE if their PaO_2 and respiratory rate are normal and if there is a low suspicion for DVT, even if these patients have a confirmed aPE, particularly if the clot is of dubious clinical significance [307]. Likewise, it has been suggested that anticoagulation could be safely withheld in patients with pulmonary embolism, as long as serial noninvasive lower-extremity study results are negative and cardiopulmonary reserve is adequate [308].

Given the likelihood that the pulmonary vascular clot burden is small in aPE patients with normal cardiopulmonary function, withholding pharmacologic anticoagulation and allowing the natural fibrinolytic processes to dissolve the clot has merit. In patients who survive an aPE, in vivo fibrinolysis begins almost immediately and continues for weeks to months. Other mechanisms contribute to the restoration of pulmonary blood flow, including clot fragmentation; changes in the location, situation, and shape of the clot; and recanalization through the thrombus [305, 306, 309, 310]. As a result, total resolution of small and large clots is possible, even in the absence of

definitive therapy such as fibrinolysis or embolectomy. The rate and extent of clot dissolution varies from person to person. It depends partially on the size of the thrombus [311–313]. Complete or near-complete recovery of pulmonary blood flow is also more likely in patients without underlying cardiovascular disease [313–315]. Obviously, the degree to which a certain patient with aPE will undergo thrombus regression is not something that the emergency physician can predict. aPE represents a spectrum of disease in regard to presentation and eventual resolution. Likewise, the mortality of untreated disease probably has significant variations, depending on the clinical circumstances.

However, current guidelines suggest prompt initiation of anticoagulant treatment. In fact, therapy should be initiated in all patients with either high or intermediate clinical probability of aPE, even when a definitive imaging diagnosis is not available [242, 316, 317]. It is clear that hypotensive patients and those with severe RV dysfunction, thrombolytic therapy has been shown to effectively resolve the thrombo-embolic obstruction and consequently reduce PVR, increasing RV cardiac output [316, 317]. Approved lytic agents include Streptokinase, Urokinase (not available in the United States), Alteplase, Reteplase (off-label use), and Tenecteplase (off label use). Currently, more than 90 % of aPE patients seem to respond favorably to thrombolysis based on both clinical and echocardiographic data within the first 36 h [316, 317] Even though the greatest benefit of thrombolytic therapy is observed when treatment is initiated within 48 h of symptom onset; thrombolysis has been used in patients who have presented with symptoms for 6–14 days prior to admission [141]. In those cases where there are absolute contraindications to thrombolysis or if thrombolysis has been used and failed; pulmonary embolectomy or catheter-based reperfusion can be considered in specialized centers [318–322].

In contrast, treatment of normotensive patients with subclinical hemodynamic impairment as detected by echocardiography, cardiac biomarkers or CTPA is somewhat less clear as some studies have shown a higher mortality rate, but this has not be proven to be a consistent finding in all case series [323, 324].

In summary, current recommended algorithm for risk stratification, diagnostic and treatment strategy to assess aPE is shown in Fig. 11.36. As

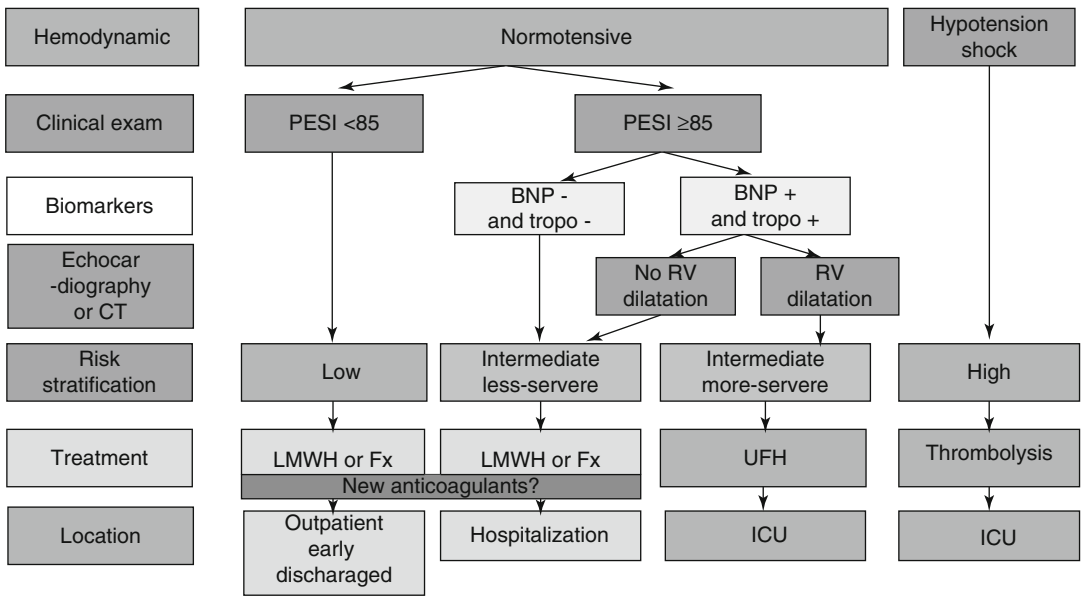

Fig. 11.36 Risk stratification, diagnostic and treatment algorithm for patients ith aPE. *BNP* brain natriuretic peptide, *Fx* fondaparinux, *ICU* intensive care unit, *LMWH* low molecular weight heparin, *PESI* pulmonary embolism severity index, *RV* right ventricle, *tropo* troponin, *UFH* unfractionated heparin (Reprinted with from Penaloza et al. [242]. With permission Wolters Kluwer Health)

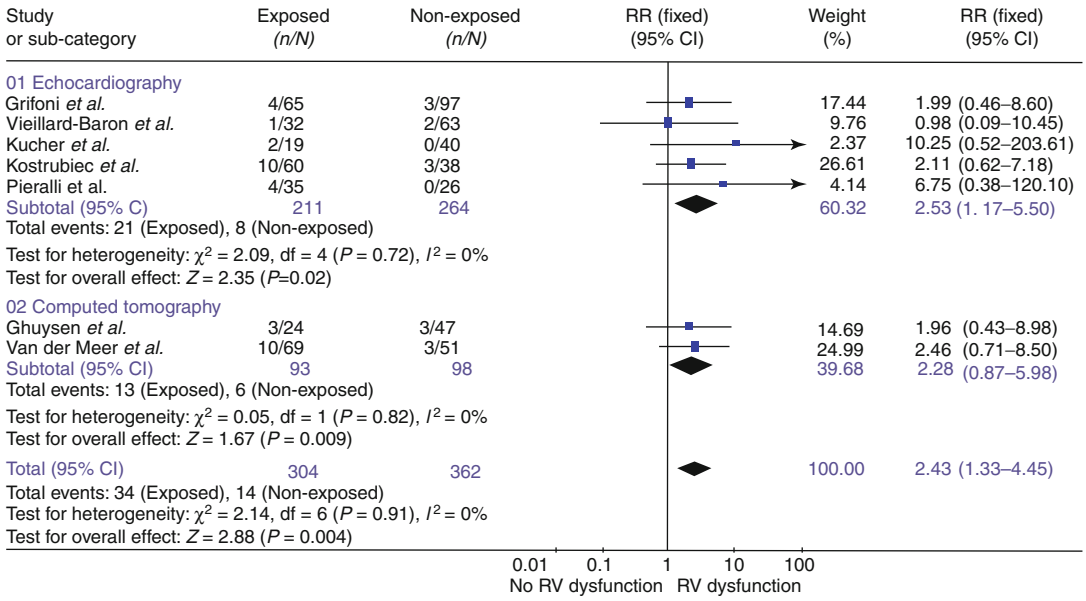

Fig. 11.37 Prognostic value of right ventricular dysfunction for mortality in patients with pulmonary embolism without shock. The outcome was in-hospital mortality for all studies, except two: (*) 40-day mortality and (†) 90-day mortality (Reprinted from Sanchez et al. [93]. With permission from Oxford University Press)

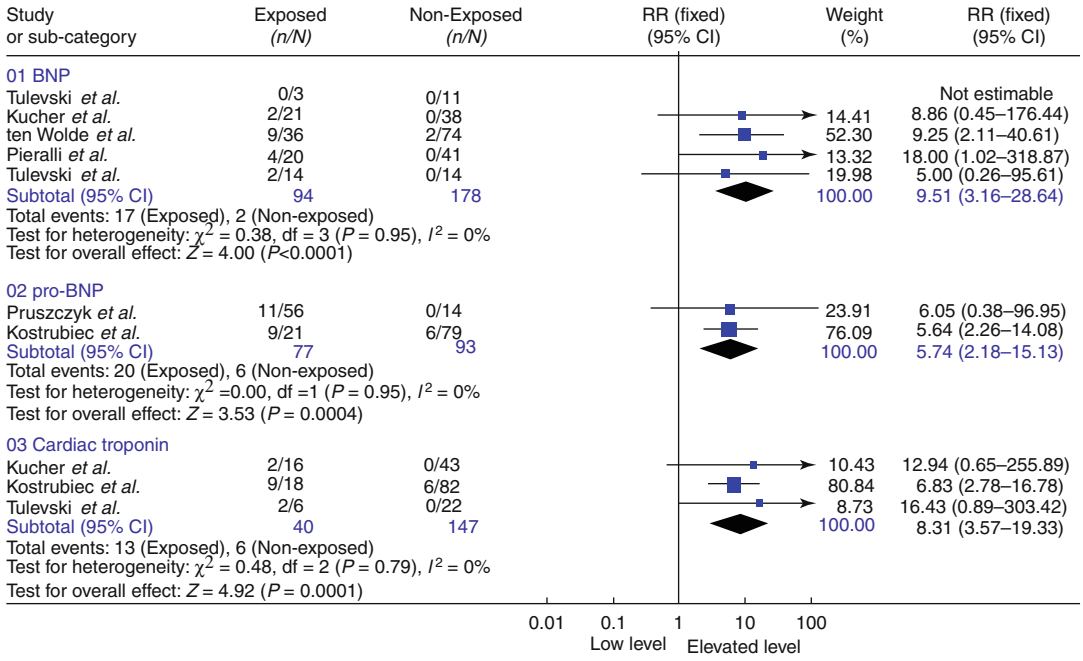

Fig. 11.38 Prognostic value of cardiac biomarkers for mortality in patients with pulmonary embolism without shock. The outcome was in-hospital mortality for all studies, except two: (*) 40-day mortality and (†) 90-day mortality (Reprinted from Sanchez et al. [93]. With permission from Oxford University Press.)

already reviewed it is critically important that objective imaging assessment of RV dysfunction (Fig. 11.37) [143, 164, 219, 324–327] or RV strain with the use of elevated cardiac biomarkers (Fig. 11.38) [214, 216, 219, 324, 326, 328, 329] be included in this analysis to identify

	Test				
	Echocardiography	Computed tomography	BNP	Pro-BNP	Cardiac troponin
Sensitivity (%) (95% CI)	70 (46–86)	65 (35–85)	88 (65–96)	93 (14–100)	81 (23–100)
Specificity (%) (95%CI)	57 (47–66)	56 (39–71)	70 (64–75)	58 (14–92)	84 (77–90)
Negative predictive value (%) (95% CI)	60 (55–65)	58 (51–65)	76 (73–79)	81 (65–97)	73 (68-78)
Positive predictive value (%) (95% CI)	58 (53–63)	57 (49–64)	67 (64–70)	63 (50–76)	75 (69–80)

Fig. 11.39 Pooled diagnostic indexes for echocardiography, computed tomography, brain natriuretic peptide (*BNP*), pro-BNP, and cardiac troponin (Reprinted from Sanchez et al. [93]. With permission from Oxford University Press)

higher risk patients. Pooled diagnostic sensitivities, specificities, negative and positive predictive values for the use of TTE, CTPA and cardiac biomarkers are shown in Fig. 11.39.

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Cor Pulmonale

12

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Abstract

Cor pulmonale refers to cardiac dysfunction consecutive to pulmonary disease. It reflects an uncoupling between the right ventricle and the pulmonary circulation. It is characterized by right ventricular (RV) overload in diastole and in systole, due to an increased right ventricular afterload. Two clinical entities are differentiated: acute cor pulmonale corresponds to an abrupt increase, leading to RV dysfunction or failure and may be observed in ARDS, anatomically massive pulmonary embolism, but also in mechanically ventilated patients in case of any situation with impaired RV contractility (sepsis, infarction,….); chronic cor pulmonale corresponds to a chronic and progressive increase in RV afterload, allowing the right ventricle to adapt up to a certain point (in this case, the right ventricle is hypertrophic). Echocardiography is the cornerstone of the diagnosis and the pivotal exam to distinguish acute and chronic cor pulmonale, even though the distinction is not always obvious and may be supported in part by the clinical scenario. We review the pathophysiology of the right ventricle and describe the diagnosis and treatment of cor pulmonale.

Abbreviations

ARDS	Acute respiratory distress syndrome
CVP	Central venous pressure
LV	Left ventricle
MRI	Magnetic resonance imaging
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure.
PAP	Pulmonary artery pressure

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Introduction

Cor pulmonale is a frequent complication of pulmonary diseases and is associated with a poor prognosis in many different clinical settings. This is obviously true in primary pulmonary hypertension [1], but also in acute respiratory distress syndrome (ARDS) [2]. This means that routine

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evaluation of right ventricular (RV) function is crucial in detecting cor pulmonale.

Cor pulmonale was first described clinically in 1831 by Testa, as a chronic process, to illustrate heart-lung interactions [3]. In 1960, Harvey and Ferrer during a symposium on congestive heart failure defined it as "a complication of certain forms of lung disease" [4]. They especially focused on chronic pulmonary emphysema, leading to RV dysfunction either by alveolar hypoventilation or by destruction of the pulmonary circulation [4]. Also called pulmonary heart disease, it is often just the clinical translation of an increased pulmonary artery pressure (PAP). Later, cor pulmonale was also reported as an acute phenomenon in pulmonary embolism, and then called acute cor pulmonale [5]. In the ICU, many situations may be responsible for such a pattern, especially in mechanically ventilated patients [6]. The reasons why are briefly explained below.

Physiological Reminders

In normal conditions, the right ventricle acts as a "passive conduit". The isovolumetric contraction pressure is negligible and there is nearly no isovolumetric relaxation time because the right ventricle continues to eject blood long after the beginning of the relaxation [7]. This is only possible because the pressure in the pulmonary circulation is low. Then, for the right ventricle, ventricular-arterial coupling is the key, even though it is unfortunately difficult to assess at the bedside because it requires generation of pressure/volume loops [8]. It can be evaluated as the ratio between end-systolic elastance of the right ventricle and elastance of the pulmonary artery (Ees/Ea) [8]. The right ventricle maintains optimal coupling by adjusting its contraction to its afterload changes [8]. However, this adaptation is limited, especially in acute conditions when an abrupt increase in afterload occurs or after a long process of severe pulmonary hypertension [9]. Any situations leading to uncoupling between the right ventricle and the pulmonary circulation may induce a pattern of cor pulmonale. This is obvious in cases of chronic or acute pulmonary hypertension where pulmonary artery elastance is significantly increased and the right ventricle has difficulty adapting. In acute pulmonary hypertension, this has been reported to be due either to proximal obstruction of the pulmonary circulation, as in pulmonary embolism [5], or to distal obstruction (at the level of the pulmonary capillaries), as in ARDS [10, 11]. But, uncoupling may also occur when RV Ees is decreased compared with only a slight increase in pulmonary artery Ea. This is especially apparent in mechanically ventilated patients with depressed RV contraction related to ischemia (RV myocardial infarction) or to inflammatory cytokines (sepsis). Both situations are illustrated in Fig. 12.1. It has long been known that positive pressure ventilation may induce increased afterload by collapse of pulmonary capillaries [12, 13]. This is related to the tidal volume or the related transpulmonary pressure [14].

Diagnosis of Cor Pulmonale

As emphasized above, cor pulmonale was initially mainly a clinical diagnosis supported by a suggestive clinical context [3, 4]. Since then, hemodynamic evaluation has been easily available at the bedside using the pulmonary artery catheter (PAC) and cor pulmonale was often defined as a central venous pressure (CVP) higher than the pulmonary artery occlusion pressure (PAOP) (Fig. 12.2) [15, 16]. But this definition is not very sensitive and is more a reflection of severe RV failure than of cor pulmonale per se. With development of echocardiography, the recognized definition is mainly now an echocardiographic one [17, 18]. It is the association of RV dilatation in diastole with a paradoxical

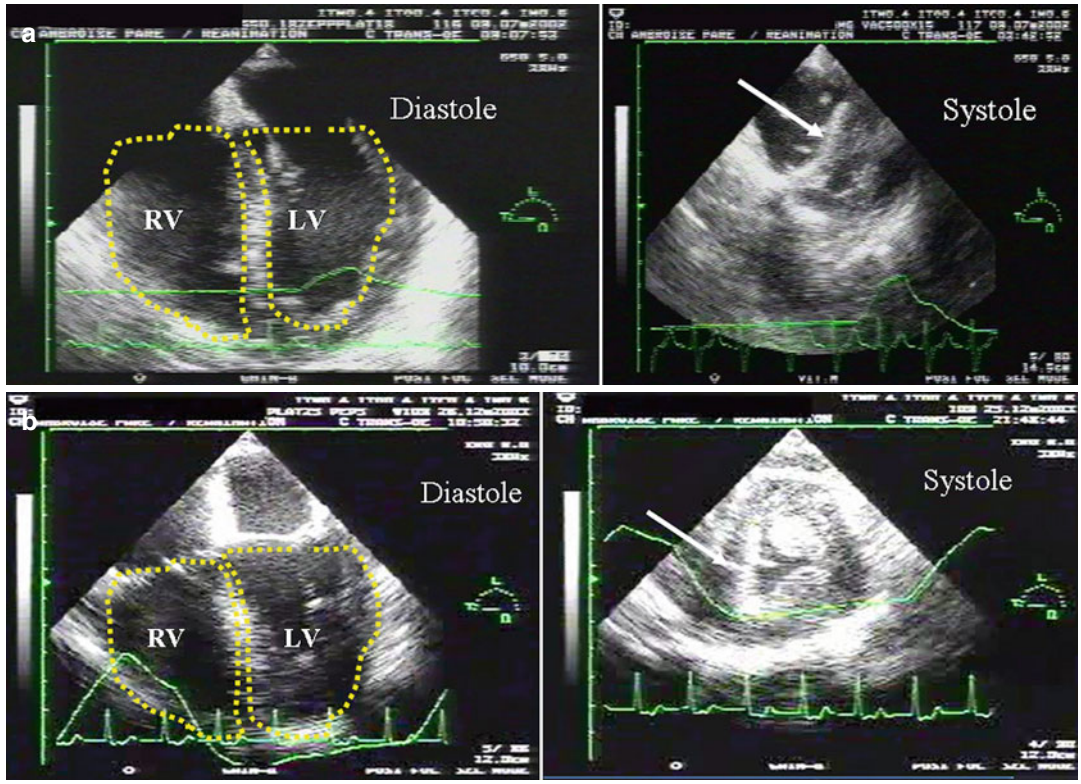

Fig. 12.1 Illustration in 2 mechanically ventilated patients, using transesophageal echocardiography, of uncoupling between the right ventricle and the pulmonary circulation, leading to a pattern of acute cor pulmonale. Panel (**a**): Patient with septic shock at admission. Note the severe dilatation of the right ventricle in diastole on a 4-chamber view, associated with paradoxical septal motion in systole on a short-axis view (*arrow*). Panel (**b**): Patient with myocardial infarction and moderate dilatation of the right ventricle with paradoxical septal motion (D-shape of the left ventricle, *arrow*). *RV* right ventricle, *LV* left ventricle

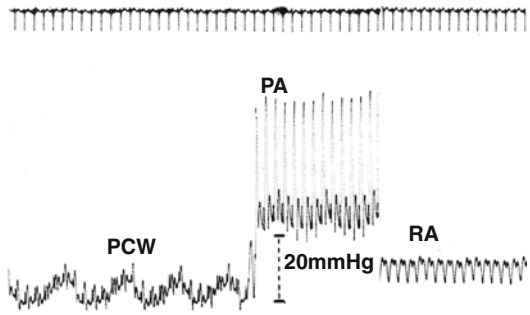

Fig. 12.2 Demonstration in a patient with massive pulmonary embolism, with right atrial pressure (*RA*) higher than pulmonary capillary wedge pressure (*PCW*), illustrating marked right ventricular failure. *PA* pulmonary artery

septal motion in end-systole (Fig. 12.3). The paradoxical septal motion is the surrogate of the inverted trans-septal pressure gradient between the right and the left ventricles (Fig. 12.4). Some studies have also recently reported the accuracy of CT-scan in detecting RV dilatation in a clinical context of cor pulmonale [19]. Moreover, cardiac magnetic resonance imaging (MRI) has become an interesting noninvasive approach to assessment not only of chronic changes, long-after embolism for example, but also acute changes in pulmonary vascular resistance [20]. Cardiac MRI could become a key exam in the

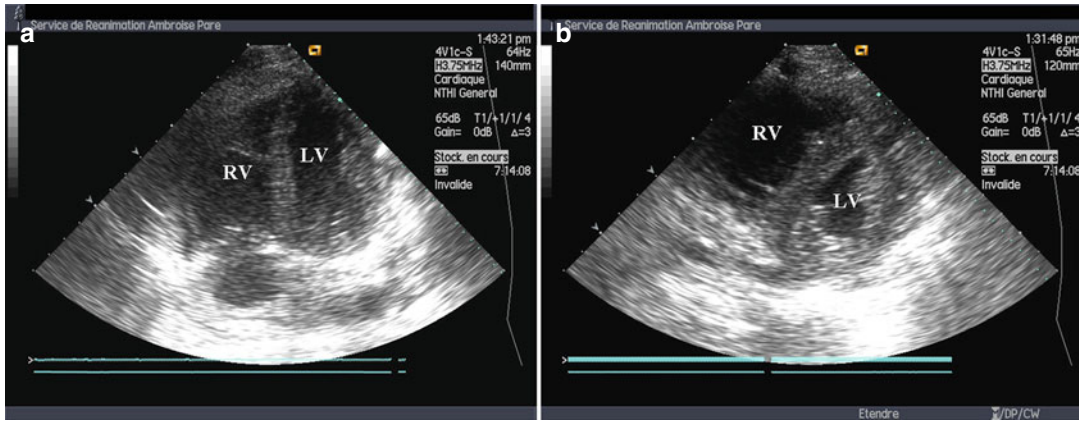

Fig. 12.3 Typical pattern of acute cor pulmonale by a transthoracic approach in a mechanically ventilated young woman with severe pneumonia related to influenza. Panel (**a**): Apical 4-chamber view showing major right ventricular dilatation (the right ventricle is bigger than the left) in diastole. Panel (**b**): Parasternal short-axis view of paradoxical septal motion in systole leading to a "D-shape" of the left ventricle and reflecting right ventricular systolic overload. *RV* right ventricle, *LV* left ventricle

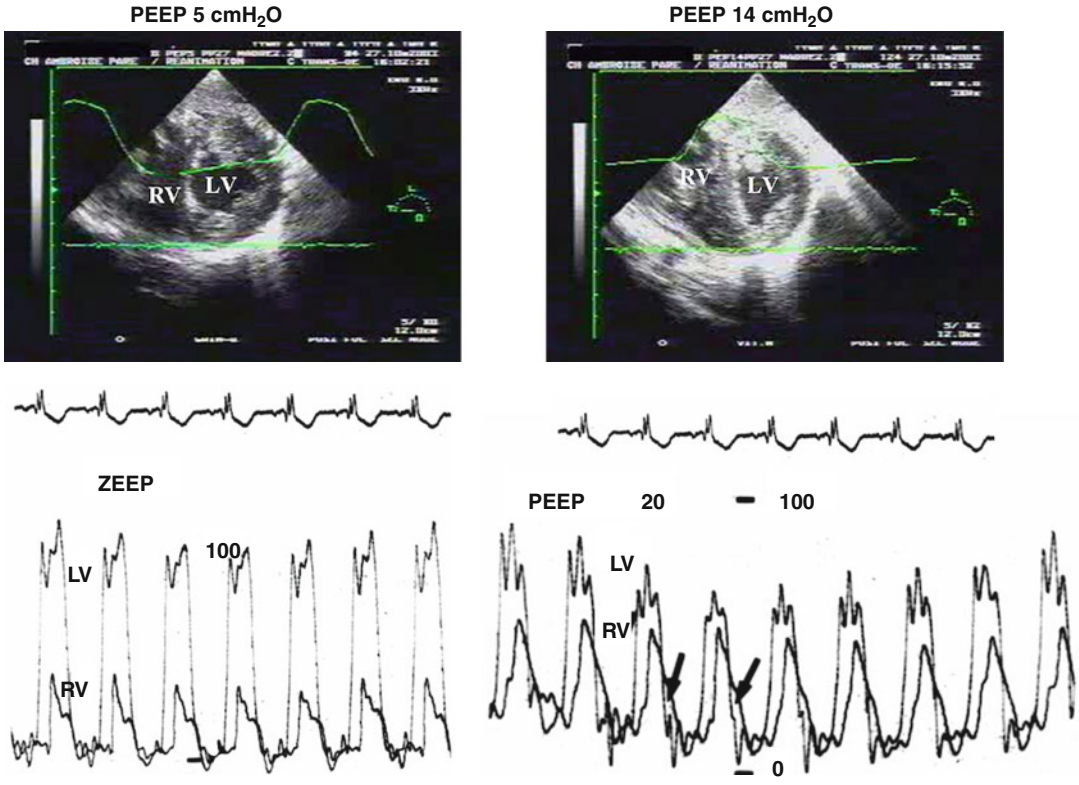

Fig. 12.4 Illustration of the mechanism of paradoxical septal motion. *Above*: parasternal short-axis view of the left ventricle in a patient ventilated for severe ARDS with PEEP of 5 cmH_2O (no paradoxical septal motion) and after applying PEEP of 14 cmH_2O (paradoxical septal motion). *Below*: recording of left and right ventricular pressures in a mechanically ventilated patient with ARDS. Note for PEEP of 20 cmH_2O the inverted pressure gradient between both ventricles at end-systole, not occurring at PEEP 0 (ZEEP). *RV* right ventricle, *LV* left ventricle, *PEEP* positive end-expiratory pressure

follow-up of patients suffering from pulmonary hypertension [21].

Differences between acute, chronic and acute-on-chronic cor pulmonale are not always obvious and the diagnosis is sometimes difficult. Briefly, the clinical context is crucial. Otherwise, chronic cor pulmonale is associated with major thickening of the RV free wall (10–12 mm for a normal value of 3 mm). However, a slight thickening (5–6 mm) has been reported in patients with acute cor pulmonale related to ARDS after only 3 days on mechanical ventilation [18]. In rats, hypoxia is also able to induce some RV hypertrophy in only 3 days [22]. In chronic pulmonary hypertension, thickening is a sign of adaptation and the cardiac output is still preserved, whereas dilatation is a sign of failure with a decreased cardiac output [9]. Another difference between acute and chronic is the level of pulmonary hypertension: it is usually moderate (systolic pressure ≤60 mmHg) in acute and more severe in chronic.

Treatment of Cor Pulmonale

Here we will not consider etiologic treatments, as pulmonary vasodilation, fibrinolysis, coronary reperfusion, etc. But whatever the disease, general support is needed in certain situations, including the use of vasoactive drugs and changes in respiratory settings, and some support has to be limited or even avoided, as fluid expansion.

Whereas it is clear that supporting the right ventricle is required in the case of cor pulmonale related to RV failure, the question is still debatable in the case of RV systolic dysfunction only. In the first situation, cardiac output is decreased (not "optimal"), whereas in the second situation, it is preserved. In general, moderate acute cor pulmonale (RV < LV) is associated with a preserved cardiac output, whereas severe acute cor pulmonale (RV > LV) is associated with decreased cardiac output [18]. But some data recently published in ARDS show that acute cor pulmonale, whatever the cardiac output, is associated with a poor prognosis [2], suggesting that something has also to be adapted in these patients. But, this is a special situation where a direct relationship between lung disease, the effect of mechanical ventilation and RV function is well described. This led some intensivists to call in these patients for an RV protective approach, based on (i) a systematic decrease in tidal volume and plateau pressure, (ii) a limitation of hypercapnia and (iii) the use of prone position in the most severely ill patients [23].

Most data regarding the use of vasoactive drugs come from experimental studies. They are based on the concept that a vicious circle is occurring: cor pulmonale leads to RV failure, and severe RV dilatation, which results in decreased blood pressure, which leads to decreased coronary perfusion pressure and RV functional coronary ischemia, which worsens RV failure, etc. This supports the use of a vasoconstrictor as norepinephrine to restore a normal blood pressure and then coronary perfusion, helping the right ventricle to adapt to the stress. This was demonstrated by Guyton et al. [24] in animals and also confirmed by Vlahakes et al. [25]. In an experimental model of major pulmonary embolism in dogs, Molloy et al. reported that norepinephrine was much more effective in terms of hemodynamic improvement and survival than isoproterenol [26]. The same results were also reported by Rosenberg et al. [27]. An example is given in Fig. 12.5 in a patient ventilated for ARDS.

Fluid management in this situation is not obvious. Clearly, RV function is known to be the main limiting factor for effectiveness of fluid expansion [24–28]. In mechanically ventilated ARDS patients, Mahjoub et al. showed that false-positive pulse pressure variation (i.e. patients who seemed fluid-responsive but in whom cardiac output actually did not increase after fluids) had echocardiographic parameters suggesting RV systolic dysfunction [29] (Fig. 12.6). Mercat et al.

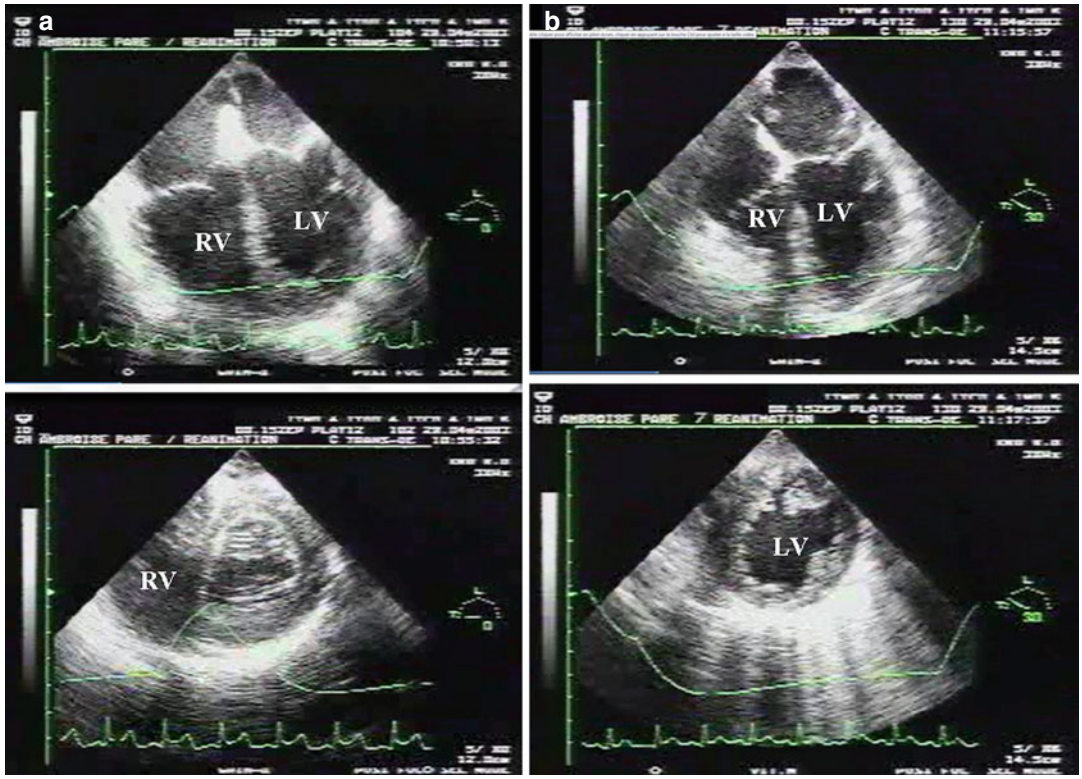

Fig. 12.5 Demonstration of the beneficial effect of norepinephrine infusion on right ventricular function. Panel (**a**): patient with acute cor pulmonale (right ventricular dilatation above and paradoxical septal motion below) and severe hypotension. Panel (**b**): after norepinephrine infusion, leading to restoration of blood pressure, right ventricular function was normalized (the right ventricle was now non-dilated and paradoxical motion disappeared). *RV* right ventricle, *LV* left ventricle

demonstrated 15 years ago in patients with pulmonary embolism that changes in cardiac index related to fluids were strongly associated with baseline RV size [30]. Fluids may not only be useless, but also deleterious in this situation by aggravating RV dilatation and then LV constriction and finally hemodynamic failure [31]. This was also nicely demonstrated in dogs in a model of massive pulmonary embolism [32].

In conclusion, cor pulmonale may be due to many different diseases or injuries, most of them leading to uncoupling between the right ventricle and the pulmonary circulation. The most efficient tool for bedside evaluation of RV function is currently echocardiography. To support the right ventricle it is necessary to evaluate how dilated it is and to be familiar with its physiology and pathophysiology.

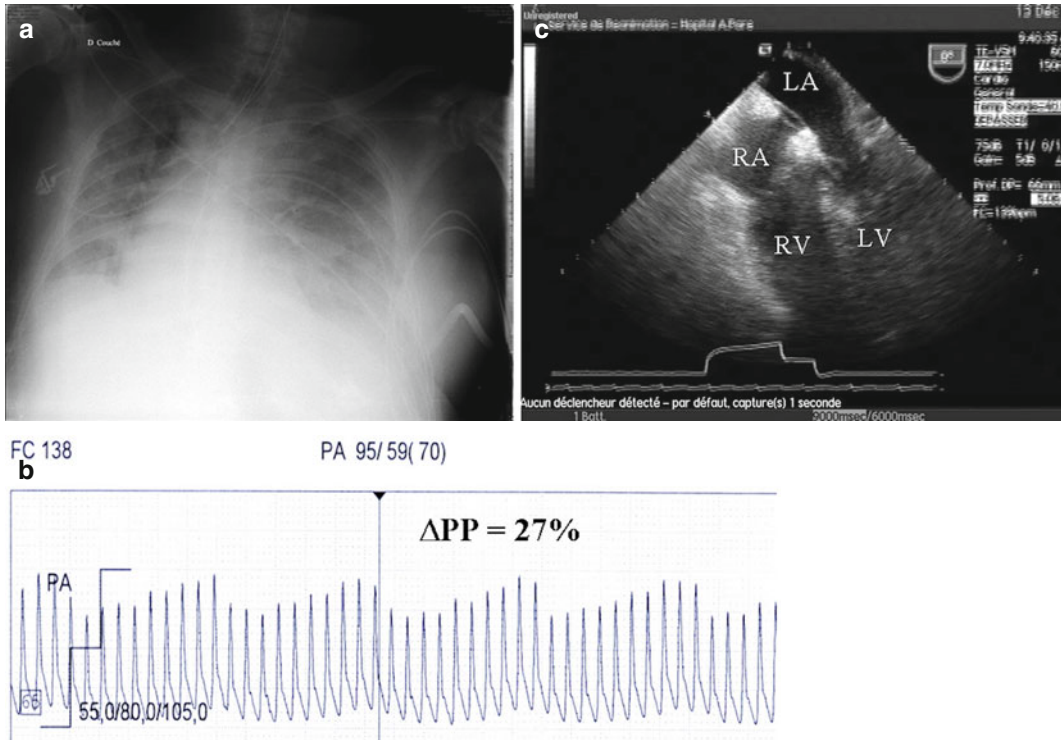

Fig. 12.6 Mechanically ventilated patient with severe ARDS, as shown by the chest X-ray (panel **a**). He exhibited significant pulse pressure variations (panel **b**, invasive blood pressure recording) due to severe acute cor pulmonale, as shown by transesophageal echocardiography, with major right ventricular dilatation (panel **c**). Cardiac output did not increase after fluid expansion. *RV* right ventricle, *LV* left ventricle, *RA* right atrium, *LA* left atrium, *ΔPP* pulse pressure variation, *FC* heart rate, *PA* systolic blood pressure

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Left Heart Failure

13

Stefano Ghio, Claudia Raineri, and Laura Scelsi

Abstract

Heart failure (HF) has been considered for many years a disease of the left ventricle. Much research has been done on left ventricular (LV) function, the determinants of its failure, and the consequent effects on morbidity and mortality of HF patients, whereas less attention has been paid to the right ventricle (RV) and its failure. Things have changed in recent years. Nowadays it has become clear to clinicians and to researchers that the right ventricle plays a critical role in patients with left heart disease.

This review summarizes available data on prevalence, clinical correlates, prognostic relevance, pathophysiologic determinants and treatment of RV failure in the context of Left Heart failure (HF). The focus is on four clinical conditions: chronic HF with reduced ejection fraction of the left ventricle, HF with preserved ejection fraction of the left ventricle, acute decompensated HF and end-stage HF patients undergoing implantation of a LV assist device.

Introduction

For many years cardiologists were not interested in studying right ventricular (RV) function and therefore the role of the right ventricle in heart failure (HF) has been largely underestimated. As a matter of fact, early research fostered the misconception that this cardiac chamber played a passive role in the maintenance of cardiac output. Needless to say, this view is completely wrong. More recently a consensus has grown among clinicians that the right ventricle plays a critical role in patients with left heart disease. RV function is in fact strongly associated with mortality and morbidity in chronic ambulatory HF patients, whether they have reduced or preserved left ventricular (LV) ejection fraction; RV function plays a critical role in acute decompensated HF; finally, in end-stage HF patients who may potentially be implanted with a LV assist device a careful and thoughtful evaluation of RV function is mandatory since RV failure is the major cause of morbidity and mortality after device implantation.

It is important to acknowledge that a great contribution to the higher awareness of the importance of the right ventricle in HF patients has come from the use of simple imaging approaches. In fact, although it is known that accurate measurements of RV volumes, RV mass and RV ejection fraction may only be obtained by

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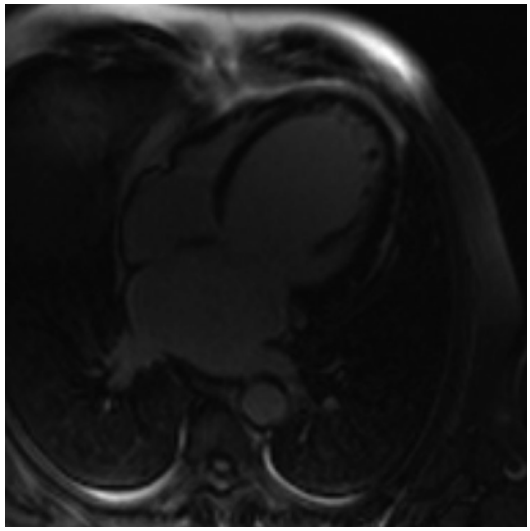

Fig. 13.1 CMR image obtained in a patient with HFrEF and a normal right ventricle

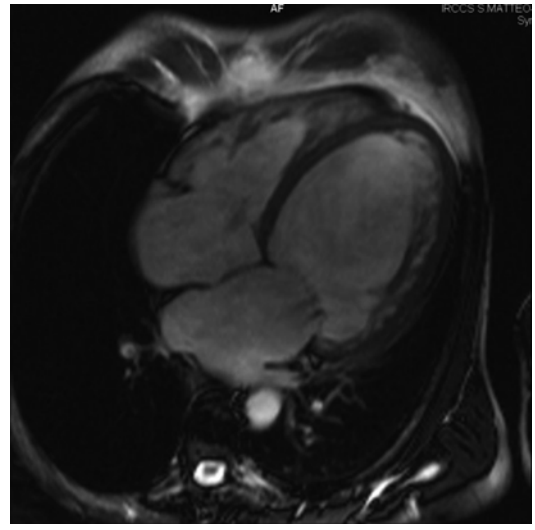

Fig. 13.2 CMR image obtained in a patient with HFrEF and a dilated right ventricle

means of cardiac magnetic resonance, it is also clear that these data are not necessary to diagnose RV dysfunction in HF patients; in such patients standard echocardiography provides simple indicators of RV function which are both pathophysiologically meaningful and clinically useful (Figs. 13.1, 13.2, 13.3, and 13.4). Finally, it is necessary to notice that, despite the increased attention that clinicians and researchers now pay to the right ventricle, we still lack a precise understanding of the reasons why RV dysfunction develops in HF. This ignorance adds to the lack of medical therapies which could target RV performance and makes the treatment of patients with HF and RV dysfunction a great challenge in the real world (Table 13.1).

RV Dysfunction in Heart Failure with Reduced Ejection Fraction (HFrEF)

What Is the Clinical and the Prognostic Significance of Right Ventricular Dysfunction in HFrEF Patients?

The importance of evaluating RV function in heart failure patients is well documented in the literature and it is an issue which has been emphasized in the most recent European Heart Failure Guidelines [1].

Symptoms and signs in ambulatory patients with chronic HF are poorly related to the degree of LV dysfunction and are more dependent on the presence or absence of pulmonary hypertension (PH) and, in particular of RV dysfunction. HF patients with elevated pulmonary artery pressure and elevated pulmonary vascular resistances have a low peak oxygen consumption at cardiopulmonary exercise testing. However, the impact of PH on cardiac output response to exercise is modulated by RV function: in fact, in a substantial proportion of HF patients with PH, exercise causes a decrease in pulmonary capillary wedge pressure and an increase in right atrial pressure, an hemodynamic profile indicating RV failure [2, 3]. Functional capacity of HF patients has been shown in several studies to be directly related to resting or to peak exercise RV ejection fraction [4, 5].

RV function is an important prognostic indicator in patients with HF regardless of etiology, whether due to ischemic heart disease or to primary dilated cardiomyopathy; this datum is extremely consistent in the literature, whichever technique (and whichever parameter) has been used to evaluate the right ventricle: rapid response

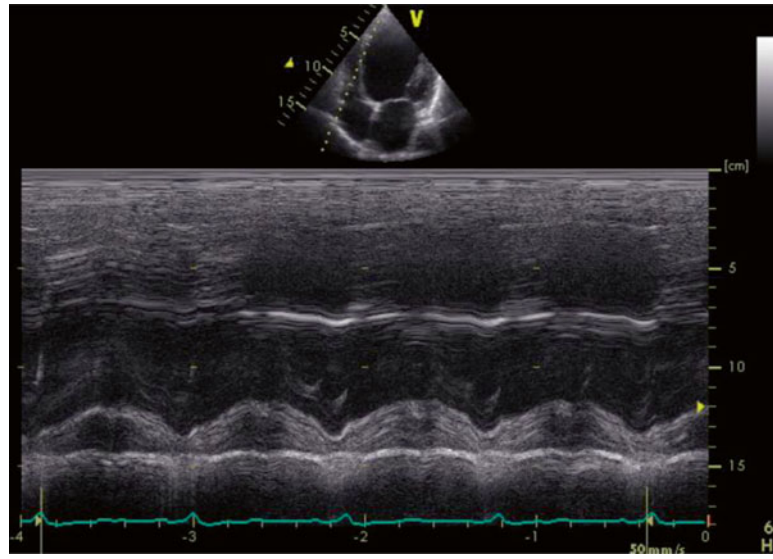

Fig. 13.3 A normal TAPSE in a patient with HFrEF

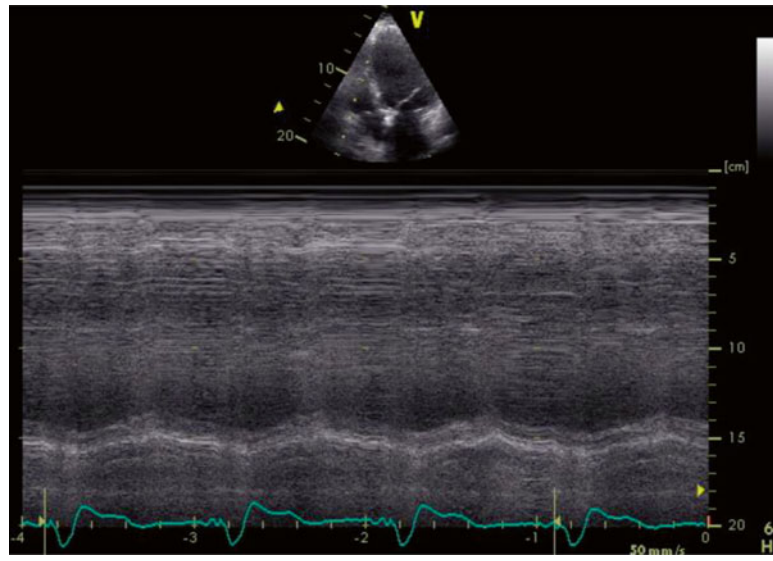

Fig. 13.4 A reduced TAPSE in a patient with HFrEF

thermodiluation or radionuclide ventriculography or echocardiography (including the RV area shrinkage, the tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler velocities or strain) [6–12]. Interestingly, the prognostic significance of RV function (assessed by the simplest M-mode echocardiographic parameter, the TAPSE) was found to be additive to other well known echocardiographic predictors such as left ventricular ejection fraction and the deceleration time of the E wave [9]. Furthermore, RV dysfunction correlates significantly with other acknowledged prognostic indicators in heart failure, such as heart rate variability or plasma brain natriuretic levels, a finding which further reinforces the relevance of the right ventricle as a determinant of prognosis in HF patients [13, 14]. Finally, a reduced TAPSE might be an important driver of an adverse prognosis regardless of the degree of LV dysfunction [12].

In a clinical context, assessing the function of the right ventricle without taking into account the level of the pulmonary artery pressure should be considered an oversimplification if not a real

Table 13.1 Right ventricular dysfunction/failure in left heart failure

	Causes of RV failure	Clinical consequences of RV failure	Specific treatment of RV failure
HFrEF	Pulmonary hypertension[a] Ischemic heart disease[a] Primary myocardial disease[b] Atrial fibrillation[b]	Increased severity of symptoms Poorer prognosis Potential preclusion of LVAD implant	No specific treatment but treatment of L heart failure
HFpEF	Same as above	Negative impact on prognosis	No specific treatment but treatment of L heart failure
ADHF	Same as above	Negative impact on prognosis	Unknown
After LVAD implantation	Several pre and post LVAD implant factors	Extremely negative impact on prognosis	RVAD

HFrEF heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *ADHF* acute decompensated heart failure, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device, *HT* heart transplant, *PH* pulmonary hypertension
[a]Main determinant
[b]Possible determinant

mistake. These two parameters are in fact tightly linked from a pathophysiological point of view, as the right ventricle is an highly afterload-dependent chamber. Furthermore, it has to be emphasized that a combined assessment of pulmonary pressure and RV function allows to obtain a much better prognostic stratification of HFrEF patients. In a study enrolling nearly 400 HF patients with reduced LV ejection fraction undergoing an hemodynamic evaluation as part of an heart transplant evaluation, the association of a mean PAP >25 mmHg and of a RV ejection fraction ≤20 % was shown to portend a particularly poor prognosis, whereas patients with a normal pulmonary artery pressure and a reduced RV function had a significantly better survival [15]. The problem with this study is that right heart catheterization is not routinely performed in chronic HF patients; it is mainly limited to heart transplant evaluations in tertiary referral centers. In routine clinical practice the assessment of pulmonary pressure and RV function must be obtained with noninvasive techniques. Doppler echocardiography has shown widespread applicability and acceptable accuracy in determining the hemodynamic profile of ambulatory patients with HF and LV systolic dysfunction [16]. The clinical usefulness of this combined approach was therefore tested in a large population of ambulatory HF patients using the non invasive Doppler evaluation of the systolic pulmonary artery pressure and the simple TAPSE as an indicator of RV function. The conclusions were similar: at Cox survival analysis (the composite end-point was death, emergency heart transplantation and appropriate recordings and treatment of ventricular fibrillation by implanted defibrillators) patients with a systolic pulmonary artery pressure ≥40 mmHg and a TAPSE ≤ 14 mm had a poorer prognosis than those with high pressures but preserved TAPSE; RV dysfunction associated with normal pulmonary pressure did not carry additional risks [17].

The reasons why RV dysfunction predicts a worse outcome in the presence of PH are unclear; it could be speculated that this association is a signal that PH is long-standing whereas normal RV function in patients who have PH could indicate a more recent onset of PH. It could also be hypothesized that RV dysfunction reduces cardiac output and thus the association of a low TAPSE and of high pulmonary pressures might indicate high pulmonary vascular resistances rather than simply high pressures in the pulmonary artery; however, when pulmonary pressure is normal, reduced RV function does not carry additional risks, and this observation makes it rather unlikely that a reduced TAPSE is always a marker of reduced cardiac output in HF patients.

The uncertainties in understanding why RV dysfunction is associated with poor prognosis reflect the uncertainties on the pathophysiological determinants of RV dysfunction.

Why Does RV Dysfunction Occur in HFrEF Patients?

"RV dysfunction is the direct consequence of the elevated pressure in the pulmonary circulation". This statement is theoretically correct since, due to its peculiar characteristics, the RV cannot easily tolerate a pressure overload [18]. An inverse relation between pulmonary artery pressure and RV ejection fraction has been shown in early studies and has been confirmed more recently [19]. In particular, the slope of the relationship between RV ejection fraction and pulmonary artery pressure was not different in patients with different etiology of the HF (dilated cardiomyopathy or ischemic heart disease), reinforcing the hypothesis that the main determinant of RV dysfunction is the presence of PH. Molecular biology also supports the hypothesis that PH is the primary cause for myocardial contractile failure of the right ventricle: the integrity of the amino (N)-terminus of distrophin (a protein which plays a key role in the transduction of physical forces in the striated muscle), is disrupted both in the left and in the right ventricle of end-stage HF patients and unloading the left ventricle via a LV assist device ameliorates the cardiac structure both in the left and in the right ventricle [20].

However, PH cannot be the only cause of RV dysfunction in HF patients since a substantial proportion of HF patients have a reduced RV function despite normal pulmonary artery pressures [15, 17]. In patients with advanced disease, reduced RV function could itself determine a low cardiac output state with normal PAP; however, given that the group of patients with RV dysfunction and normal PAP overall showed good prognosis, it is unlikely that more than a few patients were in such a condition [15, 17]. Excessive reduction in right ventricular preload due to overtreatment with diuretic drugs, and the absence of active atrial contraction in patients with atrial fibrillation are possible explanations for this finding. RV dysfunction can also be related to previous myocardial infarction if the RV wall has been directly involved by myocardial ischemia and necrosis [21]. On the other hand, a small case-controlled study (ten patients with ischemic heart disease and ten patients with idiopathic dilated) suggested that, for similar levels of LV dysfunction, RV systolic function is more altered in idiopathic dilated cardiomyopathy [22]. Another plausible hypothesis is therefore that myocardial disease could be the primary cause for RV dysfunction; as a matter of fact, it has recently observed that desmosomal protein gene mutations are quite common in patients with DCM [23, 24]. Whether the genetic background influences the phenotype in DCM patients is still unknown.

Treatment of Right Ventricular Dysfunction in HFrEF Patients

Currently there is no specifically approved pharmacological treatment for RV dysfunction. In experimental conditions, targeted metabolic modulation by dichloroacetate acutely improved RV contractility, providing evidence for a RV-specific inotropic effect [25]. Data in humans are not yet available. However, standard medical treatment of HF patients aiming at lowering pulmonary capillary wedge pressure and pulmonary artery pressure may be strongly beneficial in improving RV function, given the tight coupling between pulmonary pressure and RV function.

Unfortunately, we have not yet solved the theoretical issue of whether the main driver for poor prognosis in HF patients is RV dysfunction itself or PH leading to RV dysfunction. Therefore, we do not know whether PH or RV dysfunction should be the mechanistic target for treatment of HF patients with RV dysfunction. The answer to this question will only come whenever we will be able to directly improve RV function without changing RV afterload.

RV Dysfunction in Heart Failure with Preserved Ejection Fraction (HFpEF)

What Is the Clinical and the Prognostic Significance of Right Ventricular Dysfunction in HFpEF Patients?

Diagnosis of HFpEF may be extremely difficult as several conditions including constrictive

pericarditis, restrictive cardiomyopathy, precapillary pulmonary arterial hypertension share similar signs and symptoms. Therefore, when approaching a patient with suspected HFpEF and RV dysfunction the first step that must be performed is a detailed diagnostic examination program.

That said, we have to recognize that HFpEF is the dominant form of HF in the community, causing at least as many hospitalizations, healthcare expenditures, severe symptoms, reduced exercise tolerance and, once patients are hospitalized, having similarly poor death rates as HFrEF [26–28]. However, there is relatively little information about pathophysiology and treatment of this condition and in particular, much less attention has been paid to the clinical significance of RV dysfunction in HFpEF as compared to HFrHF patients. Few published data confirm that HFpEF patients may develop RV dysfunction and that it portends a negative clinical and prognostic significance. First of all, PH is frequently observed in HFpEF; studies report a prevalence of PH around three quarters of such patients, which would be even higher than in patients with HFrEF [29, 30]. Since RV dysfunction is mainly a consequence of increased RV afterload, then the high prevalence of PH would stand for a high prevalence of RV dysfunction among HFpEF patients. The prevalence of RV systolic and diastolic dysfunction in HF patients with preserved and reduced LV ejection fraction was studied by Puwanant et al. [31]. Based upon the three RV characteristics of: (1) RV fractional area change <45 %, (2) tricuspid annular motion <1.5 cm, and (3) peak systolic velocity obtained by tissue Doppler imaging of the lateral tricuspid annulus <11.5 cm/s, the prevalence of RV systolic dysfunction was found to be 33, 40 and 50 % respectively in patients with HFpEF.

Recently a score has been designed to help determine the prognosis of patients with PH-HFpEF. Components of the risk score are functional class, diastolic blood pressure, pulmonary artery saturation, interstitial lung disease, hypotension on initial presentation, RV hypertrophy, diffusion capacity and serum creatinine. Over a 2-year period the risk score predicted survival was 97.5, 66.4, and 24.4 % for risk scores 0–2, 3–4 and 5 ($p<0.0001$ for the trend) [32]. Data have been published suggesting that a reduced TAPSE may be an important driver of an adverse prognosis regardless of LV function [12].

Why Does RV Dysfunction Occur in HFpEF Patients?

There is no reason to hypothesize that the determinants of RV dysfunction in HFpEF are differents from those in HFrEF, but we have to remember that less data have been published than in HFrEF. In a population of patients with acute decompensated HF and most frequently preserved LV ejection fraction, RV failure was strongly associated with the severity of LV diastolic dysfunction and higher pulmonary artery pressures [33].

Treatment of Right Ventricular Dysfunction in HFpEF Patients

To date, largely neutral and disappointing outcomes have been reported in randomized drug trials on potential therapeutic interventions in HFpEF (i.e. angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers) including CHARM-Preserved, PEP-CHF and I-Preserve [34–37]. The treatment of PH and of RV dysfunction associated with HFpEF is even less clear.

A couple of single center studies suggested the potential for phosphodiesterase 5 (PDE-5) inhibition to ameliorate several key pathophysiological mechanisms in HFpEF and thus improve exercise capacity and clinical conditions [38, 39]. In a study enrolling patients with HFpEF, PH and RV dysfunction, 44 patients were randomized in a double-blind 1:1 fashion to sildenafil 50 mg three times a day or placebo. All patients were already taking conventional medications for 6 months prior to enrollment (diuretics, afterload reducers and beta-blockers) and underwent at baseline, 6 and 12 months hemodynamic measurements, pulmonary function tests and Doppler echocardiography. Throughout the course of the

study patients treated with sildenafil were found to have a substantial decrease in systolic, diastolic and mean pulmonary artery pressures. The authors stated that PDE5 inhibition provided a sustained reversal in pulmonary vasodilation and improvement in systolic RV function. The RELAX trial was designed to test the hypothesis that, compared with placebo, therapy with the PDE-5 inhibitor sildenafil would improve exercise capacity in HFpEF after 24 weeks of therapy. Contrary to the expectations, despite the strong rationale, PDE-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or in clinical status [40]. No post-hoc analysis is available in the subgroup of patients with PH and/or RV dysfunction enrolled in RELAX. Ongoing studies are also exploring the cofactor tetrahydrobiopterin, which plays a role in nitric oxide synthase uncoupling. Administration of tetrahydrobiopterin in animal models has led to enhancement of systolic and diastolic function while reducing pressure-overload hypertrophy, oxidative stress and fibrosis [41]. Further research is targeting aldosterone which plays an important role in vascular stiffening and endothelial dysfunction and the rho-kinase signaling pathway inhibitors such as statins and fasudil that may have vasorelaxation properties [42, 43].

RV Dysfunction in Acute Decompensated Heart Failure

Acute decompensated heart failure (ADHF) may be caused by abnormalities of many aspect of cardiac function and patients may present with a spectrum of clinical conditions ranging from pulmonary oedema to cardiogenic shock to a condition primarily characterized by worsening of peripheral congestion. In acute HF settings, a thorough echocardiographic evaluation of left and right heart function is not routinely performed; as a matter of fact, the most recent European Guidelines consider natriuretic peptide assessment as an alternative to echocardiography in the diagnostic algorithm of suspected ADHF [1]. Therefore, less data are available on the clinical and prognostic implications of PH and of RV dysfunction in ADHF as compared to chronic HF. This is certainly a gap of evidence because we have known for a long time that clinical signs of low output state at the time of admission (which are potentially related to RV dysfunction and failure) are associated with poor prognosis in ADHF [44, 45]. Obviously, it remains to be demonstrated that the echocardiographic assessment of pulmonary artery pressures and of RV function might help clinicians to decide the best treatment in ADHF patients, but it must be emphasized that the treatment of this condition is still largely opinion-based with little evidence to guide therapy.

Actually, there are a couple of suggestions in the literature that assessing RV function and pulmonary pressures might clinically be useful, at least to better stratify the prognosis. One study focused on the role of RV function: conventional echocardiography was performed on admission and at discharge in a series of 122 consecutive patients admitted for dyspnea due to exacerbated left-sided HF with a LV ejection fraction of less than 40 %. Cox proportional hazards analysis revealed that RV end-diastolic dimension and the serum level of creatinine on admission were independent predictors of subsequent cardiac-related death, but RV dimension at discharge and other LV parameters were not. Patients in the highest tertiles of RV dimensions on admission had a lower pulse pressure and higher serum total bilirubin levels that demonstrated low cardiac output syndrome [46]. Interestingly, only data obtained at admission, not at discharge, turned out to predictive of survival, most likely reflecting the ability of the right ventricle to cope with the elevated afterload in the acute decompensated phase (i.e. a form of RV "reserve").

The role of PH in ADHF is controversial [47, 48]. In a recent paper, after 48 h of therapy, an invasive hemodynamic evaluation allowed identification of the presence of PH and also to differentiate passive PH from reactive PH; a striking increase of mortality was observed in the subgroup of patients with reactive PH [48]. It is possible that the type of PH might be a critically

important determinant of short-term outcome in ADHF. This hypothesis might recall the role of RV function. Persistent elevation of mean pulmonary artery pressure and pulmonary vascular resistance after initial treatment for ADHF and reduction of LV filling pressures represents a hemodynamic profile that identifies a subgroup of patients at a particularly high risk for short-term mortality possibly because it could be attributed to a more advanced disease state and to a greater RV dysfunction.

RV Dysfunction in End-Stage HF Patients Undergoing LVAD Implantation

A new area of interest for the study of RV function has recently emerged: it is the assessment of end-stage HF patients who may potentially be implanted with a left ventricular assist devices (LVAD) [49].

The background is that the number of patients with end-stage HF has been increasing over the years while organ donation remained limited; therefore, although heart transplantation is the gold-standard treatment for selected patients with end-stage HF, mechanical circulatory support with LVAD is increasingly seen as an alternative to transplantation. As a matter of fact, no other field in cardiology is experiencing such an explosive growth as mechanical circulatory support for end-stage HF. This growth has been fueled by the positive clinical results so far obtained: the second generation continuous flow LVAD, HeartMate II, reported 85 % survival and higher in patients in whom it was implanted as a bridge to transplantation; more recently, the ADVANCE trial, in which a third-generation continuous flow device, the Heartware was used as a bridge to transplantation, has reported 92 % survival at 6 months [50]. Several complications may occur in patients receiving a device such as bleeding, thromboembolism, stroke, infection but it must be emphasized that RV failure (RVF) remains the major cause of morbidity and mortality after implantation; depending on the diagnostic criteria used, the incidence of RVF ranges from 9 to 44 % [49–54]. Although most patients can be maintained with prolonged inotropic support, up to 15 % may require implantation of a separate RV assist device (RVAD), which is also associated with a very poor prognosis [55]. Therefore, finding which patient or which right ventricle is susceptible to RVF following LVAD implantation has become an important objective of current research.

This is a challenging issue for several reasons. First of all the definition itself of RVF post LVAD is not yet standardized, making it difficult to compare different case series and largely accounting for the differences in incidence and in outcome of RVF reported in the literature. The INTERMACS Registry has adopted a definition of RVF based on hemodynamic and clinical data: reduced cardiac index (less than 2.2 l/min/m^2), high central venous pressure (18–22 mmHg), the need for postoperative intravenous inotropic support for more than 14 days, inhaled nitric oxide for more than 48 h, right-sided circulatory support such as RVAD, in the absence of other causes explaining circulatory failure [56]. Second, the pathophysiology of RV dysfunction following LVAD implantation is not fully understood, as device implantation itself modifies the geometry and the function of the right ventricle. In an experimental study in anesthetized dogs, LVAD support causes global impairment of RV contractility with leftward septal shift but RV myocardial efficiency is maintained through a decrease in RV afterload and an increase in RV preload [57]. Concerning preload changes, in patients with end stage HF it is likely that in the early postimplantation period an acute increase in venous return compromises rather than supports the performance of the right ventricle. Remarkably, and unlike in heart transplantation, PH does not predict RVF; as a matter of fact, LVAD placement represents the best strategy to reverse "fixed" or unresponsive PH which is currently considered a contraindication to heart transplantation. On the contrary, low pulmonary arterial pressure can be a risk factor if it is a marker of poor RV contractility [50]. Finally, there are several other factors which may contribute to RVF post LVAD implant, including

ischemia or air emboli to the right ventricle, pulmonary embolism and the inflammatory syndrome post cardiopulmonary by-pass and reperfusion injury [58]. In addition, patients with evidence of multiorgan dysfunction are at higher risk of RVF after LVAD implantation [59].

Imaging – in particular echocardiography, which is the only technique which can be easily performed at the bedside before implant and then easily repeated in the follow-up of implanted patients – has not yet been incorporated in the definition of RVF post LVAD. This is not surprising, if it is considered that all the well known difficulties in the echocardiographic assessment of the right ventricle (due to its position behind the sternum, its extensive trabeculation making difficult border recognition, its asymmetrical geometry making impossible simple volume calculations) are magnified in the early postoperative period. However, there are data in the literature concerning the potential usefulness of assessing RV geometry and function in patients to be implanted with a LVAD. Fitzpatrick et al. showed that severe RV systolic dysfunction subjectively determined by echocardiography prior to surgery is an independent predictor of RVF post LVAD [60]. Puwanant et al. reported that a tricuspid annular plane systolic excursion <7.5 mm provided a specificity of 0.91 and a sensitivity of 0.46 for prediction of RVF, whereas Kukucka et al. reported that a RV-to-LV end-diastolic diameter ratio >0.72 by transesophageal echocardiography showed a sensitivity of 0.80 and specificity of 0.74 for RVF after LVAD placement [61, 62]. More recently, there has been interest in using new echocardiographic techniques such as strain, which should be able to provide less load-dependent indices of RV function. Grant et al. found that both RV strain and the Michigan risk score are independent correlates of RV failure [63]. RV strain also emerged as a stronger correlate of RVF than tricuspid annular systolic excursion or RV to LV diameter ratio (which is a surrogate of RV size). In smaller exploratory echocardiographic studies, patients with RVF had more spherical right ventricles and more severe tricuspid regurgitation suggesting that more dilated right ventricles are more susceptible to septal shift [64, 65]. Interestingly, dobutamine-induced changes in TAPSE and in systolic pulmonary artery pressure predicted RVF within 30 days of LVAD implantation in end-stage ambulatory congestive HF patients with biventricular dysfunction much better than all baseline characteristics [66].

Over time, several studies have identified a huge number of demographic, clinical, hemodynamic or imaging predictors of post-LVAD RV dysfunction, yet no one variable can be used alone to select with high predictive accuracy good candidates for mechanical circulatory support and only few are supported by multiple investigations. Given the complex pathophysiology of post-operative RVF, it is conceivable that a score should be developed to gain information from many parameters. Future studies are needed to identify and validate a score which could be clinically useful to predict the need for as biventricular support and to identify the patients in whom the operative risk would be unacceptably high.

Conclusions

RV dysfunction and RV failure are important aspects in HF due to left heart disease. They are important determinants of the prognosis of in many HF patients and therefore may be used to guide treatment choices. The importance of the evaluation of RV function is currently underestimated but a precise and possibly quantitative assessment of RV geometry and function should become clinical routine in all centers. To this end, it must be emphasized that expensive technologies are not necessary; standard echocardiography may provide simple, non-invasive but extremely useful data to assess the right ventricle in patients with left heart failure.

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14 Assessment and Clinical Relevance of Right Ventricular Failure in Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a right heart failure syndrome. The dominant symptom of PAH is shortness of breath. However, in spite of widespread pulmonary vascular remodeling and obstruction, gas exchange in PAH is generally well maintained, with moderate hypoxemia mainly caused by a low cardiac output. Patients with PAH are hypocapnic, but this is explained by increased chemosensitivity, and there is no ventilatory limitation to exercise capacity. Thus lung function is normal or near-normal in PAH. The symptomatology of PAH is principally related to right ventricular (RV) failure. Right ventricular function is altered as soon as pulmonary vascular resistance increases. In early stage PAH, the RV tends to remain adapted to afterload, with little or no increase in right heart chamber dimensions, but less than optimal RV-arterial coupling is a cause of decreased aerobic exercise capacity by limiting maximum cardiac output. In more advanced stages, homeometric adaptation of the RV becomes insufficient for daily life activities resulting in a progressive dilatation of right heart chambers and systolic dysfunction. Along with decreased contractile reserve of the RV, diastolic dysfunction occurs, due to RV fibrosis and sarcomeric stiffening; these changes lead to limitation of flow output and increased right sided filling pressures. These in turn lead to a combination of systemic venous congestion and dyspnea occurring at lower levels of exercise and, eventually, at rest. Imaging of RV function is of major diagnostic and prognostic relevance. Treatment of RV failure in PAH relies on decreasing

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afterload with therapies targeting the pulmonary circulation, optimal fluid management of ventricular diastolic interaction, and inotropic interventions to reverse cardiogenic shock states. The potential of chronic low-dose β-blocker therapies is currently investigated.

Introduction

Pulmonary arterial hypertension (PAH) is a rare dyspnea-fatigue syndrome with clear lungs, caused by a progressive pulmonary vascular remodeling and eventual right ventricular (RV) failure [1]. The hemodynamic definition of PAH rests on invasive measurements of a mean pulmonary artery pressure (Ppa) equal or higher than 25 mmHg, a wedged Ppa (Ppw) lower than or equal to 15 mmHg and a pulmonary vascular resistance (PVR) higher than 3 Wood units. The diagnosis of PAH relies on a step-by-step work-up to exclude causal left heart conditions with increased pulmonary venous pressures, chronic lung diseases and chronic thromboembolic pulmonary hypertension (CTEPH).

Pulmonary arterial hypertension is either idiopathic or, in approximately half of the patients, associated with a series of conditions including intake of appetite suppressant drugs, connective tissue diseases (mainly systemic sclerosis), congenital cardiac left-to-right shunts, portal hypertension, schistosomiasis and human immunodeficiency viral infection [2]. Idiopathic PAH may be heritable in up to 20 % of cases.

In spite of progress with the advent of targeted therapies with prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors, PAH remains incurable, with a 3-year survival rate of 65–70 %. More basic and clinical research is needed for further improvement.

Pulmonary Gas Exchange

Shortness of breath is almost always the first and dominant symptom in PAH. Accordingly, PAH patients are often referred to chest physicians. The lungs will be found to be clear at auscultation, and the chest roentgenogram may be unremarkable. An electrocardiogram showing right ventricular strain and hypertrophy may be overlooked, and the clinical probability of acute pulmonary embolism low, or excluded by lung scintigraphy. A diagnosis of asthma is then often entertained, but excluded by lung function tests showing normal lung volumes with no or minimally increased airway obstruction. Arterial blood gases will typically show a normal or only mildly decreased arterial PO_2 (PaO_2) and, more constantly a decreased $PaCO_2$, indicating preserved gas exchange [3].

The apparent paradox of extensive pulmonary vascular remodeling and preserved gas exchange has been previously explored using the multiple inert gas elimination technique at rest [4, 5] and at exercise [6]. The approach allows for a quantification of all the pulmonary and extra-pulmonary determinants of the arterial blood gases. The results have invariably shown relatively well preserved matching of alveolar ventilation (V_A) to perfusion (Q), with little lower than normal V_A/Q, no diffusion limitation, and mild to moderate decrease in PaO_2 explained by a low mixed venous PO_2 (PvO_2). Significant shunting ($V_A/Q=0$) was found only in patients with right-to-left shunting on a patent foramen ovale or reversal of left-to-right cardiac shunts. Typical V_A/Q distributions in patients with idiopathic PAH, one without and one with shunting through a patent foramen ovale, are shown in Fig. 14.1. It can be seen that the V_A and Q modes remain matched, that there is no high higher than normal V_A/Q thus excluding an increased physiologic dead space, and that foramen ovale in allows for shunting of 20 % of cardiac output in one of the patients as a cause of severe hypoxemia.

Thus hypoxemia in PAH is cardiac rather than pulmonary origin, in the majority of cases

Hyperventilation

Patients with PAH more are more typically hypocapnic than hypoxemic [3]. Patients with PAH hyperventilate at rest and at exercise, and even

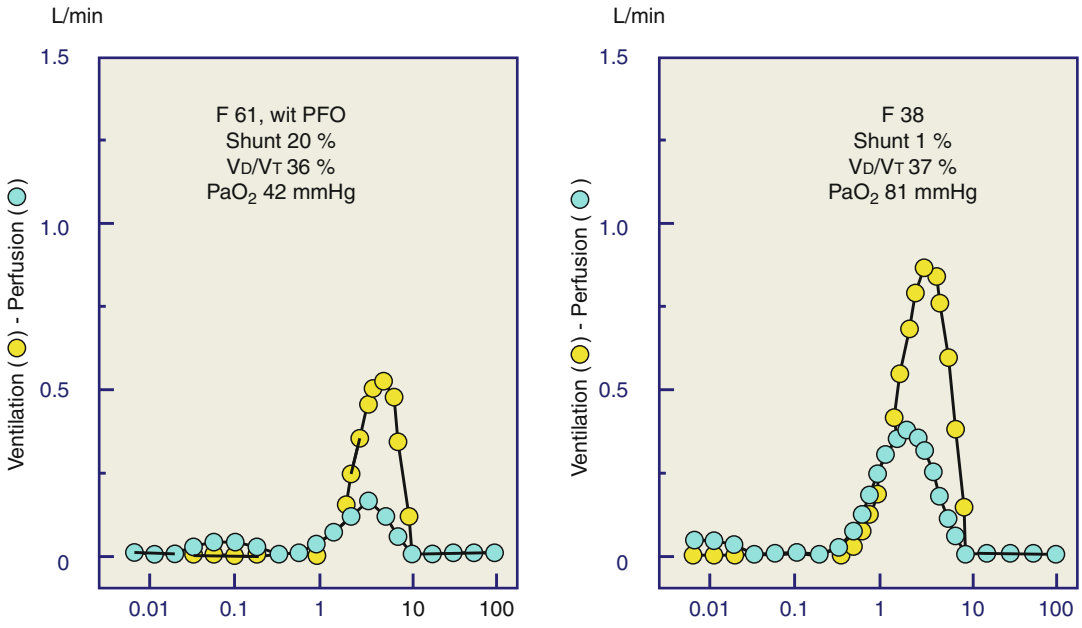

Fig. 14.1 V_A/Q distributions in two patients with idiopathic PAH. Mean V_A/Q is shifted to higher V_A/Q indication hyperventilation. There are no higher or lower than normal V_A modes. Shunting is cardiac in the patients with a patient foramen ovale (*left*)

during sleep. Hyperventilation in PAH would be intuitively attributed to an increased dead space caused by extensive pulmonary vascular obliteration. However, this does not explain decreased $PaCO_2$. Inert gas elimination studies showed a shift of mean V_A/Q to higher V_A/Q ratios, also illustrated in Fig. 14.1, reflecting an increased ventilation, but no higher than normal V_A/Q matching, indicating absence of lung regions with relative excess of alveolar ventilation [3]. Thus wasted ventilation in PAH would rather be a consequence of increased chemosensitivity than of an increased physiologic dead space. Physiologic dead space calculated by the Bohr equation shows high values but this is entirely explained by hyperventilation [3].

Chemosensitivity is increased in PAH in proportion to disease severity [3, 7–11]. Accordingly, hypocapnia, increased ventilation to CO_2 output relationships (V_E/VCO_2) and sympathetic nervous system hyper-activity a predictors of decreased survival in PAH [8–10], much like in congestive heart failure (CHF) [12, 13]. The reasons for increased chemosensitivity and related sympathetic nervous system activation in (right) heart failure are not exactly known. Both increased filling pressures of the right heart and altered baroreflex control are thought to be involved [11]. Increased chemosensitivity contributes to dyspnea. Sympathetic nervous system activation has deleterious effects in the long term on the heart and the pulmonary circulation.

The contributions of chemosensitivity and dead space to hyperventilation can be assessed by a graphical representation of the alveolar ventilation equation. Accordingly, V_E/VCO_2 is plotted as a function of either alveolar (end-expiratory) or arterial PCO_2. A $P(a\text{-}A)CO_2$ gradient of less than 5 mmHg reasonably excludes an impact of increased dead space on ventilation [3]. An increase in V_E/VCO_2 along with a decrease in $PACO_2$ indicates an increased chemosensitivity, but measurements of $PaCO_2$ are needed to identify a contribution of increased dead space [3, 11]. This is illustrated in Fig. 14.2 showing V_E/VCO_2 and PCO_2 measurements in groups of 12 patients with PAH and 12 with CHF. In that study, the measurements in each patient were collected at the anaerobic threshold to limit the effects of relative changes in dead

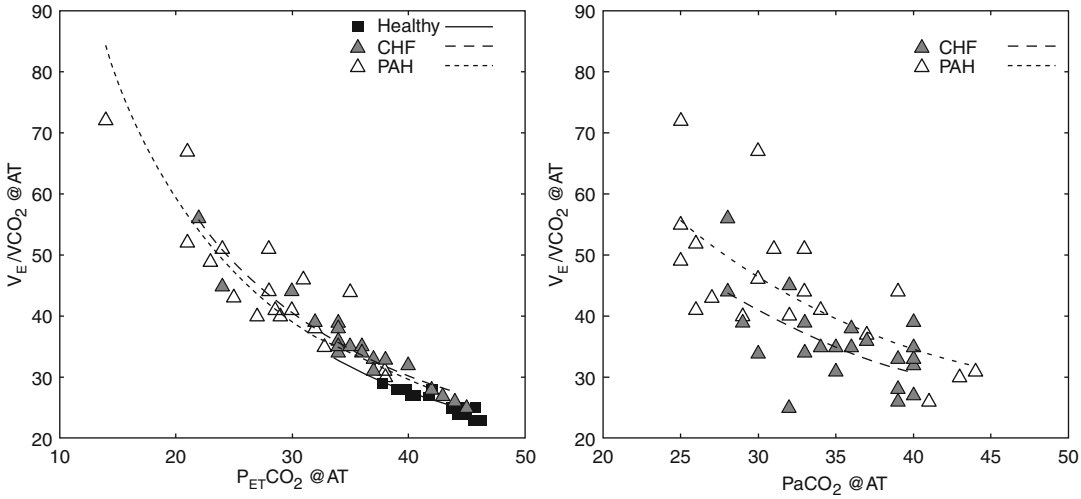

Fig. 14.2 Ventilation (V_E) versus CO_2 output (VCO_2) as a function of end-tidal PCO_2 ($P_{ET}CO_2$) in normal subjects and in patients with congestive heart failure (*CHF*) or pulmonary arterial hypertension (*PAH*), *left panel*, and as a function of $PaCO_2$ in patients with PAH or CHF, *right panel*. Increased V_E/VCO_2 at lower PCO_2 indicates increased chemosensitivity. The gradient between $PaCO_2$ and $P_{ET}CO_2$ remained within the limit of normal of 5 mmHg in the majority of the patients, but with variability, indicating minimal to moderate contribution of increased dead space ventilation in both conditions

space with increased tidal volumes during exercise The PCO_2 gradient was slightly higher than 5 mmHg in some patients with CHF, on average of 1 mmHg in patients with PAH, but with some variability, compatible with a minimal to moderate contribution of dead space on ventilation in both conditions.

Exercise Capacity

In spite of increased ventilation, there is no ventilatory limitation to aerobic exercise capacity in patients with PAH. The cardiopulmonary exercise test (CPET) in PAH is characterized by decreased maximum workload, VO_2max, VO_2 at the anaerobic threshold and VO_2pulse, increased V_E/VCO_2, increased resting but decreased maximum heart rates, and slower rates of increase and recovery of heart rate indicating altered chronotropy [7]. This is typical of a cardiac limitation to exercise capacity. Not surprisingly, CPET in patients with either PAH or CHF is similar [12, 13]. Relevant CPET measurements in patients with mild or severe PAH compared to normal subjects are shown in Fig. 14.3.

However, patients with PAH compared to CHF patients at similar functional impairment have a relatively lower VO_2max, higher V_E/VCO_2 and more limited increase in O_2 pulse, indicating more limited increase in stroke volume contribution to increased cardiac output at exercise [13]. In both cases, the ventilatory reserve (maximum voluntary ventilation minus maximum ventilation at exercise) is normal, in the range of 40–60 L/min or more, and certainly higher than the critical level of 11 L/min diagnostic of a ventilatory limitation in patients with obstructive lung diseases.

In summary, in PAH, hypoxemia reflects a decrease in cardiac output, hypocapnia reflects increased chemosensitivity and CPET discloses a cardiac output limitation to exercise capacity. The main suspect accounting for PAH symptomatology is the RV.

Right Ventricular Failure

How does the RV fail in PAH? The normal RV is a thin-walled crescent-shape structure, designed to function as a flow generator accommodating

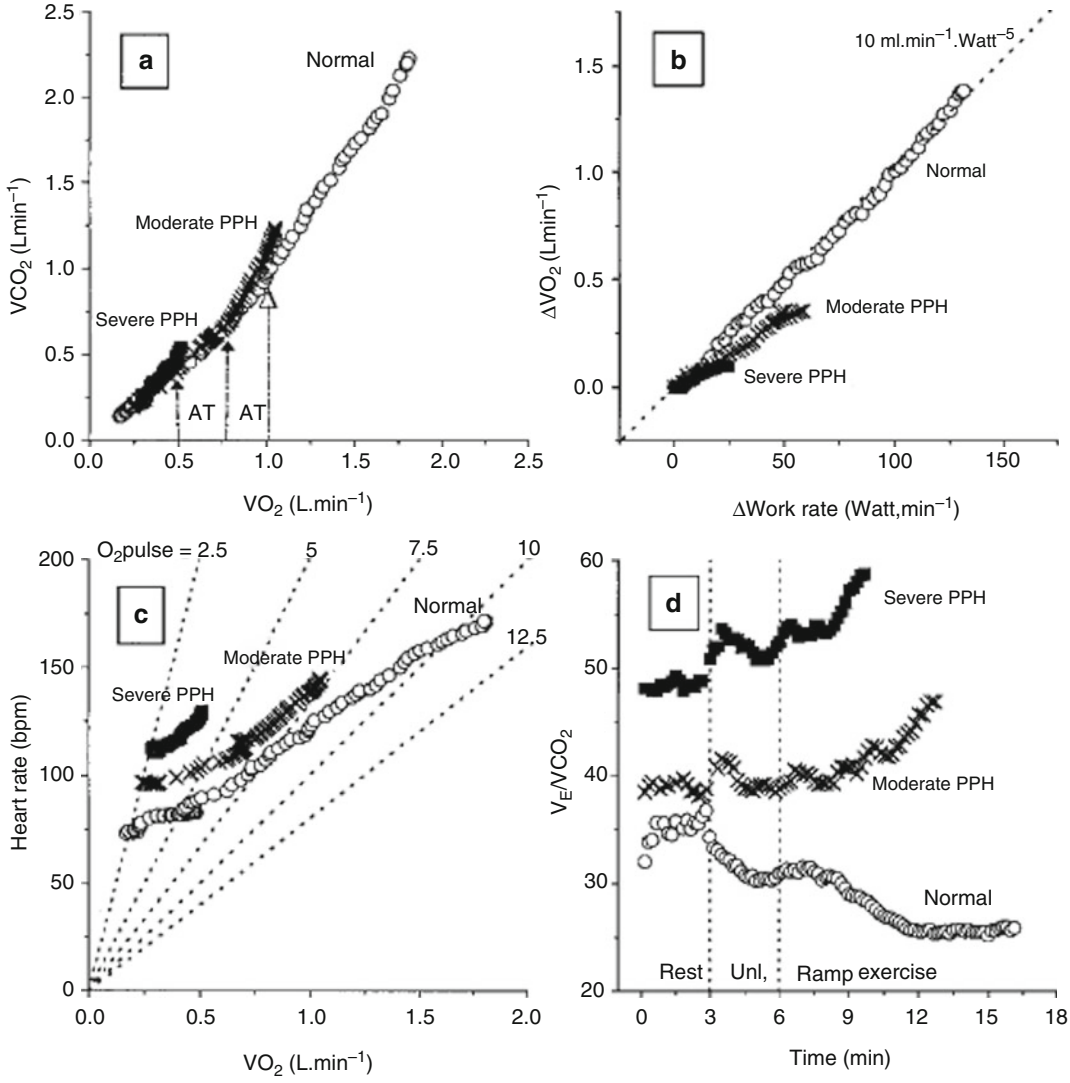

Fig. 14.3 Panels showing CO_2 production and heart rate as a function of oxygen uptake (VO_2), *left*, (**a**) and (**c**), and changes in VO_2 as a function of changes in work rate and ventilatory equivalent for CO_2 (V_E/VCO_2) as a function of time, *left*, (**b**) and (**d**) in a normal subject (*empty circles*) and two patients with moderately severe or very severe. idiopathic pulmonary arterial hypertension (*PPH*). Patients with PPH have decreased maximal values for VCO_2 and VO_2, increased resting heart rate but decreased maximal heart rate, decreased rate of increase in VO_2 as a function of rate of increase in work rate, and increased ventilatory equivalents for CO_2 in proportion to disease severity (Reprinted from Sun et al. [7]. With permission from Wolters Kluwer Health)

the entire systemic venous return to the heart [14]. Its thin walls leave it vulnerable to failure with any acute rise in wall stress. A brisk increase in PVR, for example produced by pulmonary arterial constriction to mimic massive pulmonary embolism, induces acute dilatation and rapid pump failure of the RV, showing that the structure is intrinsically poorly adapted to cope with a rapid increase in afterload [15]. However, a gradually progressive increase in PVR can allow for RV adaptation and remodeling, basically like the LV facing a progressive increase in systemic vascular resistance, such as in the setting of systemic hypertension [16]. Beat-to-beat changes in

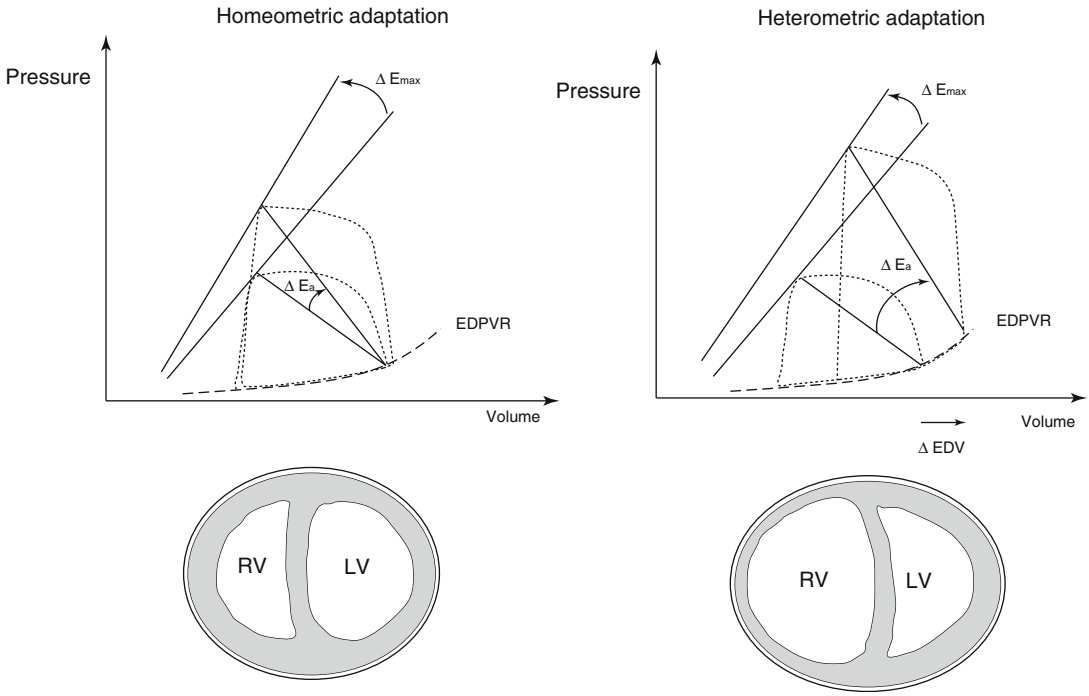

Fig. 14.4 Theoretical right ventricular pressure-volume loops before and after an increase in pulmonary artery pressure, showing left an increase in end-systolic elastance with unchanged volumes, purely homeometric adaptation, and right a predominantly heterometric adaptation with increased volumes

preload or afterload are accompanied by a heterometric dimension adaptation described by Starling's law of the heart. Sustained changes in load are associated with a homeometric contractility adaptation [17] referred to as Anrep's law of the heart after the initial observation by Gleb von Anrep in 1912 of rapid increase in LV contractility in response to an aortic constriction [18].

Homeometric adaptation to afterload (that is, without chamber dilatation) has been demonstrated on RV exposed to pulmonary arterial constriction and in conditions of constant coronary perfusion [19, 20]. Failure of systolic function, or contractility, to increase in response to loading conditions results in a heterometric adaptation allowing for maintained stroke volume (SV) at the price of increased end-diastolic volume (EDV) [16]. Homeometric versus heterometric adaptations of the RV to afterload are illustrated in Fig. 14.4.

It is therefore possible to define RV failure as a dyspnea-fatigue syndrome with eventual systemic venous congestion, caused by the inability of the RV to maintain flow output in response to metabolic demand without heterometric adaptation, and consequent rise in right heart filling pressures. This definition encompasses a spectrum of clinical situations, from preserved maximum cardiac output and aerobic exercise capacity at the price of increased RV end-diastolic volumes and wall thickness (and thence raised diastolic filling pressures) to low-output states with small RV volumes at rest. This definition has been endorsed at a recent world symposium on pulmonary hypertension held in 2013, in Nice [21].

It is noteworthy that RV failure is a very late clinical finding in one particular form of PAH; that is, in Eisenmenger Syndrome (ES, where congenital cardiac left to right communications are complicated by progressive pulmonary vascular disease with eventual shunt reversal and right to left flow through the initial cardiac defect). Despite similar structural changes in the pulmonary vasculature, life expectancy in ES is

decades longer than for idiopathic PAH [22]. Whereas this is in part due to the existence of a "decompressing" cardiac communication allowing the relief of excess right heart pressures, the RV likely performs better in this setting as it has never "detrained" after birth and remained hypertrophied and well adapted to pressure loading, throughout life [23].

Systolic Function of the RV

Because of the importance of homeometric adaptation of the RV in PAH, measurements have to be referred to a gold standard. In vivo, this is maximal elastance (Emax), or the maximum value of the ratio between ventricular pressure and volume measured continuously during the cardiac cycle (i.e. the "pressure-volume loop") [16, 21]. The Emax of the LV coincides with end-systole, and is thus equal to the ratio between end-systolic pressure (ESP) and end-systolic volume (ESV) defining an end-systolic elastance (Ees). Left ventricular Ees is equal to Emax measured at the upper left corner of a square-shaped pressure-volume loop [24]. Because of naturally low pulmonary vascular impedance, however, the normal RV pressure-volume loop has a triangular rather than square shape and Emax occurs before the end of ejection, or end-systole [25]. However, a satisfactory definition of Emax can be obtained by the generation of a family of pressure-volume loops at decreasing venous return (generated, for example, by progressive inferior vena cava occlusion with balloon inflation) [25]. With increasing impedance in pulmonary hypertension, the shape of the RV pressure-volume loop changes. Pressure rises throughout ejection and peaks at or near end-systole. Maximum elastance then typically occurs at ESP like on a LV pressure-volume loop [26]. Thus the gold standard measurement of systolic function is Emax for the RV, as it is for the LV [16, 20, 27].

Instantaneous measurements of RV volumes are difficult to obtain at the bedside, and so are manipulations of venous return. This is why single beat methods have been developed, for the LV [28] and thence adapted to the RV [29]. The single beat method relies on a maximum pressure Pmax calculation from a nonlinear extrapolation of the early and late portions of a RV pressure curve, an integration of pulmonary flow and synchronization of the signals. Emax is estimated from the slope of a tangent from Pmax to the pressure-volume curve.

Examples of Pmax and Emax calculations are shown in Fig. 14.5.

The single beat method can be applied with relative changes in volume measured by integration of ejected flow rather than with measurements of absolute volumes. This is because Emax is not dependent on preload, or EDV [16]. An excellent agreement between directly measured Pmax by clamping the main pulmonary artery for one beat and calculated Pmax has been demonstrated in a large animal experimental preparation with no pulmonary hypertension or a mild increase in Ppa induced by low oxygen breathing [29].

Measurements of RV Emax with conductance catheter technology and inferior vena cava balloon obstruction have been reported in normal volunteers [31]. A limited number of Emax determinations have been reported in patients with PAH either using the single beat approach, fluid-filled catheters and magnetic resonance imaging (MRI) [30] or a multiple beat approach with venous return decreased by a Valsalva maneuver and conductance catheters [32]. Pressure-volume loops from a patient with PAH compared to a normal control and MRI RV volume measurements are also shown in Fig. 14.5.

The single beat approach with high fidelity Millar catheters and integration of a transonic measurement of pulmonary flow were reported in a patient with a systemic RV in the setting of congenitally corrected transposition of the great arteries (where the RV is the subaortic ventricle) [33].

Most recently high-fidelity RV pressure and volume measurements and single beat Emax calculations have been reported in a small series patients with CTEPH, a condition with similar symptomatology to that of PAH [34]

These limited size reports confirm the importance of systolic function adaptation with an increased Emax to maintain RV-arterial coupling in the face of severe increases in Ppa, in agreement

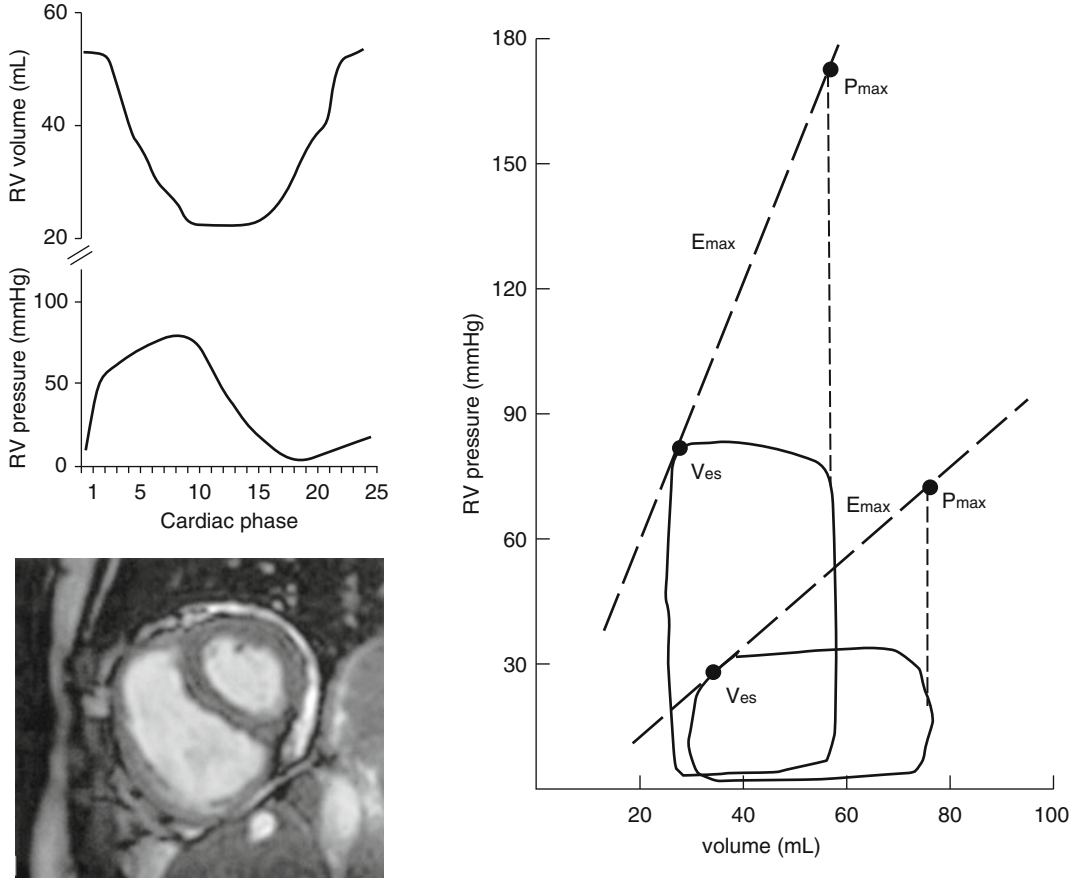

Fig. 14.5 Right ventricular (*RV*) pressure and volume curves with illustrative magnetic resonance imaging which was used for volume measurements (*left*) and derived maximal RV pressure (*Pmax*) and maximal elastance (*Emax*) in a normal control subject and in a patient with severe pulmonary arterial hypertension (PAH) (*right*). The normal subject had a Emax/Ea ratio of 1.7–2. The Emax/Ea ratio was decreased to 1 in the PAH patients, because of insufficient increase in Emax to match the increased Ea. *Ves* end-systolic volume. (Reprinted from Kuehne et al. [30]. With permission from Wolters Kluwer Health)

with previous studies in various animal species [35], or experimental models of acute [36–39] or chronic [40–43] pulmonary hypertension.

Coupling of Systolic Function to Afterload

Measurements of systolic function are ideally constant over a wide range of preload or afterload. This requirement is met by Emax in intact hearts, because this measurement is the only point of the pressure-volume curve that is common in systole to ejecting and non-ejecting beats. Therefore, Emax offers the optimal intact heart counterpart of an isolated muscle active tension length relationship. However, Emax adapts to afterload as soon as after several beats, starting after 20–30 s, with full expression of homeometric adaptation replacing initial heterometric adaptation in a couple of minutes – without requirement of a hypertrophic response [17, 19]. It is therefore important to correct Emax for afterload.

There are three possible measurements of afterload [27]. The first is maximum ventricular wall stress, which is approximated by the maximum value of the product of volume by pressure,

divided by wall thickness. This is an adaptation of Laplace's law for spherical structures, and thus problematic for the RV because of its irregular shape and thus considerable regional variations in internal radius. The second is the forces that oppose flow ejection, or hydraulic load. This calculation optimally requires a spectral analysis for the integration of arterial pressure and flow waves. The third and more straightforward approach is to derive arterial elastance (Ea) as it is "seen" by the ventricle by dividing maximal elastance pressure by SV (Fig. 14.5). The advantage of Ea to estimate afterload is that the measurement is obtained together with Emax on the same pressure-volume loop, and thus convenient to evaluate the adequacy of systolic function adaptation to afterload [16].

Thus contractility corrected for afterload is defined by a ratio of Emax to Ea. Experimental work and mathematical modeling have allowed the definition of an optimal mechanical coupling of Emax to Ea equal to one, but an optimal energy transfer from the ventricle to the arterial system at an Emax/Ea ratio of 1.5–2 [16].

RV-Arterial Coupling in Experimental Pulmonary Hypertension

RV-arterial coupling measured with the Emax/Ea ratio has been investigated in various models of pulmonary hypertension. Hypoxic pulmonary vasoconstriction, acute pulmonary microembolism, pulmonary artery banding, early stage endotoxic shock and PH on chronic aorta-pulmonary shunting were associated with a preserved RV-arterial coupling because of increased RV contractility matching the increased afterload [29, 35–40]. By contrast, insufficient increase in Emax to match increased afterload has been observed in late stage endotoxic shock [37], long-term chronic aorta-pulmonary shunting [41], monocrotaline-induced PH [42] and mild PH in overpacing-induced CHF [43].

Altogether, these studies support the notion of predominant RV systolic function adaptation to increased afterload in various models of pulmonary hypertension, but with RV-arterial uncoupling and increased RV volumes in the context of inflammation (endotoxemia, monocrotaline), long-term increase in PVR, or secondary to left heart failure.

RV-Arterial Coupling Measurements in Patients with Pulmonary Hypertension

Measurements of both Emax and Ea have been reported in a limited number of patients with PAH. In a first study on six patients with idiopathic PAH (IPAH) but no clinical RV failure, compared to six controls, Kuehne measured RV volumes with magnetic resonance imaging (MRI) and RV pressures using fluid-filled catheters, synchronized the signals and calculated Emax and Ea using the single beat method [30]. RV-arterial coupling in a patient with PAH and in a control are shown in Fig. 14.5. Emax was increased threefold, from 1.1 ± 0.1 to 2.8 ± 0.5 mmHg/ml, but Ea was increased from 0.6 ± 0.5 to 2.7 ± 0.2, so that the Emax/Ea ratio decreased from 1.9 ± 0.2 to 1.1 ± 0.1. Yet RV volumes were not increased, indicating "sufficient" coupling, at least in resting conditions.

Tedford reported on RV-arterial coupling in five patients with IPAH and seven with systemic sclerosis (SSc)-associated PAH [32]. In that study, RV volumes and pressures were measured with conductance catheters and Emax defined by a family of pressure-volume loops as venous return decreased by a Valsalva maneuver (validated against inferior vena cava obstruction). In IPAH patients, Emax was 2.3 ± 1.1, Ea 1.2 ± 0.5, and Emax/Ea preserved at 2.1 ± 1.0. In SSc-PAH patients, Emax was decreased to 0.8 ± 0.3 in the presence of an Ea at 0.9 ± 0.4, so that Emax/Ea was decreased to 1.0 ± 0.5.The authors also showed that the time constant of the pulmonary circulation, or the product of PVR by pulmonary arterial compliance, was not decreased in SSc-PAH as compared to IPAH, indicating that depressed Emax in SSc-PAH was not caused by a relatively higher pulsatile hydraulic load. Additionally, seven patients with SSc but without pulmonary hypertension maintained preserved

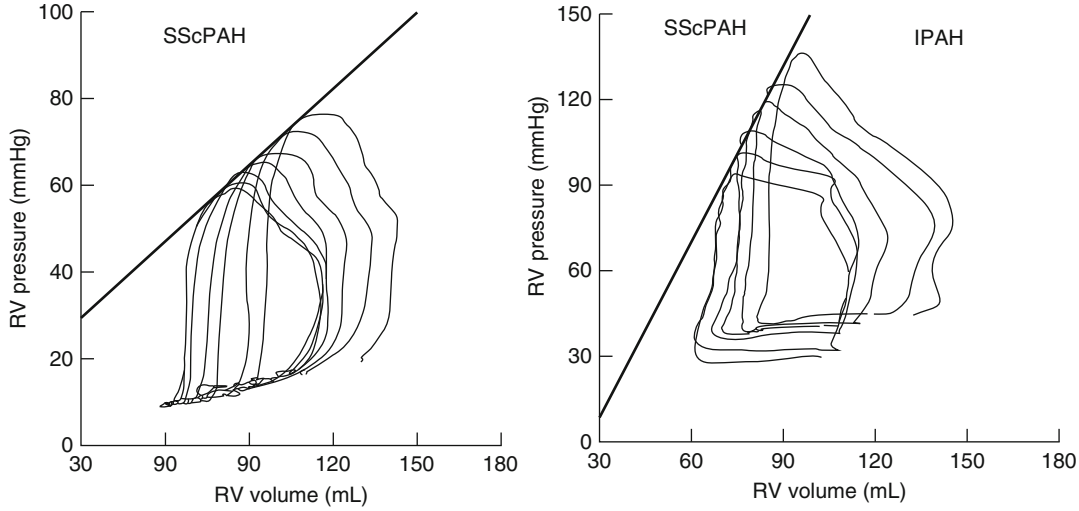

Fig. 14.6 Right ventricular pressure-volume loops at decreasing venous return in a patient with systemic sclerosis (*SSc*)- associated pulmonary arterial hypertension (*PAH*), *left*, and in a patient with idiopathic PAH (*IPAH*), *right* The slope of linearized maximum elastance pressure-volume relationship is higher at similar mean pulmonary artery pressure in IPAH (Reprinted from Tedford et al. [32]. With permission from Wolters Kluwer Health)

coupling (Emax/Ea 2.3 ± 1.2). Two examples are shown in Fig. 14.6.

Along with these studies on patients with PAH, there is a case report of a systemic RV in an asymptomatic young adult with a congenitally corrected transposition of the great arteries [33]. The systemic RV had a Emax of 1.26, while Ea was of 1.1 and Emax/Ea 1.2. The pulmonary LV had a Emax of 0.39 while Ea was 0.23 and Emax/Ea 1.7. In this patient, low absolute values for Emax of the pulmonary LV are related to a low pulmonary Ea, both probably in relation to the fact that the measurements were done during general anesthesia for surgical correction of an asymptomatic atrial septal defect [33].

McCabe reported on Emax and Ea measurements in ten patients with CTEPH [34]. Pressures and volumes were measured with with a conductance catheter. The results were compared with those of seven patients with thromboembolic pulmonary vascular disease (CTE) but no pulmonary hypertension and seven normal controls. In the CTEPH patients, Emax was 1.1 ± 0.4, Ea 1.9 ± 0.7 and Emax/Ea 0.6 ± 0.1. In the CTE patients Emax was 0.6 ± 0.3, Ea 0.5 ± 0.2 and Emax/Ea 1.3 ± 0.4. In the controls, Emax was 0.4 ± 0.2, Ea 0.3 ± 0.1 and Emax/Ea 1.5 ± 0.3.

Altogether, these results confirm the predominant role of homeometric adaptation of the RV to increased afterload, but uncoupling when the hydraulic load remains too high for too long time, or in the presence of systemic disease. On the methodological side, it is apparent that Emax and Ea show variability with possibly a trend to higher control values when measurements are based on families of pressure-volume loops rather than on the single beat method. RV volumes measured using a conductance catheter appear to underestimate ESV and EDV compared with MRI measurements [34]. Targeted therapies in PAH patients might also have affected these results.

In the above enumerated clinical studies, RV volumes remained normal, showing adequacy of RV-arterial coupling at rest with Emax/Ea ratios around 1 or even less. The level of RV-arterial decoupling needed to observe the onset of RV dilatation is not defined. Reported measurements were obtained at rest. Requirements of higher cardiac output at exercise probably triggers a heterometric adaptation with increased EDV to ensure sufficient RV flow output. This remains to be explored.

Patients with PAH at some point start to develop signs and symptoms of RV failure, with signs including positive hepato-jugular reflux,

increased liver size, edema and ascites [1]. The pathobiological events leading to RV-arterial uncoupling and increased RV volumes remain to be identified.

The current understanding of the pathophysiology of RV failure involves neuro-humoral activation, expression of inflammatory mediators, apoptosis, capillary loss, oxidative stress and metabolic shifts, with variable fibrosis and hypertrophy [21, 44, 45]. In later stages, RV ischemia may play a role [46]. The exact sequence of events and interactions are being explored, and each has still to be referred to sound measurements of function, as illustrated in recent studies which showed inflammation and apoptosis correlated to decreased Emax/Ea in acute [47] as well as chronic [48] models of RV failure as a universal mechanism.

Pharmacology of RV-Arterial Coupling in Pulmonary Hypertension

Right ventricular function is a major determinant of quality of life, exercise capacity and outcome in PAH [1, 21]. Treatment strategies in these patients logically aim at decreasing RV afterload, often assessed by a measurement of PVR – or improvement in maximum cardiac output obtained by unloading the RV assessed by exercise capacity. However, it has been hypothesized that some of the vasodilators used for this purpose might also have intrinsic positive inotropic effects. There are data suggesting that this could be the case of prostacyclins [49] or phosphodiesterase-5 inhibitors [50]. On the other hand, treatments specifically targeting the RV are currently under consideration. The most obvious would be interventions aimed at the excessive neuro-humoral activation, which have been shown to improve survival in LV failure. Finally, patients with pulmonary hypertension may be exposed to the cardiovascular effects of general anesthesia or require treatments with inotropic drugs in case of severe RV failure [51, 52]. In all these circumstances, it is important to know the effects of the interventions on the components of RV-arterial coupling.

Catecholamines are sometimes believed to cause pulmonary vasoconstriction and to induce excessive tachycaredia [51]. Moreover, catecholamines have been associated with increased mortality in RV failure [52]. The latter effect is probably due to the fact that these drugs are prescribed in the most severely ill patients, but the data nevertheless cause concern. Low-dose dobutamine increased RV-arterial coupling by an inotropic effect without [29, 53] or with [54] a decreased afterload. Low-dose norepinephrine improved RV-arterial coupling through an exclusive positive inotropic effect, which was however less pronounced than with low-dose dobutamine [54]. Acute administration of propranolol reduced RV-arterial coupling through combined negative inotropy and pulmonary vasoconstriction during an acute hypoxic exposure [29]. Chronic administration of bisoprolol improved RV-arterial coupling by an improved contractility in monocrotaline-induced pulmonary hypertension [42]. Inhaled anesthetics worsen RV-arterial coupling by combined decrease in Emax and increase in Ea [55].

Acute administration of epoprostenol or inhaled nitric oxide improved RV-arterial coupling through exclusive pulmonary vasodilating effects in overcirculation-induced pulmonary hypertension [56]. Acute epoprostenol partially restored RV-arterial coupling through an exclusive pulmonary vascular effect in pulmonary banding-induced persistent RV failure [57] or was associated with maintained RV-arterial coupling because of decreased contractility in proportion to decreased PVR in hypoxia [58]. Levosimendan improved RV-arterial coupling through combined inotropy and vasodilation in pulmonary banding-induced persistent RV failure [53, 59]. Sildenafil improved RV-arterial coupling in hypoxia because of exclusive pulmonary vasodilating effects [60], but improved the coupling with by a positive inotropic effect in monocrotaline-induced pulmonary hypertension [61]. Bosentan had no intrinsic effect on contractility in pulmonary hypertension on 3 months of aorta-pulmonary shunting [40]. Milrinone improved RV-arterial coupling by an improved contractility in overpacing-induced congestive heart failure with mild pulmonary

hypertension, while nitroprusside or inhaled nitric oxide had no effect in this model [43].

It is interesting that acute and chronic effects of interventions on RV-arterial coupling in experimental pulmonary hypertension may be quite different, as shown for β-blockers or sildenafil. This calls for testing of drugs in multiple experimental models, and extrapolation to patients with pulmonary hypertension whenever possible.

At present, there are no reports on the effects of pharmacological interventions on RV-arterial coupling in patients with PAH. One is thus limited to extrapolation from experimental animal studies, sound pathophysiological reasoning and clinical judgment.

Simplified Methods for the Measurement of RV-Arterial Coupling

Volume Measurements

A ratio of elastances can be simplified to a ratio of volumes, provided ESV is measured at the point of maximal elastance, not at the end of ejection. This is dependent on loading conditions. Pressure-volume relationships of the RV chronically exposed to increased Ppa tend to resemble LV pressure-volume loops [26], so that the approximation seems reasonable.

Sanz measured ESV and SV by MRI and showed that the SV/ESV ratio is initially preserved in patients with mild pulmonary hypertension but decreases with increasing severity of the disease [62]. A problem with the SV/ESV ratio is the inherent assumption that the ESP-ESV relationship is linear and crosses the origin. This is incorrect, because ventricular volume at a zero filling pressure has to be positive. Therefore the ESP/ESV underestimates Emax. There could be compensation by ESV being decreased compared to the ventricular volume at the point of Emax, but probably insufficiently so in pulmonary hypertension. Thus the SV/ESV as a simple volume measurement of RV-arterial coupling requires further evaluation and estimation of functional and prognostic relevance. It can ideally be reasoned that the SV/ESV ratio includes the information of RV ejection fraction (EF), or SV/EDV in a less preload-dependent manner, but the relevance of this remains to be established.

A recent study reported on the negative impact on outcome of decreased RVEF in spite of targeted therapies-associated decreased PVR in patients with PAH [63]. While this study shows the importance of RV function in the prognostication of PAH, vasodilating therapies may be a confounding factor. Systemic vasodilating effects of targeted therapies in PAH may increase systemic venous return and increase EDV, which decreases EF if SV remains essentially unchanged, while increased cardiac output may decrease PVR without any change in the functional state of the pulmonary circulation [64]. In any case, studies such as this re-emphasise the critical role of RV function in prognosis in PAH.

Current progress in echocardiography makes more accurate measurements of the pulmonary circulation and RV function increasingly possible [65] even though precision may remain an issue for individual decision-making based on cut-off values [66]. Advances in 3-dimensional echocardiography now offer the prospect of easier bedside measurements of RV volumes, [67] and thus of EF or SV/ESV for the evaluation of RV-arterial coupling. It should be noted, however, that 3D echo estimates tend to systematically underestimate RV volumes at high values [68]

Pressure Measurements

Another simplified approach for the measurement of RV-arterial coupling introduced by Trip relies on a Pmax calculated from a RV pressure curve, which is easily obtained during a right heart catheterization, mean Ppa (mPpa) taken as a surrogate of ESP, and RV volume measurements by MRI [69]. The authors calculated Emax as (Pmax−mPpa)/(EDV−ESV) and Emax assuming V0 = 0 as mPpa/ESV. V0 is the extrapolated volume intercept of the linear best fit of a multipoint maximum elastance pressure-volume relationship. The results showed that mPpa/ESV was lower than (Pmax−mPpa)/SV, on average about half the value, while V0 ranged from –8 to 171 ml and was correlated to EDV and ESV. From this the authors concluded that V0 is dependent on

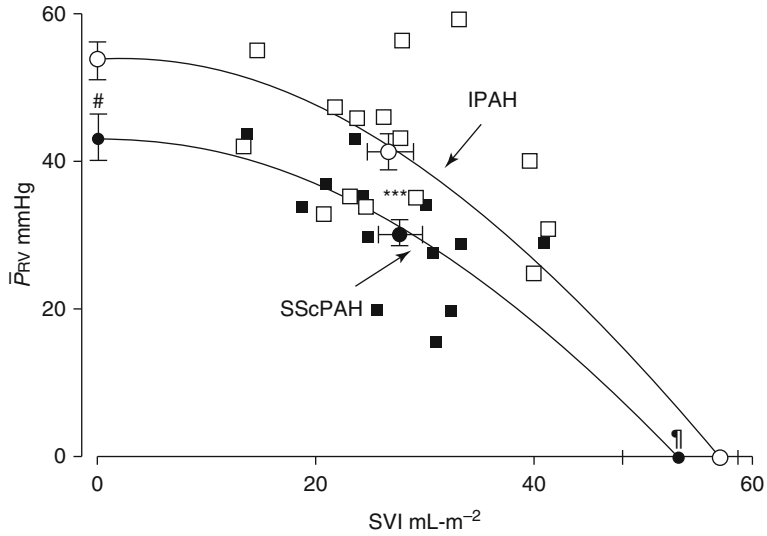

Fig. 14.7 The pump function graph of patients with idiopathic pulmonary arterial hypertension (*IPAH*) and patients with systemic sclerosis associated PAH (*SScPAH*), with indication of mean ± SEM. Stroke volume (*SV*) and maximal SV were not different but isovolumic right ventricular pressure (P_{RV}) was higher in IPAH (Reprinted from Overbeek et al. [72]. With permission from European Respiratory Society)

RV dilatation, and thus the estimated Emax more preload-dependent than previously assumed.

An alternative explanation may be in the uncertainties of extrapolations from linear fits of relationships that have been demonstrated to be curvilinear [70]. End-systolic elastance or Emax is best determined by interpolation of pressure-volume coordinates [70], with tightening by a correction for EDV [32]. Further uncertainty is related to the use of a mPpa/SV ratio or slope of (Pmax−mPpa)/SV as a surrogate of Emax determination from single or (better) multiple beat pressure-volume relationships. Extrapolations amplify errors that are made by the use of surrogate pressures and volumes.

Alternative Methods to Evaluate RV-Arterial Coupling

The Pump Function Graph

The coupling of RV function to the pulmonary circulation can also be described by pump function curves relating mean RV pressure to SV [71]. A pump function graph is built from measurements of mean RV pressure and SV, a calculated Pmax at zero SV and a parabolic extrapolation to a zero pressure SV [21, 27]. In this representation, an increase in preload shifts the curve to greater SV with no change in shape, while an increased contractility leads to a higher Pmax with no change in maximum SV. The pump function graph helps to understand that at high PVR, a fall in pressure markedly increases SV while at low PVR pressure is more affected than SV [27].

The pump function graph has been used to demonstrate more severe RV failure at any given level of mPpa in SSc-PAH as compared to idiopathic PAH [72]. This is illustrated in Fig. 14.7.

The limitations of the pump function graph are in its sensitivity to changes in preload and, as already mentioned, to the use of mean RV pressure or mPpa as surrogates of maximum elastance RV pressure.

The Contractile Reserve

Systolic function adaptation to afterload can also be tested dynamically to determine a contractile reserve, or the capacity to increase contractility at a given level of loading. Contractile or ventricular reserve determined using exercise or

pharmacological stress tests (typically an infusion of dobutamine) has been shown to be a strong predictor of outcome in heart failure [73]. The evaluation of RV contractile reserve has not been reported until now in patients with pulmonary hypertension. In rats with pulmonary arterial banding, Emax was shown to increase to the same extent in response to 2.5 μg/kg/min than in controls, suggesting preserved systolic function in this pulmonary hypertension model [39].

A simple noninvasive approach was recently introduced by Grunig et al. [74]. In that study, Doppler echocardiography was used to measure RV systolic pressure from the maximum velocity of tricuspid regurgitation at rest and at exercise in 124 patients with either PAH or chronic thromboembolic pulmonary hypertension (CTEPH). An exercise-induced increase by more 30 mmHg was a strong predictor of exercise capacity and survival; the inference being that if RV contractile reserve remains good, then a pressure response to exercise can be successfully mounted despite increased afterload. Further studies will explore improved indices with incorporation of volume measurements and end-systolic pressure determinations, as this is now becoming possible using bedside noninvasive methodology.

Surrogate Measurements of RV-Arterial Coupling

Right ventricular systolic function can be estimated by a series of invasive and noninvasive measurements easily available in daily clinical practice.

Right heart catheterization allows for measurements of Ppa, right atrial pressure and cardiac output (Fick or thermodilution) and thus calculations of RV function curves such as cardiac output, SV or stroke work (SW, mean Ppa × SV). Stroke work calculated as mPpa × SV ignores the pulsatile component of work. It has been recently estimated that the pulsatile component of SW amounts to 23 % of total work independently of type and severity of pulmonary hypertension, so that total SW = 1.3 mPpa × SV [75]. This fixed relationship is explained by the constancy of the time constant of the pulmonary circulation, or PVR × pulmonary arterial compliance (Ca), or RC-time in normal subjects and in patients with pulmonary hypertension [76]. The RC-time is actually decreased in left heart failure [77] and in patients with proximal operable CTEPH [78], but increased in purely distal pulmonary micro-vascular obstruction [79]. However, the deviations are relatively mild. The pulsatile component of RVSW would vary on average from 20 to 26 %, with extremes of from 15 to 30 %. Therefore, total work is then estimated to vary between 1.2 and 1.4 times steady-flow work. The near-constancy of the RC-time thus implies a relatively stable prediction of total RVSW. It remains that right atrial pressure is an imperfect surrogate of preload, which is measured in the intact heart by an EDV.

Right ventricular contractility can be measured by preload recruitable SW (PRSW) defined by SW–EDV relationships at variable venous return [80]. The slope of PRSW has been shown to be reproducible and sensitive to changes in contractile state. However, whether PRSW is useful to evaluate RV-arterial coupling has not been clearly shown. The measurement requires invasive volume and high-fidelity pressure measurements with a manipulation of venous return, and is thus difficult to implement at the bedside.

Imaging techniques such as MRI or 3-dimensional echocardiography allow for measurements of RV volumes, ejection fraction, and SV/ESV ratios. The limitation of imaging is in the absence of direct pressure measurements. Guazzi has recently been proposed to use noninvasive echocardiographic measurements of a tricuspid annular plane excursion (TAPSE) as a measure of RV systolic function and of the maximum velocity of tricuspid regurgitation-derived systolic Ppa (SPpa) as a measure of afterload, and derive a TAPSE/SPpa ratio as an estimation of RV-arterial coupling [81]. This indirect index of RV-arterial coupling may be useful as it has been shown to predict survival in patients with left heart failure and decreased or preserved ejection fraction.

A series of imaging-derived indices of RV systolic function, such as MRI-determined EF or Doppler echocardiographic measurements of

fractional area change measured in the 4-chamber view (a surrogate of EF), TAPSE, tissue Doppler imaging (TDI) of the tricuspid annulus systolic velocity S wave and isovolumic acceleration (IVA) or maximum velocity (IVV), strain or strain rate have been shown to be related to functional state and prognosis in severe pulmonary hypertension [21, 65]. Isovolumic phase indices such as the IVA or IVV are probably the less preload-dependent, and as such the closest estimates of Emax measurements [82, 83].

Diastolic Function

The present review has focused on RV systolic function and RV-arterial coupling as the essential biomechanical mechanism of ventricular function adaptation to increased afterload in PAH. However, a Starling heterometric adaptation may occur at any stage of disease progress depending on rate of progression, more or less inflammatory nature of pulmonary hypertension and systemic conditions affecting cardiac function. There is thus interest in taking into account diastolic function in the RV adaptation to pulmonary hypertension.

Diastolic function is described by a diastolic elastance curve determined by a family of pressure-volume loops at variable loading. It is curvilinear thus impossible to summarize as a single number. Several formulas have been proposed [27]. Most recently Rain reported on 21 patients with PAH in whom RV diastolic stiffness was estimated by fitting a non-linear exponential curve through the diastolic pressure-volume relationships, with the formula $P=\alpha\ (e^{V}\beta-1)$, where α is a curve fitting constant and β a diastolic stiffness constant [84]. In that study, the diastolic stiffness constant β was closely associated to disease severity. The pathogenesis of RV diastolic dysfunction was related to increased RV collagen content (ie fibrosis) and stiffness of the RV sarcomeres, in turn due to reduced phosphorylation of titin, a key protein regulating myocyte stiffness

A series of surrogate measurements of diastolic function are provided by Doppler echocardiography: isovolumic relaxation time and a decreased ratio of transmittal E and A waves or mitral annulus tissue Doppler imaging E′/A′ waves, increased right atrial or RV surface areas on apical 4-chamber views, altered eccentricity index on a parasternal short axis view, estimates of right atrial pressure from RV diastolic function indices or inferior vena cava dimensions, pericardial effusion, and the so-called Tei index, which is the ratio of isovolumetric time intervals to ventricular ejection time and thus integrates diastolic and systolic function. [65].

Ventricular Interaction

Right ventricular function has to be understood in the context of its direct and indirect interactions with LV function. Direct interaction, or ventricular interdependence, is defined as the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral or circulatory effects [85]. Diastolic ventricular interaction refers to the competition for space within indistensible pericardium when the RV dilates, which alters LV filling and may be a cause of inadequate cardiac output response to metabolic demand. Right heart catheterization and imaging studies have shown that in patients with severe pulmonary hypertension, pulmonary artery wedge pressure and LV peak filling rate are altered in proportion to decreased RV ejection fraction [86]. Systolic interaction refers to positive interaction between RV and LV contractions. It can be shown experimentally that aortic constriction, and enhanced LV contraction, markedly improves RV function in animals with pulmonary arterial banding [87]. Similarly, in electrically isolated ventricular preparations in the otherwise intact dog heart, LV contraction contributes a significant amount (~30 %) to both RV contraction and pulmonary flow [88]. This is explained by a mechanical entrainment effect, but also by LV systolic function determining systemic blood pressure which is an essential determinant of RV coronary perfusion. Increased RV filling pressures and excessive decrease in blood pressure may be a cause of RV ischemia and decreased contractility. An additional cause of negative

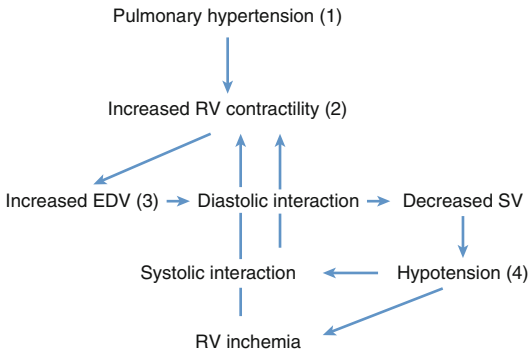

Fig. 14.8 A global view on right heart failure, with targets of interventions

ventricular interaction disclosed by imaging studies is asynchrony, which has been shown to develop in parallel to increased pulmonary artery pressures, and contributes to altered RV systolic function and LV under-filling [89].

A Global View on RV Failure

Thus pulmonary hypertension increases RV afterload requiring a homeometric adaptation. When this adaptation fails, the RV enlarges, decreasing LV preloading because of competition for space within the pericardium. This decreases stroke volume and blood pressure, with negative systolic interaction as a cause of further RV-arterial uncoupling, which may be aggravated by RV ischemia from decreased coronary perfusion pressure (gradient between diastolic blood pressure and right atrial pressure).

As shown below, in Fig. 14.8, these interactions may allow one to identify targets of interventions: (1) increased PVR (prostacyclins, phosphodiesterase-5 inhibitors, inhaled NO, endothelin receptor antagonists…) (2) relative insufficiency of RV contractility (dobutamine) (3) excessive RV preload (diuretics) and systemic hypotension (norepinephrine).

Conclusions

In 1989 Jack Reeves called for more research on the pathophysiology and pathobiology of RV failure in pulmonary hypertension. It was already known at his time that pulmonary hypertension is a common complication of cardiac and pulmonary diseases, and that symptoms, exercise capacity and outcome in patients are considerably influenced by RV function. Yet, he had to deplore that the RV was getting insufficient attention in clinical and basic research programs on the pulmonary circulation [90].

The awareness of the importance of the RV in PAH has made considerable progress. There is nowadays a clearer view of the RV and the pulmonary circulation as a functional unit, and imaging is being used with improved focus on functional relevance. Robust measurements of RV-arterial coupling allows for the identification of pulmonary vascular versus RV myocardial effects of therapeutic interventions, and could serve as indispensable tools for bedside translation of cell and molecular biological discoveries.

A lot of work remains to be done to identify the most relevant measurements of RV function and RV-arterial coupling, including awareness of those that can be applied easily in clinical practice, as well as in a research setting. What is thus needed is measurements that are noninvasive, easy to implement at the bedside and in outpatient clinics, and which physiologically meaningful. At present, it appears that 3D echocardiography with portable devices offers the best perspective, as discussed in Chap. 8.

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The Right Heart in Chronic Thromboembolic Pulmonary Hypertension

15

Stefan Aschauer, Irene M. Lang, and Diana Bonderman

Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is an uncommon complication of pulmonary embolism that results from mechanical obstruction of proximal pulmonary vessels by non-resolving thromboemboli and distal arteriopahty due to non-occluded area overperfusion. Increased right ventricular (RV) afterload challenges the RV and leads to changes in its morphology and function: RV hypertrophy is followed by tricuspid regurgitation, dilatation and left-ward bowing of the interventricular septum. Sustained pressure overload results in RV failure and death.

Pulmonary endarterectomy (PEA) represents the treatment of choice. In a vast majority of affected patients, organized thrombotic material can effectively be removed by PEA, which in turn leads to a reduction in RV afterload. As a result, most of the RV hemodynamic and structural changes reverse to near normal. In parallel, patients' clinical condition and long-term outcome improve. In some cases PEA can be insufficient due to accompanying small vessel disease, or not possible due to distal thrombus location and/or patients co-morbidities. For patients in whom surgery is not an option or insufficient, recent trials with beneficial pharmacotherapeutic effects have raised new hopes.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) belongs to the spectrum of pulmonary vascular diseases, but is classified as a separate entity due to its unique aetiology and the surgical treatment options. In recent years it has been recognized as one of the most common causes of underlying pulmonary hypertension (PH). Two

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pathobiological processes characterize the disease: Organized thrombotic material, which completely or in part occludes the major pulmonary arteries leading to vascular remodelling, and a small vessel arteriopathy that is indistinguishable from classical pulmonary arterial hypertension (PAH).

Consequently, pulmonary vascular resistance increases and vascular compliance decreases, resulting in an increased right ventricular (RV) afterload and finally right heart failure. Patients suffering from CTEPH carry a high morbidity and mortality. Early recognition and diagnosis is important and the key to improved outcome and survival of affected patients. In contrast to other types of PH, CTEPH patients can be completely cured by a surgical intervention i.e. pulmonary endarterectomy (PEA).

The present chapter focuses on RV haemodynamic and structural changes in CTEPH and its remodelling processes before and after successful treatment.

Definition

CTEPH is defined as chronic elevation of mean pulmonary arterial pressure (mPAP) ≥25 mmHg in the presence of a pulmonary arterial wedge pressure (Pawp) ≤15 mmHg. Besides detection of precapillary PH the presence of one or more segmental or larger perfusion defects is mandatory for the diagnosis, provided that patients were on adequate anticoagulation for at least 3 months prior to the diagnosis [1].

Clinical Symptoms

Clinical symptoms are caused by progressive right heart failure. A vast majority of patients present with dyspnoea and gradually progressive exercise intolerance. In more advanced stages of the disease, when RV function deteriorates, palpitations, chest pain on exertion and syncope may occur. Clinical signs of right heart failure are leg oedema, ascites, pleural and pericardial effusion, and distended neck veins. Finally, RV failure leads to progressive disability and early death [2].

Diagnosis

Because of rather uncharacteristic symptoms such as exercise intolerance, fatigue, or dyspnoea that are compatible with many diseases carrying a higher prevalence and incidence, CTEPH patients often face diagnostic delay. On an average the disease is diagnosed 2 years after onset of symptoms [3]. The fact that 20–40 % of affected patients do not report a history of venous thromboembolism makes the condition even more difficult to diagnose.

Physical findings include a prominent component of S2 on auscultation, left parasternal heave and a systolic murmur in case of tricuspid regurgitation (TR). In advanced disease states signs of RV failure, as mentioned above, are the pathological features that raise the suspicion for CTEPH. Patients with suspected CTEPH should be referred to specialised expert centres with an experienced PH team and surgical expertise on site. Figure 15.1 shows the suggested diagnostic algorithm proposed by Hoeper et al. [4].

Epidemiology and Prognosis

The exact prevalence and incidence of CTEPH are unknown. Recent data derived from registries suggest that CTEPH occurs with an incidence of 3–30 cases per million in the general population. Usually, estimates of disease prevalence refer to the number of CTEPH cases per survived pulmonary thromboembolic event and report cumulative incidences between 0.1 and 9.1 % [5–11]. In a majority of affected patients, a history of previous venous thromboembolic events has been documented. Wolf et al. found 60 % of 116 French CTEPH patients with a medical history of venous thromboembolism [12]. Similar observations were found in the UK national registry, 58 % of the 469 CTEPH patients had previous thromboembolism [13]. An interesting observation in these studies was that those patients with a history of symptomatic venous thromboembolism were more often surgical candidates than patients without a thromboembolic event. In the database combining information from Vienna, Bratislava, Prague and Homburg previous thromboembolism was reported in 70 % of CTEPH

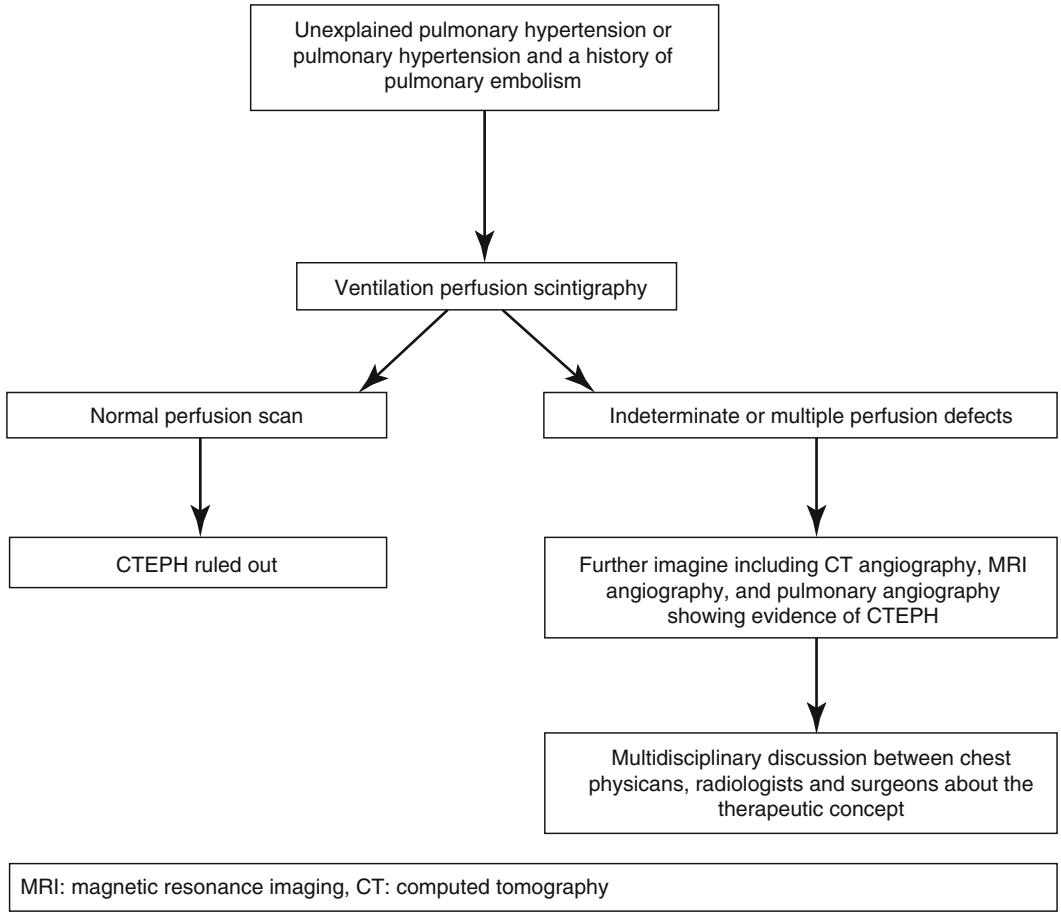

Fig. 15.1 Diagnostic algorithm proposed for patients with suspected CTEPH. *MRI* magnetic resonance imaging, *CT* computeed tomography (Reprinted from Hoeper et al. [4]. With permission from Elsevier)

patients [3]. CTEPH patients carry high mortality. If left untreated, 3-year survival after CTEPH diagnosis has been reported as 78–85 % in affected patients from Japan [14] and 70 % in inoperable versus 76 % in operable patients within the UK [15]. In comparison, contemporarily treated patients with idiopathic, familial or anorexigen- associated pulmonary arterial hypertension face a 3- year survival of 69.9 % [16].

Pathophysiology and Pathobiology

CTEPH evolution is triggered by thrombotic obstruction of the pulmonary vascular tree by single or repetitive thromboembolic events arising from sites of venous thrombosis. Typically, it appears that thrombi fail to resolve and undergo a fibrotic organisation process. In histological examinations, PEA specimens looked organized with white to yellow colour replacing the normal intima. In contrast, thrombi originating from an acute PE appeared freshly red and less organized. The obstruction of pulmonary arterial vessels by the organised thromboembolic material leads to increased resistance to flow through the pulmonary arteries. Concomitant vascular remodelling in the major vessel compartment and subsequent vascular remodelling in small-unobstructed vessels occurs. Progressive mechanical rarefication of the pulmonary vascular bed leads to a gradual rise in PVR, increased RV afterload and RV failure.

Independent of thrombus burden, there appears to be uncertainty regarding the nature and occurrence of secondary small vessel arteriopathy [17]. The role of small- vessel pulmonary vascular

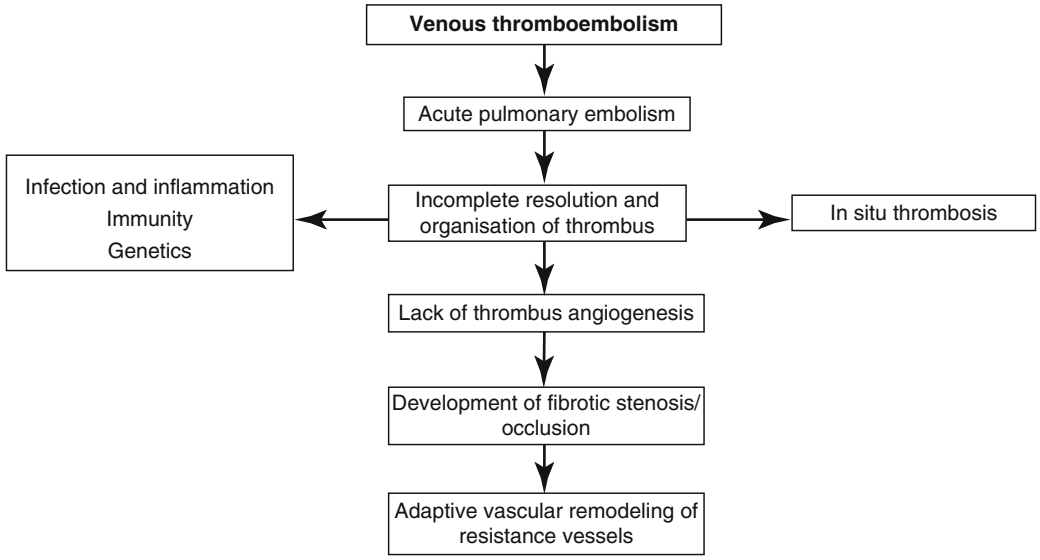

Fig. 15.2 The concept of misguided thrombus resolution in CTEPH (Reprinted from Lang et al. [19]. With permission from European Respiratory Society)

remodelling seems to be critical for the reversibility of hemodynamics after surgery. When present, it mainly affects unobstructed vascular areas and is histologically indistinguishable from other types of PH [18]. Moreover, small vessel disease is believed to arise in response to increased flow and subsequently increased shear stress.

Figure 15.2 shows the current pathophysiological understanding of CTEPH that evolves after incomplete/deficient thrombus resolution leading to vascular remodelling in proximal and distal vessels.

In recent years, studies of large cohorts have demonstrated a clear association between distinct medical conditions and the occurrence of CTEPH. While the hypercoagulable state has been clearly associated with the development of CTEPH, only few specific thrombophilic factors, such as phospholipid antibodies, lupus anticoagulant and elevated factor VIII, are statistically associated with CTEPH [19]. Besides, patients with a history of previous splenectomy or thyroid hormone replacement, cancer survivors and carriers of ventriculo-atrial shunts for the treatment of hydrocephalus are at an increased risk for CTEPH [19]. Recently, it has been shown that also carriers of infected pacemakers [20] or patients with a device infection display increased risk for CTEPH. The current understanding is that staphylococcal species enhance fibrotic vascular remodelling and impair thrombus resolution [21]. Also low monocytes levels as well as elevated inflammatory markers such as C-reactive protein [22], and tumor necrosis factor-alpha [23] were observed in plasma and thrombi of CTEPH patients. Moreover it has been proposed that angiogenic deficiency [24] is involved in the failure to resolve vascular obstruction [19].

Right Ventricular Remodelling in CTEPH

The behaviour of the right ventricle (RV) is crucial for patients' functional status, it determines disease course and survival [25, 26].

Under normal conditions, the RV pumps the same stroke volume as the left ventricle (LV), but with less effort (<25 %) due to the specific characteristics of the pulmonary circulation: a low pressure and high compliance circuit. Based on these specific requirements for the RV, its anatomical structure and geometry substantially differ from the concentric-shaped thick-walled LV: the RV has a semilunar shape in cross-section and a much thinner free wall compared to the

LV, normally not exceeding 2–3 mm [27]. These characteristics create a lower volume to surface area ratio, thereby increasing RV compliance and helping the ventricle to rapidly accommodate to conditions of volume overload [28]. On the other hand, the thin-walled RV is more sensitive to conditions of increased afterload.

In CTEPH, the combination of proximal pulmonary artery obstruction and distal pulmonary vasculopathy results in an increased RV afterload, which is the main burden for the RV, mainly determined by pulmonary vascular resistance and compliance. To maintain pulmonary vascular flow the RV undergoes a remodelling process: RV wall thickness increases in parallel with gains in size, systolic and diastolic volume. Boogard et al. [29] and others [30] explained these changes referring to the LaPlace's law: a thin wall sphere, has to change either its internal radius or its wall thickness to cope with increased wall stress caused by high intraluminal pressure. This adaption mechanism is very similar to LV hypertrophy due to systemic hypertension, to reduce wall stress. Hypertrophy can mainly be explained by increase in myocyte volume through the addition of sarcomeres and enhanced protein synthesis.

RV geometry and function deteriorate as the disease progresses. The ventricle dilates with loss of its typical triangular shape, followed by development of tricuspid regurgitation (TR) and bowing of the interventricular septum, reflecting RV systolic overload (Fig. 15.2). Interventricular septum bowing has been shown to correlate with the LV end-diastolic volume and stroke volume, equitable with severity of PH in CTEPH patients [31].

A close relationship between structural RV changes and exercise capacity has been reported in CTEPH patients [32]. Those with a shorter 6-min walking distance had significantly larger RV diameters and a significantly lower fractional-area change as well as a higher myocardial performance indices [33]. TR, caused by tricuspid annular dilation, is present in a majority of CTEPH patients with an averaged TR velocity of 4 m/s [34].

Assessment of RV function is challenging due to its complex anatomy. Unlike the LV, RV ejection fraction cannot reliably be measured. Therefore, other parameters reflecting RV function such as the Tei index [35] or the tricuspid annular plane systolic excursion (TAPSE) have been introduced into the clinical routine. In CTEPH patients TAPSE ranges between 14.5 and 15.0 mm compared to >20 mm in healthy controls [36, 37]. It has already been demonstrated that low TAPSE is an independent risk factor for early mortality [37].

The Tei index is unaffected by RV geometry and can simply be assessed by tissue Doppler imaging of the lateral tricuspid annulus. In CTEPH patients, the Tei index is elevated compared to normal controls, mainly due to long isovolumetric contraction time and a decrease in RV ejection time, caused by an increased afterload and poor RV function (0.52 $\pm$0.19 in CTEPH versus 0.27 $\pm$ 0.09 in controls). The Tei index also correlates well with mPAP, cardiac output (CO) and PVR [35].

Inter-ventricular electrical and mechanical dys-synchrony is another characteristic of RV remodelling in CTEPH. It seems that increased RV wall stress impairs electric conduction and right-to-left ventricle synchrony [31]. Hardziyenka et al. reported a delay in the RV to LV peak shortening, which leads to left-ventricular septum bowing. Consequently, the RV shortens without ejection, resulting in decreased RV contractile efficiency and reduced CO [38].

Right Ventricular Failure in CTEPH

RV adaption can be very effective, given the fact that patients often have only mild symptoms despite severe pulmonary vascular changes. Also pulmonary pressures may exceed systemic pressures in some patients, indicating a well-adapted RV.

However, the RV is not capable to sustain long-term pressure overload: uncoupling of the ventricle with decrease in contractility despite increasing afterload results in RV dilatation and failure. Little is known about mechanisms underlying the transition from hypertrophy to dilatation in more advanced disease stages. Animal studies indicate that in conditions of chronic pressure overload, such as CTEPH, the density of cardiomyocytes in papillary muscles decreases with a proportional increase in connective tissue [39]. These structural changes could

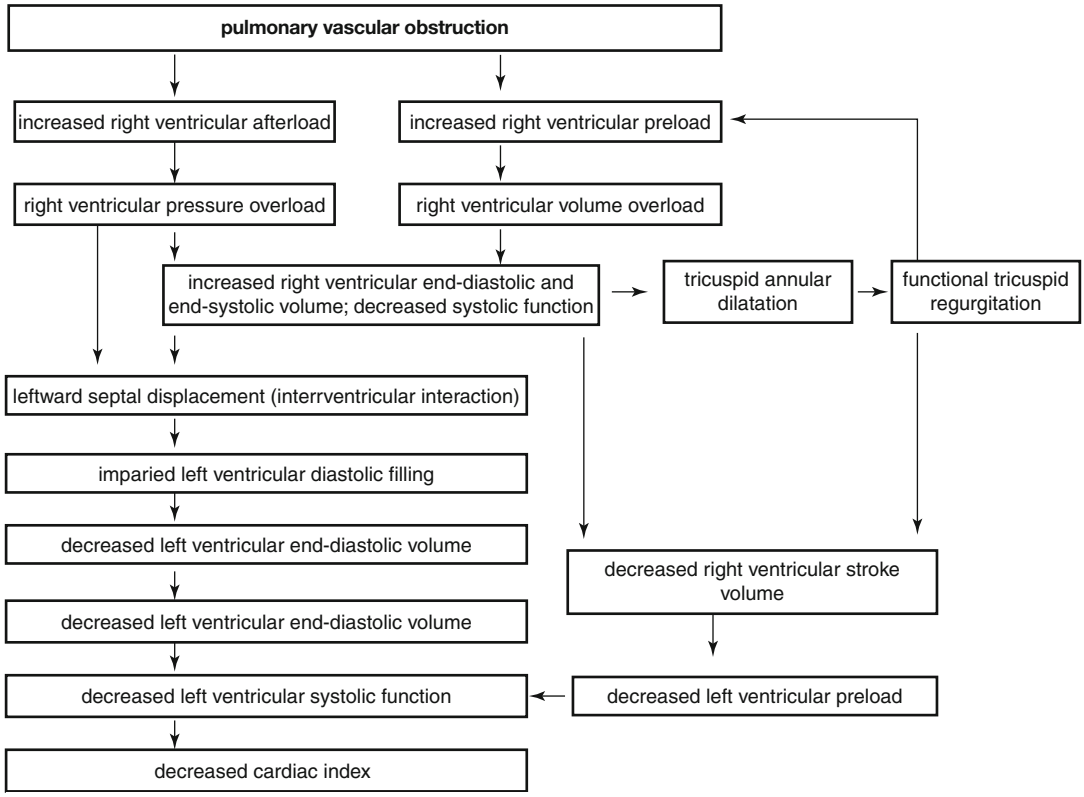

Fig. 15.3 Pathophysiology of left and right-sided heart failure in patients with CTEPH according to Menzel et al. [48] (Reprinted from Menzel et al. [48]. With permission from American College of Chest Physicians)

provide a rationale for the observed functional abnormalities. In PAH patients a down-regulation of the α-myosin heavy chain gene and up-regulation of the β-myosin heavy chain gene has been shown [40]. Similar changes are though to occur in CTEPH, and have been demonstrated in animal models of CTEPH [41].

Moreover, increased oxygen demand is believed to play a key-role in RV failure [25, 42]. Under normal conditions, the oxygen demand of the RV is low due to a lower mass as well as a lower pre-and afterload. Unlike in the LV, RV perfusion is maintained during the whole cardiac cycle. In animal studies, occlusion of the right coronary artery did not affect RV function in the healthy heart. However, coronary perfusion is negatively affected by pressure overload. Interestingly, hyperperfusion of the coronary arteries led to an increased compensation ability of the ventricle [43]. It can be speculated that similar mechanisms are present in CTEPH, with increased wall tension leading to chronic ischemia of the RV and consequently RV failure.

With progression of right heart failure, LV geometry changes and its function deteriorates. It has also been shown that advanced right heart failure is associated with decreased LV mass [44]. RV dilatation and hypertrophy shift the interventricular septum leftward resulting in decreased LV cavity size and compliance [45]. Consequently, decreased LV filling and decreased LV ejection fraction have been proposed as critical pathophysiologic mechanisms underlying impaired CO seen in all types of PH [46, 47].

RV dilatation with negative impact on the Frank-Starling mechanism, chronic ischemia and accompanying LV failure with consequently decreased CO certainly contribute to heart failure in CTEPH patients. Figure 15.3 summarizes

pathological processes leading to right and left-sided heart failure in patients with CTEPH proposed by Menzel et al. [48].

Differences Between PAH and CTEPH

Currently it is unknown whether the RV remodels in a different manner in CTEPH than in other types of PH.

Typically, clinical characteristics of CTEPH patients differ from those observed in PAH: Lang et al. [49] compared 436 CTEPH patients with 158 PAH patients, who were enrolled in eight European PH centres (Table 15.1). Not surprisingly, the most distinctive feature was a medical history of acute venous thromboembolism, which was found in 80.2 % of all CTEPH patients compared to 7 % of PAH patients [49]. Also, older age was strongly associated with CTEPH, whereas diabetes mellitus, higher mPAP and female gender were independent risk factors for PAH. Another distinctive feature was the course of disease and progression to right heart failure and death. CTEPH patients survived twice as long as PAH patients after the initial diagnosis [14] and displayed an episodical disease course. Typically, after a thromboembolic event that may cause symptoms or not, a so-called honeymoon period follows, characterized by absence of symptoms. Besides differences in mPAP, also differences in the time constant of the pulmonary circulation (RC time constant) have been reported. RC time constant represents the exponential pressure decay in the pulmonary artery during diastole, calculated as the product of PVR and pulmonary arterial compliance (PAC). This relationship between PAC and PVR has been shown to remain unaltered in various forms of PH and does not change after drug treatment. Interestingly, the RC time constant is significantly lower in CTEPH patients with proximal pulmonary arterial obstruction compared to PAH patients, which can be explained by structural differences of the pulmonary circulation and indicates a higher RV workload [50].

Table 15.1 Demographic and pulmonary haemodynamic parameters in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) published by Lang et al. (49)

	CTEPH (n = 436)	PAH (n = 158)
Age, years	65 [53;73]	59 [42;69]
6-MWD, m	324 [250;425]	352 [257;425]
mPAP, mmHg	48 [39;55]	52 [44;60]
PAWP, mmHg	10 [8;14]	10 [7;12]
PVR, $dyn \cdot s \cdot cm^{-5}$	724 [492;968]	821 [612;1131]
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.2 [1.8;2.7]	2.2 [1.8;2.6]

Reprinted from Lang et al. [49].with permission from Schattauer GmbH

Data are presented as medians with first and third quartiles [Q1;Q3]

6MWD 6-min walking distance, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary artery wedge pressure, *PVR* pulmonary vascular resistance, *CI* Cardiac Index

To date, no study exists that compared RV remodelling in CTEPH versus PAH. The fact that mPAP is lower despite similar PVR has led to the assumption that RV adaption may be poorer compared to PAH patients. This was recently discussed by Delcroix et al. [42] who speculated that impaired RV adaptation can either be explained by the higher age of affected individuals or by specific differences of the two diseases.

A higher pulse pressure has been reported in CTEPH [51]. This can be explained by increased stiffness of the proximal arteries and a higher pressure decay during diastole. That implies that the RV has to work more to reach similar mPAP levels, and may explain the observed differences in mPAPs and a decreased RC time constant between PAH and CTEPH.

In summary, increased afterload is the main burden for the RV in all types of PH, determined by PVR, PAC and impedance [52]. There might be differences in PVR and PAC, but in both PAH and CTEPH, the RV has to overcome the product of increased resistance and decreased compliance – increased afterload. Therefore, it can be speculated that RV remodelling in CTEPH and PAH is very similar, certainly depending on the degree of pulmonary vascular disease severity. Pressure volume loops in age-matched patients with both forms of PH would help clarify true differences.

Treatment

CTEPH is the only type of PH that can be cured by PEA. The objective of the surgical intervention is to remove a maximal amount of thrombotic material from the obstructed pulmonary arteries to achieve normalization of pulmonary haemodynamics. Besides PEA, specific PAH drug therapy may play a role in patients who are not considered candidates for surgery, in patients where preoperative treatment is deemed appropriate to improve haemodynamics and in patients who present with symptomatic residual/recurrent PH after PEA [1]. Although no expert agreement on the criteria defining operability exists, inoperability is mostly attributed to pronounced small vessel disease and comorbid conditions. Besides specific therapy patients should receive life-long anticoagulation, usually with vitamin K antagonists adjusted to a target INR between 2.0 and 3.0.

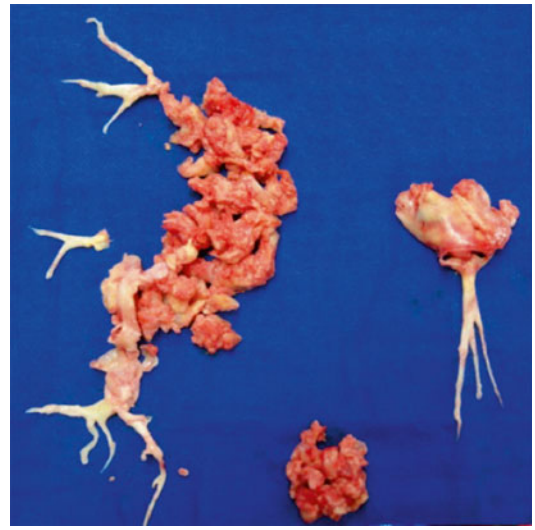

Fig. 15.4 Thromboembolic specimens removed from the right and left pulmonary arteries during pulmonary endarterectomy

Pulmonary Endarterectomy

PEA is a complex cardio-thoracic surgical intervention with a 30-day mortality rate of less than 5 % in experienced centres [26]. Experienced centres are institutions that perform more than 20 PEA surgeries per year with a mortality rate <10 % [1]. This recommendation is supported by reports of the San Diego Health Center, the first institution that performed PEA. The mortality rate initially averaged at 17 % and decreased constantly to 4.4 % after 2,700 cases. Similar improvements over time were reported in other centres [20].

Surgery is performed via median sternotomy with cardiopulmonary bypass, total circulatory arrest and profound hypothermia (18–20 °C). Endarterectomy is performed during circulatory arrest with total bloodless field. PEA includes dissection and removal of the intimal layer, not only thrombectomy. Usually, the circulatory arrest is limited to 20 min, which leaves for an experienced surgeon enough time for an entire unilateral endarterectomy. A complete endarterectomy including the smallest vessels is the key for a good outcome. It has been recently reported [53] that the amount of thrombus tails that can be removed is directly related to the decrease in PVR. Figure 15.4 shows a typical example of the thromboembolic material that is removed during a representative bilateral pulmonary endarterectomy procedure. Postoperative care takes place at an intensive care unit with inotropic support mechanical ventilation and aggressive diuresis. On an average, 5 days at the ICU and a total of 10 days in the hospital are required [54].

Selection for Pulmonary Endarterectomy

Criteria have been defined to ensure optimal patient selection for PEA, yet, operability is determined by numerous factors, e.g. center experience, that cannot easily be set into an algorithm. Patients with more distal obstructions, or even lacking visible thromboembolic obstructions are thought to be poor candidates for surgery, although a patient should not be considered inoperable as long as at least one experienced PEA surgeon has not reviewed the case [1]. Another key issue in the preoperative assessment of CTEPH patients is the degree of concomitant small vessel arteriopathy and its contribution to PVR [55].

Other criteria for PEA, except surgical accessibility, are a confirmed diagnosis of CTEPH in New

York Heart Association functional classes II-IV, a preoperative PVR exceeding 300 dyn·s·cm^{-5}, absence of severe comorbidities and patient consent [56].

Data from a recent European registry showed that 63.3 % of all CTEPH patients underwent surgery. Inoperability was stated due to surgical inaccessibility of thrombi in 50 % of patients, imbalance between PVR and the amount of accessible occlusion (10 %), comorbid conditions (13.4 %), and PVR greater than 1,500 dyn·s·cm^{-5} [57]

Several studies have shown that baseline PVR determines outcome after surgery. Jamieson and colleagues [58] reported on 1,500 PEA cases and found a mortality rate of 22 patients after 500 operations. 18 of these patients had a PVR higher than 1,000 dyn·s·cm^{-5} [58] before PEA, which resulted in a mortality rate of 10.1 % compared to 1.3 % in patients with lower PVR. Similar results were shown by Madani et al. [34] who reported a threefold higher mortality risk in patients with PVR higher than 1,000 dyn·s·cm^{-5} prior to surgery. Despite a significantly higher postoperative risk, patients with higher PVR can benefit from surgery as shown by Thistlethwaite, et al. They reported a higher reduction in PVR in patients with a very high mean PVR of 1,299 dyn·s·cm^{-5} when compared to patients with modest PVR elevations [59].

CTEPH is a dual compartment disease and PVR is determined by the thrombus load, as well as by the degree of concomitant small vessel disease and RV function. Various diagnostic techniques and classifications have been developed to predict surgical outcome.

The Jamieson classification helps to classify thrombus location and type according to outcome. Four groups have been defined with more favourable outcome in types 1 and 2. Type 1: fresh thrombus in main lobar arteries, Type 2: organized thrombus and intimal thickening in proximal segmental arteries, Type 3: intimal thickening and fibrosis in distal segmental arteries, and Type 4: distal arteriolar vasculopathy.

This classification is a useful tool for assessment of the extent of thrombotic/fibrotic material but cannot sufficiently predict heamodynamic outcome after PEA. There is often a substantial gap between angiographic findings and the degree of PH [60] which can be explained by concomitant small vessel disease. Also the persistence or recurrence of PH, affecting 5–35 % [20, 59] of patients after PEA, is mainly attributable to small vessel disease [61]. Histologically indistinguishable from other forms of PH, small vessel disease mainly affects unobstructed pulmonary vascular areas and causes a persistently increased PVR. The degree of secondary small vessel arteriopathy is therefore an important determinant of postoperative outcome and long-term mortality [62].

To predict haemodynamic recovery after PEA, pulmonary arterial occlusion pressure waveform analysis has been introduced in the clinical practice of high-volume centres. During right heart catheter, occlusion by the balloon of the Swan Ganz catheter changes the waveforms into smaller altitude curves, reflecting postcapillary wedge pressure. The transition from pulmonary artery into pulmonary capillary wedge pressure curves can be used to estimate precapillary pressure and to estimate the degree of small vessel disease. After occlusion the curve consists of two different components: a larger arterial (up-stream) and small arterial plus venous (down-stream) component. The first reflects the stop of flow through arterial resistance, and the second, slower component reflects the emptying of compliant capillaries through a venous resistance [42]. Kim [63] postulated that patients with higher up-stream resistance have mainly proximal large vessel disease whereas low up-stream resistance indicates small vessel disease (Fig. 15.5). With respect to outcome they showed that lower up-stream resistance was associated with persistent PVR elevation and higher mortality rate after technically successful PEA [62, 63]. Toshner et al. [64] was able to relate low upstream resistance with distal disease. More experience and further research is required for the future use in clinical routine.

Surgical Outcome

PEA is the therapy of choice for patients with accessible thrombi. PEA substantially improves symptoms, haemodynamics and survival in a vast majority of patients. Most patients are in World Health Organization (WHO) functional class III

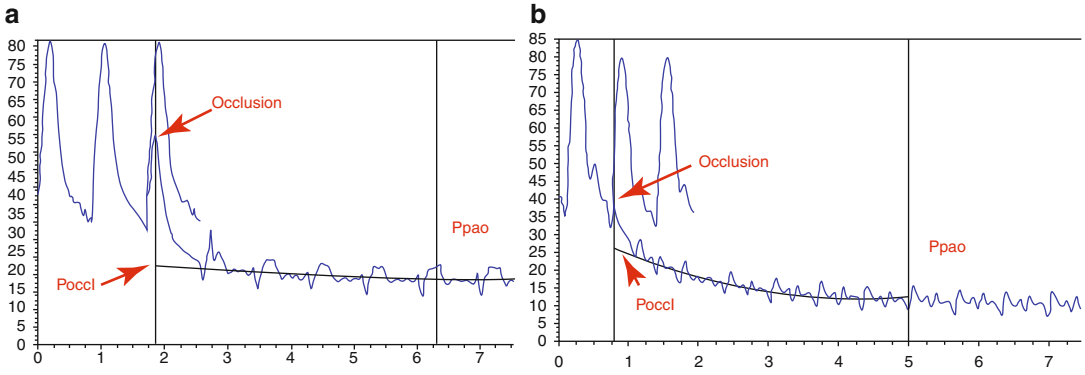

Fig. 15.5 Pulmonary artery occlusion waveforms from two patients with (**a**) upstream resistance with a rapid drop in pressure to pulmonary arterial occlusion pressure (*Ppao*) and (**b**) significant downstream resistance with a longer time needed for the pressure to reach Ppao. *Poccl* pulmonary capillary pressure after occlusion (Modified from Kim et al. [62]. With permission from Wolter Kluwers Health)

Table 15.2 Pre- and postoperative haemodynamic results from 500 with CTEPH published by Madani et al. [34]

n = 500	Preoperative			Postoperative		
PVR (dyn · s · cm^{-5})	719	±	383	253	±	149
CO (L/min)	4.3	±	1.4	5.6	±	1.4
sPAP(mmHg)	75.5	±	19.1	41.7	±	14.1
mPAP (mmHg)	45.5	±	11.6	26.0	±	8.4
Triscuspid regurgitant velocity (m/s)	4.0	±	0.8	2.9	±	0.6

Reprinted from Madani et al. [34]. With permission from Elsevier
Data are shown as mean ± standard deviation
PVR pulmonary vascular resistance, *CO* cardiac output, *sPAP* systolic pulmonary arterial pressure, *mPAP* mean pulmonary arterial pressure

or IV before PEA and return to near-normal activities after surgery.

After successful PEA acute load changes occur with a subsequent remodelling process of the RV. RV cavity dimensions change significantly: recent three-D echocardiography data showed a mean end-diastolic volume change from 121 ± 37 ml to 80 ± 33 ml and an end-systolic volume change from 91 ± 30 ml to 54 ± 31 ml [65]; RV end-diastolic area and end-systolic area decreased from 35.8 ± 4.4 cm^2 to 26.6 ± 4.8 cm^2 and from 27.1 ± 3.8 cm^2 to 17.9 ± 3.8 cm^2, respectively. TR improved from a mean grade of 3.1 ± 0.5 to 2.2 ± 0.7 [66]. Similar results have been reported in other studies [54, 67].

RV wall thickness decreases within a longer time period, although a constant decrease is detectable when measured. Besides geometry, haemodynamic improvement is observed. Table 15.2 demonstrates haemodynamic data from a large CTEPH registry, recorded before and after PEA.

Immediate postoperative reduction of PVR is the best predictor of long-term outcome, as recently shown by Skoro-Sajer et al. [53]: In this study, a PVR of 590 dyn · s · cm^{-5} was the threshold for differentiation between long-term favourable and adverse outcome (mortality and/or lung transplantation). Moreover, it could be demonstrated that patients with PVR < 290 dyn · s · cm^{-5} face a better outcome than those with PVR between 292 and 450 dyn · s · cm^{-5}. In the group with a post-operative PVR < 290 dyn · s · cm^{-5} no patient died or needed lung transplantation.

The time course of changes after surgery has been previously described. Most distinct changes were observed within the first 3 months [68]. Instantaneously after PEA, mPAP normalizes. 2 days after PEA an average decrease of 37 % in PVR and a 35 % increase in cardiac index was

described [69]. In most studies RV function improved within 6–12 months but remained impaired compared to healthy individuals [36]. The Tei Index, decreased significantly from 0.52 to 0.33 indicating better RV function after PEA and correlated well with the decrease in PVR [35]. Skoro-Sajer et al. [53] reported an increase in RV stroke volume from preoperative 58.4 ± 16.8–61.1 ± 20.9 immediately after PEA and to 71.6 ± 18.6 ml 1 year later. Assessment of RV ejection fraction by magnetic resonance imaging revealed an improvement from 34 % ejection fraction at baseline to 50 % ejection fraction after PEA [70]. However, despite significant improvement in RV function after PEA, an ejection fraction of 50 % is still reduced compared to a mean ejection fraction of 62 % in healthy individuals [70]. The reason for the remaining reduced RV function after PEA is unknown. Whether RV remodelling is partly irreversible due to diffuse fibrosis, or subtle scarring of the endarterectomised pulmonary circulation limits adequate adaptation under conditions of exercise, or RV recovery may take longer than studies follow-up time, has to be answered in future studies.

Also 6-MWT showed a significant improvement and correlated well with patients' haemodynamic improvement [32]. Corsico et al. [68] examined long-term outcome after PEA and showed that exercise capacity constantly increased during 4 years of follow-up.

In parallel to improvement in RV function, changes in LV function are observed. Unlike the well-trained RV that is adapted to increased afterload, the LV is adapted to reduced diastolic filling. Postoperatively, the LV is challenged by abrupt increase in filling. In most cases, LV function returns to normal. LV end-diastolic volume increases, with normalisation in LV ejection fraction and LV-diameter, as well as the LV filling. Furthermore, an increase in wall thickness and more circumferential shortening in echocardiographic strain studies can be observed, indicating improved LV function, which is also crucial for the normalization of exercise capacity [71].

However, some patients with normalized resting PVR after PEA do not return to normal functional status and exercise capacity. Besides physical deconditioning and persistently altered gas exchange, there is growing awareness for the importance of the pulsatile component of hydraulic load – PAC. PVR reflects mean flow but does not account for changes in pulsatility of the pulmonary circuit [72, 73]. Moreover, PEA mainly affects major vessels, which appear to be the main determinants of PAC. These considerations are in line with reports of a strong association between PAC and outcome [74]. It has been suggested that PAC could even serve as stronger outcome parameter than PVR. As shown by de Perrot et al. [74], patients after PEA with persistent poor PAC face adverse outcome despite dramatic decreases in PVR. The authors explain their findings of reduced PAC by progressive structural damage caused by proximal vascular remodelling and consequently persistently increased afterload. Also patient age seems to affect vascular compliance, which can be explained by decreased vascular elasticity in the elderly [74]. Reduced PAC also affects exercise capacity. In healthy subjects, to meet augmented oxygen demand during exercise, PVR decreases and PAC increases, to enhance CO. Vascular stiffness due to persisting thrombotic material or operation scars may explain these findings. An inverse response to submaximal exercise was observed in patients who had undergone successful PEA, with normalization or near-normalization in PVR. PVR increases while PAC decreases, which is most likely to explain a limitation in exercise capacity [72]. Both PVR and PAC seem to determine patients' disease course after surgery. Immediate postoperative PVR seems to be the best predictor of long-term survival [53].

Medical Treatment

Due to a similar pathobiology of pulmonary small vessel disease in CTEPH and PAH, there is a strong rationale for the use of pulmonary vasodilators in CTEPH. Established PAH therapy concepts, targeting the endothelin-, the nitric oxide- or the prostacyclin pathway have been studied in the past. The BENEFIT study examined the effects of bosentan in inoperable CTEPH patients in a

randomized, controlled manner. 157 patients received either bosentan or placebo for 16 weeks. The study demonstrated a significant therapy effect of bosentan on haemodynamics (−24.1 % of PVR, −193 dyn·s·cm^{-5} total pulmonary resistance from baseline) but only minor improvement in 6-min walking distance, which had been defined as the co-primary endpoint (+2 m) [75].

Prostacyclins have been tested in smaller series. Epoprostenol [76] and beraprost [77] showed improvements in various aspects e.g. functional class or quality of life. Iloprost has been tested as part of the "Aerosolized Iloprost Randomization" (AIR) study that included 57 CTEPH patients. Subgroup analyses failed to show a significant benefit of inhaled iloprost on haemodynamics or exercise capacity [78] in CTEPH patients. By contrast, subcutaneous treprostinil sodium showed an improvement in 5-year survival in 25 patients ineligible for surgery: 50 % survival in the treatment group compared to 15 % survival in a historical control [79]. Interim analysis of the on-going multicentre CTREPH trial confirmed previous positive results. Patients with non-operable CTEPH or persistent/recurrent PH post PEA displayed an increase in 6-MWD of 57.4 m compared to baseline, after 6 months of treatment with subcutaneous treprostinil [80].

Phosphodiesterase type-5 (PDE-5)-inhibitors showed promising results with respect to exercise capacity and haemodynamics [81, 82]. Nevertheless, larger randomized placebo-controlled studies for prostacyclins and PDE-5-inhibitors are still lacking to support their clinical use.

Besides studies with well-established PAH-targeted pharmacotherapies, a novel substance class has recently raised attention. Riociguat, a soluble guanylate cyclase stimulator, has been shown beneficial in previous small clinical studies [83], which recently has been confirmed by a multicentre, randomized, double-blind, placebo-controlled trial. 261 CTEPH patients deemed inoperable or suffering from persistent or recurrent PH after PEA were randomly assigned to receive placebo or riociguat. After 16 weeks, the riociguat-treatment group demonstrated increased walking distance (+39 m), a decrease in PVR (−226 dyn·s·cm^{-5}) and proNT-BNP (−291 pg/ml) as well as an improvement in functional class [84].

In conclusion, PEA remains the first treatment choice for CTEPH patients, providing the most powerful relief of RV afterload. Nevertheless, a substantial number of patients either deemed inoperable or suffering from persistent/recurrent PH after PEA, may benefit from pharmacological therapy.

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Part IV

Treatment of Right Heart Dysfunction

Acute Right Heart Failure in Pulmonary Hypertension

16

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Abstract

Right ventricular failure may occur in the course of pulmonary arterial hypertension (PAH) but can also occur, sometimes without pulmonary hypertension (PH) in conditions such as right ventricular infarction and others such as pulmonary embolism where the pressure may not be very high because the afterload increase was so rapid in onset. For patients with PAH, these episodes of right heart failure are severe and in-hospital mortality rates of up to 60 % in the most severe patients have been described but, no evidence based recommendations have been published to date and diagnostic and therapeutic strategies vary considerably between centres. Some prognostic factors have been identified from cohort studies: systemic arterial pressure, serum levels of sodium, creatinine and brain natriuretic peptide (BNP). Echocardiography also plays a role, though its utility overall remains uncertain. The advantages of right heart catheterization (RHC) have to be balanced with the potentially increased side effects of this tool in these fragile patients. Treatment goals should focus on addressing the pathophysiological components of right heart failure: preload balance, right ventricular afterload reduction, optimisation of cardiac contractility and systemic arterial pressure support. The identification and management of any underlying trigger of cardiac decompensation is very important. In patients with kidney failure, renal replacement therapy is feasible, though associated with a poor prognosis. Despite these treatments,

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some patients exhibit refractory heart failure and develop life threatening multi-organ failure. Lung or heart-lung transplantation may be considered as a rescue therapy in this setting, with extra corporeal life support a potentially lifesaving bridge to surgery in certain circumstances. However, the appropriate timing of this transplantation remains very challenging as no standardized monitoring protocol exists. More studies are needed to increase our knowledge of this devastating complication in PAH patients.

Introduction

Chronic thrombo-embolic pulmonary hypertension (CTEPH), pulmonary hypertension (PH) due to chronic lung diseases and/or hypoxia and pulmonary arterial hypertension (PAH) are causes of chronic pre-capillary PH and subsequent right heart failure (RHF) [1]. Some PH patients require hospitalization in the intensive care unit (ICU) because of clinical deterioration due to heart failure [2]. However, optimal management of these patients remains very challenging. Previous studies have documented mortality of 40–60 % for PH patients experiencing acute heart failure that necessitate inotropic or vasoactive drugs [3–5]. To date, no evidence based guidelines are available to guide physicians in the management of this specific subset of patients. Current diagnostic and therapeutic strategies for RHF in the setting of PH are therefore mostly based on experimental data or extrapolated from management approaches for when this complication develops in other clinical contexts, such as acute pulmonary embolism [6]. In the last 5 years, clinical data, expert opinion from leaders in the field of PH and reviews contributed to a better understanding in the management of PH patients presenting RHF.

In this context, the present chapter will report pathophysiological issues and clinical experience in the field of PH complicated by severe RHF. In addition, current treatment strategies are discussed and available monitoring methods are evaluated, with a brief description with other causes of RHF.

Epidemiology

Only few data are available regarding the epidemiology of acute worsening of PH. A recent U.S. study examined the circumstances of death in this population and documented 132 deaths in a cohort of PAH patients over a 4 year period. After excluding non-PAH cases (i.e. not belonging to World Health Organization group I of the pulmonary hypertension classification system) and those with missing data, there were 84 patients remaining for evaluation. The investigators showed that PH was deemed the direct cause of death (attributable to right ventricular failure or sudden death) for 44 % of them. Only 8 % of patients died as a result of a new disease deemed unrelated to underlying PH. It is noteworthy that death occurred in the course of an ICU admission in 80 % of patients. Furthermore, half of the cohort received catecholamines during the hospital stay [7]. From this, we estimate that approximately two PAH patients were admitted each month to the ICU over the course of the study period in this centre. Another study evaluated the outcome of cardiopulmonary resuscitation (CPR) in PH patients. During the study period of 4-years, 3,130 patients were followed in 17 centres. Among these patients, 513 presented in circulatory arrest. Cardiopulmonary resuscitation was attempted in 132 patients. Sixty three percent of these patients were in ICU at the time of cardiac arrest. Right heart failure and unexpected cardiac arrest accounted for two third of the deaths [8].

These demographic data underline the relatively high incidence of right heart failure in PH population, especially in PH referral centers across the world. To give an order of ideas, 46 PH patients required amines during a period of 18 months during a prospective clinical study in the ICU of the French referral centre of pulmonary hypertension [4]. In another recent study in the same unit, 53 PH patients were admitted in the ICU for monitoring or treatment with catecholamines to manage a rapid worsening of their functional status on a 5-months period [9]. Despite these experiences, few data exist on the epidemiology and management of PH patients experiencing acute heart failure. Moreover, the potential impact of underlying triggering factors and the subsequent consequences on baseline disease underscore the need for greater study in this arena.

Right Heart Failure Pathophysiology

Hypertrophy and progressive rounding of the normally crescent shaped right ventricle (RV) cross-sectional area are usual RV adaptation to a chronically elevated afterload [10]. This hypertrophy is the result of an increase in both protein synthesis and number of sarcomeres. We also see an augmentation of the myocardial cell population, and an increase in collagen fibers in the extracellular matrix [11]. These adaptative mechanisms eventually lead to right ventricular failure (RVF) by several combined pathways:

- a mismatch between perfusion of the right ventricle (due to inadequate coronary blood flow) and increase in metabolic demand
- a progressive fibrosis of the extracellular matrix [12]
- a change in the nature of the contractile fibers of myocytes with resultant drop in systolic function [13]

Moreover, other phenomena induce cellular damage leading to decreased performance of the right ventricle. This includes activation of the neurohormonal system [14], oxidative stress and increased apoptosis [15], inflammation and disorders of cellular energy metabolism [16]. Progressive RV dilatation occurs at the expense of the left ventricle (LV), due to the inelastic nature of the pericardium through a gradual reversal of the septal curvature. This leads to a reduction in LV preload by reducing venous return and also to impaired LV diastolic compliance. All of these modifications lead to a fall of cardiac output (CO) and systemic blood pressure, further reducing coronary perfusion of the RV, while its oxygen demand is increased. This further undermines its function. These constitutional changes also impair diastolic heart function, such that both diastolic and right atrial pressures are increased, in turn contributing to liver and/or kidney function impairment [17].

Therapeutic Issues

Identification and Treatment of a Possible Cause of the Acute Episode

Chronic diseases are characterized by a delicate balance between persistent functional impairment and adaptation factors. In most chronic diseases, identification of a triggering factor of an exacerbation is one of the mainstays of the therapeutic strategy. This is especially true when considering rapidly correctable triggering factors, such as fluid retention in left heart disease. However, some triggers such as sepsis may induce major pathophysiological changes that cannot be corrected rapidly. Indeed, severe sepsis has been proven to alter myocardial function affecting both ventricles [18, 19].

Few data exist regarding triggers that lead to acute worsening of PH. Recently, analysis of a retrospective cohort of PAH patients displaying RVF indicated that mortality was higher when there was an underlying infectious etiology, as compared to patients with other causes of worsening (drugs withdrawal or arrhythmias for

instance) or without recognized triggering factors. Nevertheless, there was no difference in mortality in this study according to whether a triggering factor to acute right heart failure was identified or not [3]. In another retrospective study, both sepsis and acute respiratory failure were also associated with an increased mortality, but no such association was found with the other reported potential triggering factors [20]. The experience of the French National Pulmonary Hypertension Referral Centre is broadly similar, with sepsis being associated with less favourable outcomes despite appropriate antimicrobial therapy and support measures. Again, there was no significant difference in outcome according to whether a precipitating cause was apparent or not [4, 9]. Besides infections, which are common causes of severe heart failure in PAH patients, arrhythmias are frequently involved and may carry a prognostic value, supporting the concept that maintenance of sinus rhythm is of crucial importance in order to avoid arrhythmias-induced decrease of cardiac output [21]. In addition, it is generally recommended for PAH patients to be treated with anticoagulants in order to prevent venous thrombo-embolic events that may precipitate RHF [3]. In PAH patients treated with intravenous epoprostenol, central line infection and pump failure are major causes of RVF, as is withdrawal of any chronic specific PAH therapy [4]. Even though clear cut evidence that screening for and treating any of the aforementioned potential triggers of acute right heart failure changes outcome is lacking, such an approach nonetheless seems logical and appropriate in the management of these unstable patients.

Right Ventricle Preload Balance

Fluid retention is a common feature of RHF. However, little clinical evidence is available regarding the preload balance, even in cases of acute RHF without pre-existing right heart disease [22, 23]. The aim of preload balance is to avoid volume overload on a failing RV, which can lead to distension and ischemia of the right heart chambers, and to decreased CO, at least in part due to ventricular interdependence [17]. One of the most challenging issues in this setting is therefore to determine the appropriate preload. The best method of monitoring this variable is also a matter of debate. Intravenous diuretics are usually the first line therapy for overt fluid overload [2]. Renal replacement therapy (RRT) has also been suggested in case of severe life threatening metabolic abnormalities or fluid overload insufficiently treated with diurectics [24, 25]. Nevertheless, the indications and potential benefit of RRT in PH patients has received little attention even though the potential drawbacks of this therapeutic modality in very unstable subjects is now better understood. In an attempt to study the role and benefit/risk ratio of RRT, our group performed a retrospective analysis of PH patients with acute heart failure requiring RRT in ICU. This work analysed 36 continuous and 32 intermittent RRT sessions in 14 patients over an 11-years period. Significant systemic hypotension requiring a therapeutic intervention occurred in roughly half of the sessions for both modalities. The ICU-related, 1-, and 3-month mortality of these patients was 46.7, 66.7, and 73.3 %, respectively [26]. Given such poor outcomes, consideration should be given to extra corporeal life support (ECLS) and lung or heart-lung transplantation in eligible patients undergoing RRT.

Right Ventricle Afterload Reduction

The relevance of urgent initiation of PAH specific therapy in patients hospitalised in ICU for acute right heart failure remains a matter of debate for several reasons. First, these agents are not considered to be emergency medications. PAH specific therapy is contemplated to act at least in part through his long-term anti-proliferative and vasodilatory properties [27]. Second, there is concern about possible systemic hypotensive effects in unstable patients with heart failure, low CO and hypotension. In our experience, the use of continuous inhaled nitric oxide (NO) (10 ppm) was safe, and may have been useful in a series of PH patients with decompensated RHF [4]. In another recent cohort of PH patients experiencing right

heart failure, the use of NO was associated to a worse outcome, probably due to disease severity of treated patients [20]. Nevertheless, one must state that there is no randomized controlled study of this agent in decompensated PAH. One case report suggested inhaled iloprost as a useful and safe drug in the setting of acute circulatory shock due to PAH [28]. Iloprost has also been used in a cohort of patients as a bridge to atrial septostomy [29]. In addition, successful use of inhaled milrinone, a phosphodiesterase 3 inhibitor that works to increase heart's contractility, has been reported in acute PAH worsening of unknown origin. In a retrospective analysis, Kurzyna et al. found that the addition of a therapy aimed at decreasing pulmonary vascular resistance during an episode of acute heart failure was associated with a favourable outcome [3]. In our practice, PAH patients presenting abrupt RVF have been treated with continuous intravenous epoprostenol and/or oral bosentan on the top of other supportive measures (oxygen, diuretics, dobutamine and/or norepinephrine) as rescue therapy. However, it is important to stress that there are no randomized controlled studies of any of these different agents in the setting of decompensated PAH. In summary, there is an urgent need for more data in order to firmly conclude on the role of these therapies in acute worsening of PAH. While there are safety concerns about the use of vasodilators in such cases, the reduction of right ventricle afterload and improvement of ventriculo-arterial coupling might be one key of therapeutic success. Lastly, right ventricular assistance device, in case of refractory heart failure, could be an interesting rescue therapy in this difficult-to-manage PAH population (see below).

Right Ventricle Contractility Optimisation

Inotropic and/or vasoconstrictive agents remain important drugs in the management of severe hemodynamic impairment. The main goals of such treatments are to enhance CO without increasing pulmonary vascular resistance or decreasing systemic arterial pressure. There is no systematic clinical study of these agents in PAH patients with decompensated RVF. However, they are widely used in acute heart failure complicating the course of PAH and data are now available. Dobutamine seems to be a treatment of choice for the management of acute right heart failure in PAH. This inotropic agent improves right ventricle-pulmonary artery coupling by increasing CO and decreasing pulmonary vascular resistance. The dose often proposed to patients does not exceed 5–10 μg/kg/min [30]. Theorically, higher doses may induce systemic hypotension by activation of peripheral β-adrenoreceptors. In our clinical practice, dobutamine at a dose ranging from 2.5 to 15 μg/kg/min has been helpful in the management of acute worsening of PAH. Higher doses often necessitate addition of systemic vasoconstrictor agent such as norepinephrine [3]. Dopamine has been proven to increase cardiac output and systemic pressure in acute pulmonary embolism [31]. It has been reported as first line therapy in PH patients harbouring RVF in one study [3]. Because of an increase of mortality in the subgroup of patients receiving this drug in this study, authors eventually suggested that dopamine was not a suitable therapy in this setting. Overall, there is less experience with dopamine as compared to dobutamine in this setting, at least in part because tachycardia and arrhythmia are the main side effects of this drug, raising concern about its potential benefit/risk ratio in that indication.

Systemic Arterial Pressure Support

The maintenance of systemic arterial pressure is very important in order to ensure blood flow to organs to satisfy their oxygen demand. Norepinephrine, like dobutamine, improves right ventricle-pulmonary artery coupling [30]. There is consistent experimental information on the beneficial effects of norepinephrine on coronary artery blood flow and right ventricular performance [32]. In our practice, norepinephrine is a drug of choice in acute right heart failure and persistent hypotension despite dobutamine therapy [2, 4].

There are no available data to support the use of epinephrine in PAH patients. Phenylephrine and vasopressin have been shown to have potential paradoxical effects, leading to an increase in pulmonary vascular resistance and decrease in cardiac output [33, 34].

Other Therapies

Oxygen therapy is recommended in PAH patients with decompensated RVF as marked hypoxemia and low mixed venous oxygen saturation is common in this setting. Significant shunt, as a consequence of opening of a patent foramen ovale may also further lower systemic arterial oxygen tension. Intubation and mechanical ventilation are always a difficult matter of discussion in PAH patients because the risk of life-threatening acute hemodynamic worsening is important [5, 20].

Despite all the aforementioned therapeutic options, some patients exhibit refractory RVF.

Right ventricular assist devices (RVAD) have been used in the setting of right ventricular myocardial infarction, post surgery RV failure, post left ventricular assist device insertion, after orthotopic heart transplantation and in a patient with mitral valve endocarditis induced RVF [35–37]. The principle is to pump blood from the right atrium and re-inject it in the pulmonary circulation, thus unloading the right ventricle [38]. The main pitfall in RVAD in the setting of PH patients is the high pulmonary vascular resistance. Pulmonary hemorrhage have already been described in one PH patients undergoing RVAD, leading to a switch from RVAD to another ECLS for hemodynamic suppport [39].

Lung or heart-lung transplantation remains often the last therapeutic option for these patients. Nevertheless, the delay between emergency listing to transplantation can be fatal because of the associated impairment of the different organs systems. Extra corporeal life support (ECLS) might be necessary to control organs failure as a bridge to transplantation. Several options are available for consideration for such patients, though experience is mainly based on small series and none have been rigorously evaluated in randomised studies of acute RVF in PAH patients. According to the method of veno-arterial extracorporeal membrane oxygenation (ECMO), venous blood is pumped from right atrium through a tube inserted in a femoral vein and after oxygenation, is reinjected in the arterial circulation, usually through a femoral artery. This intervention has been used as a bridge to transplantation in five patients with severe RVF and led to a rapid improvement in renal failure [40]. Patients remained free of the ventilator, avoiding all the associated drawbacks of mechanical ventilation. Four patients were transplanted between 18 and 35 days after the initiation of veno-arterial ECMO, with three patients surviving to at least one year. Another option is the pumpless assist device inserted into the pulmonary circulation. The concept is based on the insertion of a oxygenation membrane between the main pulmonary artery and the left atrium. With right ventricular systole, blood flows through both the pulmonary circulation and the membrane, obviating the need for a dedicated pump [41, 42]. Despite limited experience, it has been suggested that ECLS may reduce the mortality of PAH patients on active transplantation waiting lists. Furthermore, some patients can breath spontaneously on ECLS, leading to better physical condition of patients before surgery. In addition, these patients present improved kidney and hepatic function [43]. Altogether, these data support the use of ECLS in PH patients as a bridge to transplantation. Nevertheless, a rigorous evaluation of a given patient's suitability to transplantation should be undertaken prior to initiation of this form of therapy, since no patient went off the device without transplantation to our knowledge. This can only be achieved in dedicated centres staffed by expert PH physicians, intensivists and thoracic surgeons.

Monitoring

Hemodynamic Monitoring

The appropriate monitoring for this specific subset of patients remains a matter of uncertainty. An ideal tool should monitor cardiac variables that

are the targets of treatments (RV preload, CO and pulmonary vascular resistance) and not be associated with adverse effects such as arrhythmias or infections. Such a tool should also be able to evaluate the adequacy of initiated treatments on peripheral organs function. Ideally, the monitoring equipment should be easy to set up and repeatable over time.

Echocardiography is an attractive option in this regard in many respects. Nevertheless, over reliance on this diagnostic modality may lead to potential pitfalls in patient assessment. The crescent shape of the RV renders the precise assessment of its function difficult. Furthermore, echocardiography yields a plethora of information only a small proportion of which have been evaluated in the context of RVF. Haddad et al. previously attempted to determine the utility of echocardiography by examining the ultrasonography of 189 episodes of RVF in PH patients [44]. It was found that neither right heart chambers size nor right atrial pressure estimation was associated with outcome. In univariate analysis, tricuspid regurgitation (TR) and eccentricity index were the only variables with prognostic relevance. In multivariate analysis, only TR remains statistically significant. This has led several authors to question the reliability of echo in the day-to-day management of PH patients [3, 45].

Right heart catheterization remains the gold standard test for the diagnosis of pulmonary hypertension, to determine its severity, and to assess the haemodynamic response to treatment [46]. It is a safe investigation when performed in stable patients [47]. However, concerns have been raised regarding both safety and efficacy of invasive haemodynamic testing in the setting of RVF in PH patients. In a retrospective analysis of 99 PH patients with RVF requiring ICU admission, Huynh and al evaluated the impact of RHC in 45 patients. Following this investigation there were therapeutic changes (increased diuresis or introduction of a new PH specific drug) in 30 patients. No changes were made according to pulmonary hemodynamic for the remaining 15 patients. No association was documented between performed RHC and the outcome in ICU. However, pulmonary artery catheter placement within 3 days was associated with a better 6 months survival [20]. It was hypothesized that early pulmonary hemodynamic monitoring allowed early initiation of new PH specific drugs leading to a better outcome at 6 months. In our experience, PH patients admitted in ICU with RVF who develop a central line infection have an extremely poor outcome [4]. Therefore, the risk of inserting a dedicated central line has to be weighted against the benefit of this specific monitoring. It must be emphasized that the potential consequences related to side effects of pulmonary artery catheter placement in this subset of patients have not been rigorously evaluated. This is particularly important given how frail and unstable these patients often are. Further data are clearly required to better understand the risk/benefit ratio of right heart catheterization in this setting.

Cardiac magnetic resonance imaging (CMRI) is regarded as the "gold standard" imaging modality for assessment of the RV, the complex structure of which makes accurate assessment by 2-dimensional methods challenging [48]. However, MRI has never been evaluated in the setting of RVF in PAH patients. Furthermore, the clinical availability, technical confines and costs of this tool are practical limitations.

Novel devices that use transpulmonary thermodilution based methods to determine CO have generated considerable interest in the general ICU population. This technology provides information regarding numerous physiological variables including systemic arterial pressure, cardiac output, stroke volume, systemic vascular resistance and thoracic extra vascular lung water. RV dilation and tricuspid regurgitation are major limitations to the device's reliability however, and transpulmonary thermodilution method has never been formally validated in PH patients. It is therefore not recommended that this investigative tool be used to monitor this population in routine clinical practice.

Severity Markers

A number of biological markers have potential applicability in the assessment of RV dysfunction.

However, evidence supporting their use to date has been derived only from in observational studies. As such, the precise utility and indications in routine clinical practice for these markers remains to be further evaluated.

Circulating Biomarkers

Serum levels of brain natriuretic peptide (BNP) and NT-proBNP are associated with long-term outcome in PAH [49, 50]. BNP is secreted by cardiac ventricles through a constitutive pathway and is increased according to the degree of myocardial stretch, damage and ischemia. Recent data suggest that BNP and NT-proBNP levels are reliable prognostic markers in acute worsening of PAH [3–5, 20].

Troponin has been shown to be associated with prognosis in PAH when evaluated in stable patients [51]. Short-term outcome and right ventricular dysfunction in acute pulmonary embolism are also associated with elevated serum level of troponin [52]. However, raised serum troponin levels do not appear to be associated with survival in acutely worsened PAH, mainly because levels of this biomarker are not commonly elevated in PAH, raising the possibility that detection methods in severe PAH are not sufficiently sensitive [3, 4]. Improved new methods of monitoring of troponin have not been evaluated in the setting of PH [53].

Elevated C reactive protein (CRP) plasma levels may be in favour of an infectious background in PAH patients displaying acute heart failure. In our experience, high CRP levels are indeed predictors of poor prognosis in acute worsening of PAH, even without evidence of infection, raising the potential involvement of inflammation among several pathophysiological injuries [4].

Renal impairment and water regulation imbalance have been extensively studied in left ventricular failure [54]. By contrast, few studies have addressed these problems in acute right-heart failure complicating the course of PAH. Recent data suggest however that cardiac output and right atrial pressure in pulmonary hypertension might be part of a complex pathophysiological network including renin-angiotensin-aldosterone system, natriuretic peptides, vasopressin and sympathetic nervous systems resulting in metabolic abnormalities [55]. In left heart disease, data suggest that perturbations of the homeostatic balance between these physiological systems are associated with survival [56]. In stable PAH patients, hyponatremia is predictive of survival [57]. A recent study also provides evidence that serum creatinine is associated with survival in patients with stable PAH [58]. Similarly, a link has been shown between serum creatinine and sodium levels and outcome of PH patients in the ICU [4, 5, 59].

Beyond the prognostic value of a single measurement of any of the aforementioned biomarkers, it is also noteworthy that the changes in the values of some of these parameters may predict outcome in the ICU, as has been shown in one cohort study [4] (Fig. 16.1).

Artery Applanation Tonometry

Imaging studies have highlighted the consequences of RV dilation on LV size and function in stable PAH patients presenting major RV overload. It has been shown that LV volume and stroke volume may decrease in PAH patients, and that these modifications carry a prognostic significance [60]. Right-to-left dysynchrony has been shown to be the result of RV dysfunction and increased RV wall tension [61]. A delay in RV peak pressure leads to a transseptal gradient and septal bowing in the LV that impairs LV filling and decreases stroke volume [60, 62]. Using MRI, Marcus et al. found mean reductions of 25 % and of 12 % respectively in the time to peak of shortening of the LV free wall and time to aortic valve closure in PAH patients [61]. Therefore, our group recently tested the value of left ventricular ejection time (LVET), monitored through aplanation tonometry in PH patients admitted in ICU. Arterial tonometry is a simple, quick, painless and safe non invasive method for estimating central aortic pressure from peripheral recording of pulse waves at the radial or carotid artery level. It also allows calculating the LVET and left ventricle diastolic time [63–65] (Fig. 16.2). It is already widely used in systemic hypertension to study arterial stiffness and estimate risks of end organs damage [66]. In a prospective study that

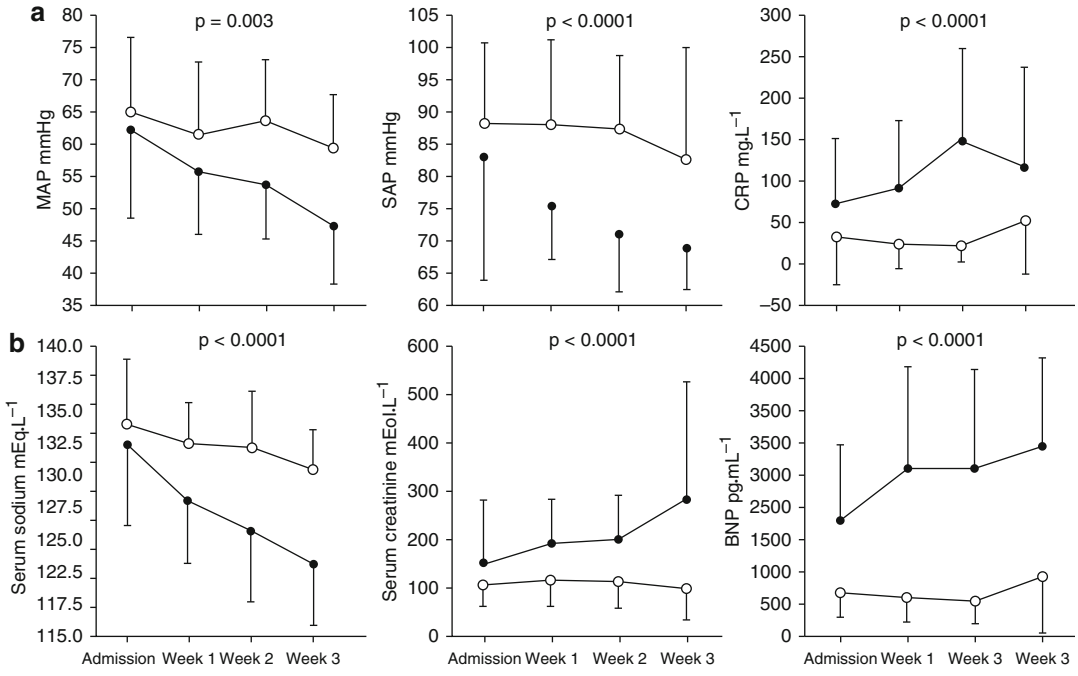

Fig. 16.1 Clinical and biochemical data during ICU stay according to survival in ICU. *White circles* represent patients discharged from the ICU (survivors), *black circles* represent patients dead in ICU (non-survivors). (**a**) Evolution of mean systemic arterial pressure (*MAP*) during ICU stay. (**b**) Evolution of systolic systemic arterial pressure (*SAP*) during ICU stay. (**c**) Evolution of C reactive Protein (*CRP*) serum levels during ICU stay. (**d**) Evolution of sodium serum levels during ICU stay. (**e**) Evolution of creatinine serum levels during ICU stay. (**f**) Evolution of Brain Natriuretic Peptide (*BNP*) serum levels during ICU stay. (Reproduced with permission of the European Respiratory Society. Sztrymf et al. [4]. Copyright remains with European Respiratory Society©)

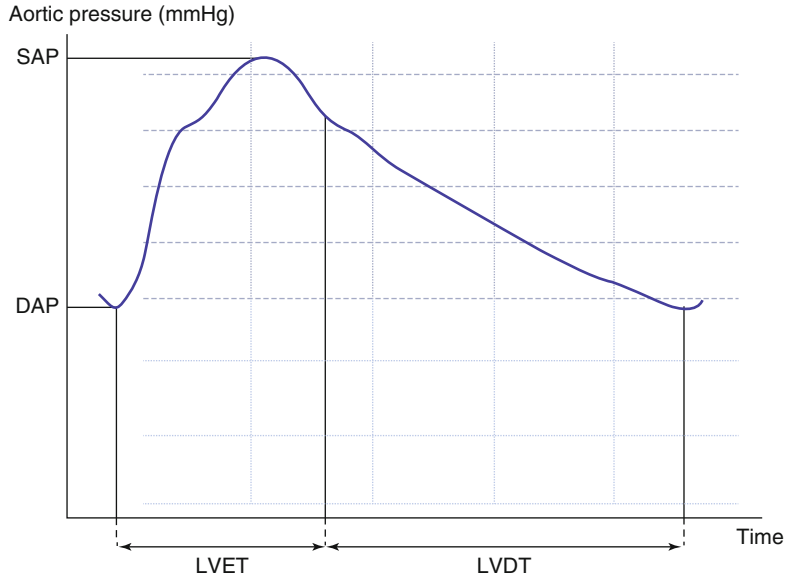

Fig. 16.2 Typical aortic pressure waveform obtained by arterial tonometry in a PH patient. *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *LVET* left ventricular ejection time, *LVDT* left ventricular diastolic time

included 53 PH patients admitted in ICU for evidence of RHF, it was found that a shorter LVET was associated with a worse outcome (228 ms (212–278) vs 257 ms (237–277), p = 0.032). It was hypothesized that lower LVET in non survivors may be explained either by markedly decreased inotropic state or by major RV-LV interaction, thus impeding LV ejection or reduction in LV preload [9]. Additional data to confirm these observations are required however.

Therapeutics

In clinical studies, some therapeutics showed to carry a prognostic significance. For example, the use of inotropic and vaso active drugs is consistently linked to a worse outcome in patients treated for RHF. The increase of the drugs doses has also been found to be of prognostic value [4]. These observations are unlikely to be explained by a drug effect per se, but rather represent a marker of the severity of the patient's condition. Nevertheless, in a retrospective analysis, Kurzyna et al. suggested that dopamine was an unsuitable drug for acute RVF in PH patients [3]. It has to be kept in mind that no evidence based approach on which to select the individuals' therapies is lacking.

Hypoxemia is common in PH patients due to ventilation-perfusion mismatch [67], low mixed venous oxygen saturation due to decreased cardiac output [68], low diffusion capacity [69], right-to-left shunt due to a reopening of patent foramen ovale, and cardiac septal defects or pulmonary arterio-venous malformations in patients with associated conditions [70]. The recommendations is to maintain oxygen saturation above 90 % in PH patients [71]. In a prospective cohort of patients admitted in ICU for clinical deterioration, it was found those patients who had an unfavourable outcome required a higher oxygen flow (15 (9.3–17.5) L/min vs 4 (2–6) L/min, p = 0.004) to achieve this target [9].

These therapeutics obviously carry a prognostic value. According to the aforementioned data, their use and their changes in doses over time indicate a worse outcome. This has to be weighed against the achievement of therapeutic goals to rate the treatment's success, and is therefore part of the multi-disciplinary discussion about ECLS and lung/heart-lung transplantation indication in eligible patients.

Survival

To the best of our knowledge, only six studies have reported on the short-term survival rates of PH patients affected by right heart failure [3–5, 9, 20, 39]. The diagnosis of RV failure was mostly based on clinical assessment, and treatment protocols were different among these studies, somewhat limiting the comparisons of the different datasets. The wide range of the reported mortality rates, which varied from 14 to 100 % (Table 16.1), is likely explained by the spectrum in the severity of illness of evaluated patients. In two studies, mortality of patients not requiring inotropic of vaso-actives drugs were 14 and 17 % respectively [4, 5] while it was as high as 41.3–60 % in patients requiring these drugs [3–5, 9, 20]. Use of renal replacement therapy was associated with a dismal prognosis [20, 26], as was the need for invasive mechanical ventilation [5, 20].

One study analyzed the prognosis in survivors of a right heart failure episode. Six out of the 27 patients discharged alive from ICU were dead at 3 months, giving a 3-month mortality of 22.2 %. In this study, 7 out of the 27 patients discharged from ICU, were subsequently referred at least a second time to the ICU for similar symptoms within the 18 months of study period [4].

It is noteworthy that the outcome of cardiopulmonary resuscitation in PH patients having cardiac arrest is very poor. One study found that only 6 % of patients in whom a CPR was attempted survived without neurological impairment [45].

Comprehensive Care

As emphasized throughout this chapter, there is a lack of evidence-based data to enable creation of guidelines for RV failure in PH patients.

Table 16.1 Reported cohorts of acute right heart failure in PH patients

	Kurzyna et al. [3]	Campo et al. [5]	Haddad et al. [39]	Huynh et al. [20]	Sztrymf et al. [4]	Sztrymf et al. [9]
Design	Single centre retrospective	Single centre retrospective	Single centre retrospective	Single centre retrospective	Single centre prospective	Single centre prospective
Study period	2005–2007	2000–2009	1997–2009	2004–2009	2005–2007	2011–2012
Number of patients (n)	60	115	119	99	46	53
Age (years)	47 ± 18	55 ± 15	ND	51.9 ± 13.6	50 (16.2–77.4)	63.3 (47.8–71.9)
Characteristics at admission:						
Systolic arterial pressure (mmHg)	94 ± 14	113 ± 20	111 ± 15	ND	87 ± 15	112 ± 20
Diastolic arterial pressure (mmHg)	65 ± 12	68 ± 13		ND	ND	66 ± 13
Heart rate (bpm)	102 ± 13	95 ± 16	89 ± 16	ND	109 ± 20	89 ± 14
Creatinine serum level (μmol/L)	ND	115.3 ± 70.4	115 ± 88	132 ± 149	129 ± 76	124 ± 69
Sodium serum level (mEq/L)	131 ± 6	136 ± 5	136 ± 5	134.5 ± 5.1	133 ± 6	134 ± 4
Nt-proBNP (mmol/L)	9,733 ± 4767	3,602 (2,082–6,897)	ND	ND	ND	ND
BNP (mmol/L)	ND	ND	ND	384 (197–839)	809 (567–1,300)	579 (234–957)
Admission in ICU (n)	ND	29	28	99	46	53
Inotropic and/or vaso-active drugs intake (n)	33	35	32	44	46	7
Mechanical ventilation (n)	0	9	10	34	0	0
Renal replacement therapy (n)	0	3	4	20	0	0
Length of stay (days)	ND	7 (4–12)	9 (2–96)	10 (5–16)	9 (4–16)	5 (3–10)
Mortality:						
Whole cohort (%)	31.6	14	38	30.3	41.3	17
Patients receiving catecholamines (%)	60	45.7	ND	50	41.3	42.8
Patients undergoing RRT (%)	NA	ND	ND	70	NA	NA
Patients undergoing MV (%)	NA	100	ND	71	NA	NA

ND not done, *NA* not applicable

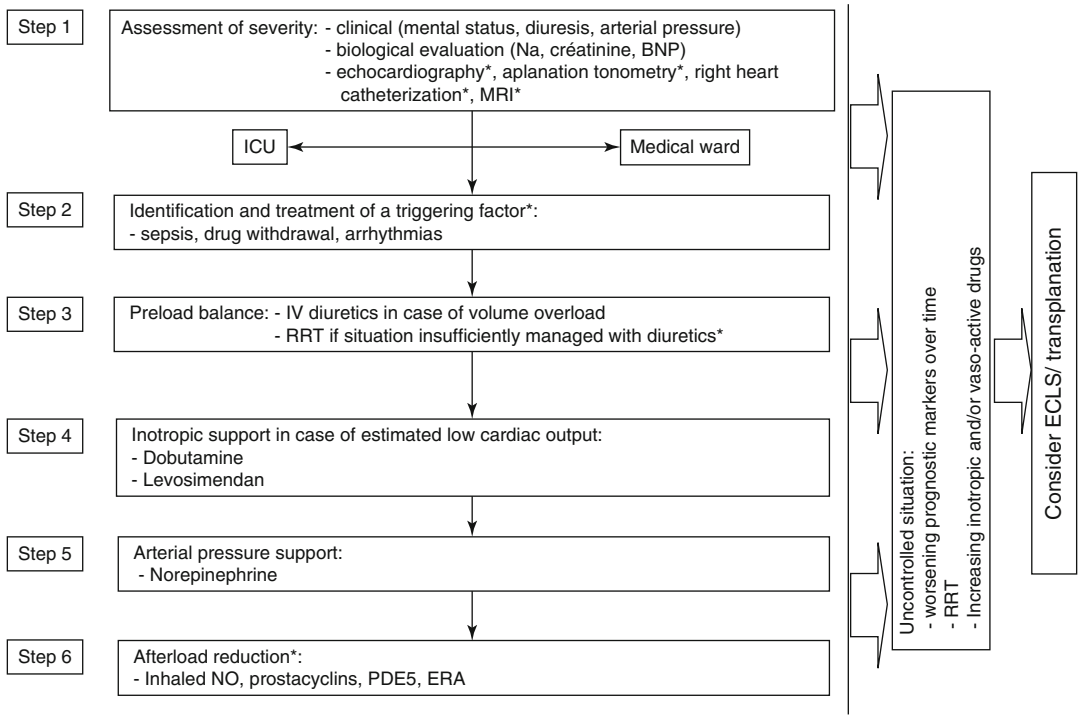

Fig. 16.3 Comprehensive care of PH patients affected by RV failure. * indicates procedures whose efficacy remain debatable

Nevertheless, based on previously reported pathophysiological data and expert consensus, some recommendations can be proposed.

The first step in the management is the evaluation of the severity, based on clinical, biological and hemodynamic variables. This stage is of paramount importance, and will guide clinicians as to the most appropriate setting for continuing patient care (i.e. ward or ICU).

It is very difficult to recommend an optimum monitoring strategy. From what has already been said, there are some important some clinical, biological and hemodynamic therapeutic endpoints which should be sought. Dynamic monitoring of the chosen variables over time, in order to enable early identification of evidence of treatment failure and possible subsequent referral for rescue therapy in eligible patients is appropriate. This careful assessment approach should therefore continue from admission until eventual discharge (Fig. 16.3).

Acute Right Heart Failure in Patients Without Previous Pulmonary Hypertension

Apart from PAH a number of circumstances can lead to RVF. For example, any process interfering with RV filling (preload or diastolic process), RV inotropic state or RV afterload can induce RVF. The most common causes are: left ventricular dysfunction, RV ischemia, sepsis, pulmonary embolism, hypoxic pulmonary vasoconstriction (such as in Acute Respiratory Distress Syndrome), acute chest syndrome in sickle cell disease, cardiac tamponnade, myocarditis [25]. Congenital malformation and valvular abnormalities may precipitate RVF. It is important to underline that in these circumstances, RVF is often a marker of severity.

The pathophysiology of RVF depends on the etiology, and encompasses ventricular interdependence, RV ischemia, cytokine induced injury

and afterload increase. These mechanisms often occur in the setting of the diseases mentioned above.

The therapeutics aims are the same as in patients with pulmonary hypertension, namely preload balance, RV contractility optimization, afterload reduction when appropriate and systemic arterial pressure support if necessary. The treatments used to achieve these goals are those previously described, and their precise indications is beyond the scope of this chapter. RVAD can be used when the RV afterload is not increased when pharmacological treatment leads to insufficient control of the patient.

Conclusion

Right heart failure in pulmonary hypertensive patients is a common problem that is associated with a high mortality and seems to affect the course of the underlying disease. A careful and comprehensive management strategy is necessary even though there is a lack of evidence-based data to guide clinicians. In refractory heart failure, extra corporeal life support can be used as a bridge to urgent transplantation in eligible patients. Further studies are required such that an optimum and appropriate monitoring and management strategy of these devastating events can be pursued.

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Arrhythmias in Right Heart Failure due to Pulmonary Hypertension

17

Michele D'Alto and Giangiacomo Di Nardo

Abstract

The clinical relevance of cardiac arrhythmias has not been systematically studied in patients with right heart failure and pulmonary arterial hypertension (PAH) despite being important contributors to morbidity and mortality. Electro-anatomical remodeling of the right ventricle and right atrium in response to longstanding pressure and volume overload, resulting from altered autonomics, repolarization abnormalities, and ischemia, may be the underlying substrate predisposing to enhanced arrhythmogenicity in patients with right heart failure and PAH.

Supraventricular tachycardias, such as atrial fibrillation, atrial flutter and more rarely atrio-ventricular nodal reentry tachycardia, are associated with worsened outcomes, and maintenance of sinus rhythm is a goal. Given the significant potential side effects of antiarrhythmic drugs for supraventricular tachycardias, percutaneous catheter ablation represents a safe and reliable alternative approach.

In contrast to patients with advanced left heart disease, life-threatening arrhythmias, such as ventricular tachycardia and ventricular fibrillation, are relatively rare in patients with PAH. Conversely, patients with PAH may often show bradycardia as pulseless electrical activity. Prophylactic antiarrhythmic therapy is not indicated for primary prevention of sudden cardiac death, and an implantable cardioverter-defibrillator should be

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offered as a treatment option to PAH patients who manifest either syncope or cardiac arrest in the setting of documented ventricular tachycardia/fibrillation. The role of pacing in PAH patients for relative bradycardia is not well established, highlighting the intrinsic difficulty in clinical management of PAH patients during cardiac arrest. Finally, the exact role of cardiac resynchronization therapy in these patients remains undefined.

Abbreviations

6MWD	Six-minute walk distance
AF	Atrial fibrillation
AFl	Atrial flutter
APD	Action potential duration
AVNRT	Atrio-ventricular nodal reentry tachycardia
CPR	Cardiopulmonary resuscitation
CTEPH	Chronic thromboembolic pulmonary hypertension
CTI	Cavo-tricuspid isthmus
ECG	Electrocardiogram
I_{to}	Transient outward potassium current
LV	Left ventricle
NCX	Na^+-Ca^{2+} exchanger
PAH	Pulmonary arterial hypertension
QTc	Corrected QT interval
RV	Right ventricle
SCD	Sudden cardiac death
SR	Sinus rhythm
SVT	Supraventricular tachycardia
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

The term "*cor pulmonale*" classically refers to the associated hypertrophic and/or dilated remodeling of the right ventricle that may accompany a variety of chronic respiratory diseases [1]. Right heart failure occurs in many diseases associated with dysfunction of the pulmonary circulation [2–4], including pulmonary arterial hypertension (PAH) [2] and chronic lung diseases such as chronic obstructive pulmonary disease [5, 6]. In particular, right ventricular (RV) failure, that is the major cause of death in PAH [2], is associated with RV electrical remodeling [7, 8] and a higher risk of arrhythmias [9, 10].

Pathophysiology

Remodeling of the right ventricle and right atrium in response to longstanding pressure and volume overload is responsible for the underlying arrhythmogenic substrate in patients with right heart failure. Different electrophysiological changes predispose to arrhythmias in right heart failure and rely on the underlying heart disease. These include alterations in Ca^{2+} handling, remodeling of the extracellular matrix and ion channels, presence of scars, activation of the sympathetic nervous and renin–angiotensin–aldosterone systems, dilatation and stretch, and delayed cardiac repolarization, all of which result in enhanced QT dispersion [11]. In addition, insufficient blood supply associated with heart failure may also affect the heart, leading to acute myocardial ischemia that has its own arrhythmogenic mechanisms [12].

Modulation of autonomic activity plays a key role in predisposing to cardiac arrhythmias. Folino et al. [9] assessed the arrhythmic profile in nine patients with PAH and its correlation with autonomic features, echocardiographic indexes and pulmonary function. PAH patients showed increased sympathetic activity (reduced heart rate variability) that correlated with higher RV systolic pressure at echocardiography. Premature ventricular beats were more frequent in subjects with higher adrenergic drive and lower oxygen saturation. Moreover, patients with episodes of syncope showed a relatively higher vagal activity, and effective mechanisms of adjustment in blood oxygenation during effort. In addition to

reduced heart rate variability, elevated levels of plasma norepinephrine and selective down-regulation of beta-adrenergic receptors in the right ventricle in PAH patients were indicators of increased sympathetic activity affecting the right ventricle. The increased sympathetic activity correlated positively with right heart failure severity [13]. Thus, the increase in pulmonary pressure and subsequent reduction in cardiac output may induce changes in autonomic activity resulting in increased sympathetic drive, well known for its pro-arrhythmic effects [14].

Another important factor involved in RV electrical remodeling is delayed cardiac repolarization that leads to enhanced QT dispersion. The latter has been shown to be a precursor of arrhythmias and a predictor of all-cause mortality [15]. In a study of 201 patients with PAH, mean heart rate-corrected QT (QTc) and QTc dispersion positively correlated with mean pulmonary arterial pressure and were significantly increased in patients with severe PAH [16].

Finally, RV myocardial ischemia has been suggested as a mechanism of ventricular arrhythmias in patients with PAH. This may be due to a number of factors, including RV subendocardial ischemia resulting from intra-myocardial arteriolar compromise, decreased perfusion pressure gradient, and increased myocardial oxygen demand as a result of RV pressure overload [12, 14].

Electro-anatomical remodeling in failing ventricular myocytes plays a key role in determining life-threatening arrhythmias. This has been intensively studied in the clinical setting of left heart failure [17–22]. Prolongation of the ventricular action potential is a hallmark of heart failure. Studies in animal models and in humans with heart failure have consistently revealed action potential duration (APD) prolongation due to functional down-regulation of transient outward potassium current (I_{to}) [23, 24], functional up-regulation of inward Ca^{2+} current and changes in Ca^{2+} current inactivation [25, 26], or increases in late sodium currents [27, 28]. APD prolongation may prolong Ca^{2+} channel opening and thereby contribute to preservation of contractile force. However, it also increases the risk of Ca^{2+} overload, which may contribute to abnormal triggered impulses and perturbed signaling events. Although all myocardial cell layers exhibit significant APD prolongation in heart failure, such prolongation is typically heterogeneous. In a mouse model of pressure-overload heart failure, Wang et al. [29] found that APD was more prolonged in subepicardial than in subendocardial myocytes due to a more significant reduction in transient outward potassium currents. The dispersion and heterogeneous prolongation of repolarization between cell types across the ventricular wall represent an electrophysiological mechanism for unidirectional block, reentry, and arrhythmogenicity.

The Na^{+}-Ca^{2+} exchanger (NCX) is a surface membrane protein that transports one Ca^{2+} ion in exchange for three Na^{+} ions. Its activity is said to be "forward" when Na+ is transported into the cell and Ca^{2+} is extruded outwards, and "reverse" when ions are transported in the opposite directions. Most studies from hypertrophied and failing human hearts have demonstrated an increase in both NCX mRNA and protein levels [30–33], which has been posited to preserve diastolic extrusion of cytosolic Ca^{2+}. At the same time, increased NCX activity may impair systolic function by favoring transport of Ca^{2+} out of the cell rather than back into intracellular stores.

I_{to}, a major determinant of the early phase of action potential repolarization, also plays a key role in modulating action potential plateau and repolarization profiles. In fact, down-regulation in I_{to} contributes to changes in action potential morphology observed in many forms of heart disease [34–36].

Further, APD prolongation and abnormal handling of intracellular Ca^{2+} promote abnormal increases in focal activity and automaticity. In addition, heterogeneous APD prolongation within the ventricular wall amplifies dispersion of repolarization, an established mechanism contributing to re-entry. Finally, spatially different changes in I_{to} across the ventricular wall in heart failure alter cellular coupling current.

Taken together, these changes, along with the alteration of gap junctions and tissue alignment, lead to significant changes in electrical conductivity and sequence, which are important mechanisms underlying the increased propensity to

ventricular arrhythmia and sudden cardiac death (SCD) in heart failure.

Therefore, right heart failure is not characterized by a single set of electrophysiological changes.

Three possible electrophysiological mechanisms are involved in the development of cardiac arrhythmias in the presence of right heart failure: (a) increased automaticity, (b) triggered activity, and (c) reentry phenomena around an anatomical obstacle. *Automaticity* is the property of cardiac cells to undergo spontaneous diastolic depolarization and initiate an electrical impulse in the absence of external electrical stimulation [37]. *Triggered activity* is a term used to describe impulse initiation in cardiac fibers that is dependent on after-depolarizations. These are oscillations in the membrane potential that follow the upstroke of an action potential [37, 38]. The fundamental requirements for *reentry* are unidirectional conduction block, a core of unexcitable tissue around which the wave front propagates, and maintenance of excitable tissue ahead of the propagating wave front (an excitable gap) that is facilitated by either slowing of conduction, shortening of the refractory period, or both [38].

Awareness of arrhythmias in patients with PAH and/or right heart failure has occurred for long time. In 1962, James [39] first described autopsy findings of sino-atrial and atrio-ventricular nodal artery disease in three patients with severe PAH and syncope who died suddenly. In 1979, Kanemoto and Sesamoto [40] assessed 171 electrocardiograms (ECGs) from 101 patients with PAH and found arrhythmias in 27 % of the considered patients. The main types of arrhythmias were sinus tachycardia, sinus bradycardia and first-degree atrio-ventricular block, which accounted for 70 % of the total, whereas ventricular arrhythmias were very rare.

Supraventricular Arrhythmias

RV failure and supraventricular tachycardias (SVTs), in particular atrial flutter (AFl) and atrial fibrillation (AF), may be part of a vicious circle. From one side, SVTs are mainly due to structural changes in the right atrium secondary to chronic pressure overload and alterations in autonomic tone. In fact, they are more often present in advanced stages of right heart failure or PAH. From the other side, the occurrence of SVT may compromise cardiac function and worsen the prognosis of PAH. Actually, the observation that sinus rhythm restoration was followed by marked and rapid clinical improvement suggests some degree of causal role of SVTs in precipitating and/or worsening RV failure. Such clinical deterioration appeared to be related to the deleterious hemodynamic effects of the loss of atrial transport mechanism and/or compromise in diastolic filling time resulting from rapid heart rates in the presence of ventricular dysfunction. In particular AFl, but also AF, almost invariably leads to further clinical deterioration [41]. In these patients, RV function is a main determinant of clinical stability and outcome and SVTs constitute a relevant problem. Data about SVT incidence and clinical role are based on a small number of retrospective studies.

In a retrospective single-center analysis involving 231 consecutive patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (CTEPH), Tongers et al. [42] observed that the cumulative incidence for SVT was 11.7 % (annual risk 2.8 % per patient), including AFl, AF and atrio-ventricular nodal reentry tachycardia (AVNRT). SVT onset was almost invariably associated with marked clinical deterioration and RV failure (84 % of SVT episodes). The outcome was strongly associated with the type of SVT and restoration of sinus rhythm (SR). In fact, cumulative mortality was lower when SR was restored (all cases of AVNRT and AFl). In contrast, the vast majority of patients with permanent AF (9/11) died from RV failure at one-year follow-up. In this study, the average interval between diagnosis of pulmonary hypertension and onset of SVT was 3.5 years, suggesting that these arrhythmias are mostly manifestations of long-standing pulmonary hypertension.

In another retrospective single-center analysis [43] involving 281 patients with PAH, the average interval between PAH diagnosis and SVT onset was 60.3 ± 55.9 months. The cumulative

incidence of SVT, consistent with Tongers' study [42], was 10 %. The type of arrhythmia distribution was AF in 42.8 %, "uncommon" AFl in 25 %, "common" AFl in 17.8 %, and AVNRT in 14.2 %. AF and AFl occurred in older patients compared with AVNRT. Most episodes of SVT (82 %) were symptomatic with clinical worsening or RV failure. In particular, the mean distance at the 6-min walk test (6MWD) decreased after SVT onset (423.7 ± 74.6 vs 252.1 ± 145.8 m; $p < 0.001$). Patients with AFl presented the most marked decrease in 6MWD. Restoration of SR was associated with clinical improvement in all patients, with an average increase in 6MWD of 196 ± 163 m. After a first episode of SVT, and despite restoration of SR or adequate control of ventricular rate, 46.4 % of patients needed an increase in PAH-specific therapy due to progressive clinical deterioration or right heart failure. The average time between SVT onset and death or transplantation was 17.8 months.

Recently, Olsson et al. [44] in a 5-year, prospective study, involving 157 patients with PAH and 82 patients with inoperable CTEPH observed that the cumulative incidence of new-onset AFl and AF was 25.1 % (95 % confidence interval, 13.8–35.4 %). The development of these arrhythmias was frequently accompanied by clinical worsening (80 %) and signs of right heart failure (30 %). Stable sinus rhythm was successfully re-established in 21/24 (88 %) of patients initially presenting with AFl and in 16/24 (67 %) of patients initially presenting with AF. New-onset AFl and AF were an independent risk factor of death ($p = 0.04$, simple Cox regression analysis) with a higher mortality in patients with persistent AF when compared to patients in whom sinus rhythm was restored (estimated survival at 1, 2 and 3years 64, 55, and 27 % versus 97, 80, and 57 %, respectively; $p = 0.01$, log rank analysis).

Finally, Medi et al. [45] evaluated atrial electrical and structural remodeling in 8 patients with longstanding PAH compared to 16 controls. PAH patients showed prolongation of corrected sinus node recovery time without significant changes in atrial effective refractory period and an increase in AF inducibility. PAH was associated with lower tissue voltage, increased low voltage areas, and the presence of electrically silent areas. Conduction velocities were slower and fractionated electrograms and double potentials were more prevalent in PAH patients compared with controls, respectively. Taking these data together, they concluded that PAH is associated with right atrial electro-anatomical remodeling, characterized by generalized conduction slowing with marked regional abnormalities, reduced tissue voltage, and regions of electrical silence. These changes provide important insights into the isolated effects of PAH, fundamental to a range of clinical conditions associated with AF.

Therapy

Given the detrimental hemodynamic effects of SVT on clinical outcome, restoration and maintenance of SR represent a key target in the management of PAH patients.

Similarly to AF in the setting of left heart disease (i.e. systemic hypertension, mitral or aortic valve disease, left ventricular [LV] systolic or diastolic dysfunction), "non-antiarrhythmic" therapy must be optimized. This means that background therapy (such as warfarin, diuretics, digoxin if necessary) and PAH-specific therapy (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogues) have to be individually adjusted and personalized. Following optimization of PAH-specific therapy, treatment options for SVT may include rate control (i.e. digoxin, calcium channel blockers) or rhythm control (i.e. antiarrhythmic agents or non-pharmacological treatment).

The need for systemic anticoagulation should be considered in all patients with AF/AFl [46].

With regard to atrio-ventricular nodal active drugs in patients with AF, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial [47] randomized 4,060 patients with AF at high risk of stroke or death to a rate control vs rhythm control strategy. In the rate control arm, different therapies were allowed to achieve adequate heart rate control, including digoxin, beta-blockers, calcium channel blockers (verapamil and diltiazem), or combinations of

these drugs. In the rhythm control arm, antiarrhythmic drugs included amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, or combinations of these drugs. The strategy of rate control vs rhythm control was randomized, whereas the choice of specific agents used was left to the discretion of the treating physician in both arms. During a mean follow-up of 3.5 years, there were 356 deaths (23.8 %) in the rhythm control group vs 310 deaths (21.3 %) in the rate control group, a directionally but not significantly lower mortality with rate control ($p = 0.08$). Two reports from the AFFIRM trial [48, 49] explored the association of digoxin use with mortality among patients with AF, reaching conflicting conclusions: one reported that digoxin use was associated with a significant increase in all-cause mortality [48] and the other documented no association of digoxin use with mortality [49]. Several factors contributed to these different conclusions. Given the non-randomized, observational design of both studies, these findings should be considered "hypothesis generating", and not even the most sophisticated statistical methods, such as propensity-matched analysis, can replace randomization [50].

Digoxin has been traditionally largely used in the setting of chronic obstructive pulmonary disease also in patients with SR [51, 52]. In a single open-label study [31], digoxin was shown to improve ventricular function only if LV function was reduced and despite the improvement in ventricular function, digoxin has failed to improve pulmonary function, cardiopulmonary response to exercise or general feeling of well-being. Moreover, at present the role of digoxin in patients with pulmonary hypertension and AF/AFl is not well established. Current guidelines on pulmonary hypertension [41] suggest that digoxin may be considered in patients with PAH who develop atrial tachyarrhythmias to slow ventricular rate.

Calcium channel blockers are commonly used as part of the PAH treatment regimen for "vasoreactive" patients. The use of verapamil or diltiazem for arrhythmia management may be challenging because the effects of these drugs in "non-vasoreactive" patients are not known and because of their negative inotropic activity. As a consequence, no specific recommendations can be given at this time.

Beta-blocker therapy, often used in patients with portal hypertension to reduce the risk of variceal bleeding, has been shown to worsen hemodynamics and exercise capacity in portopulmonary PAH patients [53]. Thus, the use of beta-blockers for the treatment of SVT in patients with PAH is currently discouraged because of their negative inotropic effects [41].

The use of many antiarrhythmic agents in the PAH population is limited due to the significant side effect profile and lack of data. For instance, in patients with structural heart disease and/or heart failure, class IC antiarrhythmic agents (i.e. sodium channel blockers such as propafenone and flecainide) are not recommended because of increased risk of premature death [54].

The class III antiarrhythmic agent sotalol prolongs the QT interval and possess negative inotropic effects due to its beta-blocker action.

In the absence of more effective pharmacological options, the need to restore SR using antiarrhythmic agents with no negative inotropic effects makes amiodarone an ideal drug in the acute setting for controlling hemodynamically significant arrhythmias. Nevertheless, the role of chronic prophylactic administration of amiodarone in maintaining SR remains uncertain, given significant potential side effects, such as development of pneumonitis/fibrosis, and its potential drug-drug interaction with PAH-specific drugs. Moreover, amiodarone is a CYP2C9 inhibitor and may cause a significant increase in plasma bosentan levels [41].

The safety and efficacy profiles of newer antiarrhythmics, such as ivabradine and dronedarone, have not been well established yet.

A reliable alternative approach to SVT, in particular AVNRT [42, 43] and AFl [42, 43, 55–57], is percutaneous catheter ablation (Figs. 17.1 and 17.2). Data from a retrospective analysis of 22 patients with AFl and PAH or CTEPH [55] showed that cavo-tricuspid isthmus (CTI) ablation can be performed successfully without

Fig. 17.1 Ablation lines of typical right atrial flutter. Abbreviation: see Fig. 17.3

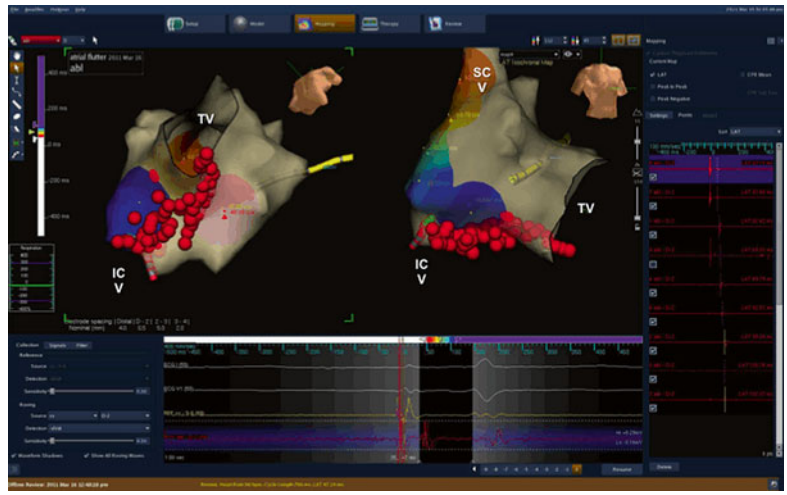

Fig. 17.2 Validation of ablation lines showing bidirectional block. Abbreviation: see Fig. 17.3

complications, leading to a significant clinical improvement in terms of functional class. In addition, the absence of changes in echocardiographic parameters after catheter ablation suggested that acute improvement in clinical status was secondary to SR restoration rather than cardiac remodeling. In a retrospective single-center study [56] involving 38 PAH patients with CTI-dependent AFl undergoing an ablation procedure, a bidirectional block of the CTI was achieved in all patients. Nevertheless, patients with severe PAH had a significantly longer procedure, longer ablation time and a greater amount of cumulative tissue lesions than patients without PAH. Finally, in another single-center retrospective study, catheter ablation was performed in 12 PAH patients with AFl resistant to medical management. Acute success was obtained in 86 % of procedures. After catheter ablation, echocardiographic estimated pulmonary artery systolic pressure decreased from 114 ± 44 to 82 ± 38 mmHg ($p = 0.004$) and B-type natriuretic peptide levels were lower (787 ± 832 vs 522 ± 745 pg/mL, $p = 0.02$). A total of 80 % of patients were free from AFl at 3-month follow-up and 75 % at 1 year.

Thus, according to available limited data [42, 43, 55–57], treatment of AFl (Fig. 17.3) or AVNRT by catheter ablation is feasible, safe, and effective in patients with PAH.

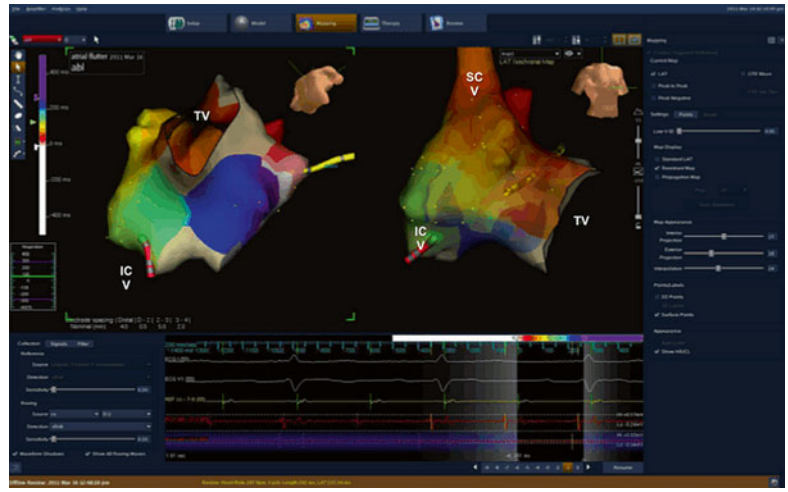

Fig. 17.3 Electro-anatomical reconstruction of typical right atrial flutter. *SCV* superior cava vein, *ICV* Inferior cava vein, *TV* tricuspid valve

Ventricular Arrhythmias

A prolonged QRS duration (>120 ms) is common in patients with left-sided heart failure and is associated with more advanced myocardial disease, worse LV function and prognosis, and higher all-cause mortality compared with patients with a narrow QRS complex [58–61]. QRS prolongation results in systolic ventricular dyssynchrony, which can further decrease cardiac output of the left side of the heart.

Although previous studies have demonstrated interventricular dyssynchrony also in patients with PAH [62], only limited data on the prevalence of QRS prolongation across the spectrum of idiopathic PAH are available at present. In a recent retrospective study including 212 consecutive patients with idiopathic PAH [63], 35 patients (16.5 %) had a prolonged QRS duration (>120 ms). QRS duration was positively correlated with right atrial and RV dimensions, suggesting a possible role of RV overload in its pathogenesis. Interestingly, QRS prolongation was associated with a worse WHO functional class and 6MWD and higher serum uric acid when compared with patients with normal QRS duration ($p<0.05$). Moreover, QRS prolongation was an independent predictor of mortality and was associated with a 2.5-fold increased risk of death ($p=0.024$). Therefore, QRS duration >120 ms may be considered a new predictor of adverse outcome in patients with idiopathic PAH, and screening for prolonged QRS duration should be part of the routine assessment of patients with idiopathic PAH for risk stratification and treatment.

Recently, an experimental study on male Wistar rats receiving monocrotaline to induce either RV hypertrophy or failure, investigated the electro-anatomical ventricular remodeling and the possible mechanisms responsible for the pro-arrhythmic state [64]. Failing hearts showed greater fiber angle disarray that correlated with APD. Failing myocytes had reduced sarcoplasmic reticular Ca^{2+}-ATPase activity, increased sarcoplasmic reticular Ca^{2+} release fraction, and increased Ca^{2+} spark leak. Moreover, in hypertrophied hearts and myocytes, dysfunctional adaptation had begun but alternans did not develop. The authors concluded that increased electrical and structural heterogeneity and dysfunctional sarcoplasmic reticular Ca^{2+} handling increase the probability of alternans, a pro-arrhythmic predictor of SCD. These mechanisms are potential therapeutic targets for the correction of arrhythmias in hypertensive, failing right ventricles.

The clinical course of pulmonary hypertension and PAH is one of progressive deterioration combined with episodes of acute heart failure [41]. RV failure and SCD are the most common causes of death in PAH.

Nowadays, RV failure (36 %) and SCD (28 %) together account for the majority of deaths in

patients with PAH [65, 66]. However, in contrast to patients with advanced left heart disease, life-threatening arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) are relatively rare in patients with PAH. Conversely, patients with PAH may often show bradycardia as pulseless electrical activity. The major determinant of prognosis in PAH patients is RV function and SCD is more likely to occur in such patients with severe hypoxia [67]. Less common "non-arrhythmogenic" causes of SCD should also be considered, including rare cases of dissection or rupture of the pulmonary artery [68] or left main extrinsic compression by dilated pulmonary artery [69–71].

In a recent study [72] evaluating a total of 84 PAH patients (mean age 58 ± 14 years, 73 % female) who died between June 2008 and May 2012, PAH was the direct cause of death (for right heart failure or SCD) in 37 (44 %) and PAH contributed but did not directly cause death in 37 (44 %) patients. Moreover, 50 % of all patients with PAH and 75.7 % of those who died of right heart failure received parenteral prostanoid therapy and less than half of patients had advanced healthcare directives.

A retrospective multicenter study [73] on the frequency and results of cardiopulmonary resuscitation (CPR) in patients with PAH considered a total of 3,130 patients with PAH treated between 1997 and 2000 in 17 referral centers in Europe and in the United States. During this 3-year period, 513 (16 %) patients had circulatory arrest and CPR was attempted in 132 (26 %) of them. Although 96 % of the CPR attempts took place in hospitalized patients (74 % in intensive care units or equally equipped facilities) and although there was only minimal delay between collapse and initiation of CPR, resuscitation efforts were primarily unsuccessful in 104 patients (79 %). Only 8 patients (6 %) survived for more than 90 days. The initial ECGs at the time of CPR showed bradycardia in 58 cases (45 %), electro-mechanical dissociation in 37 cases (28 %), asystole in 19 cases (15 %), VF in 10 cases (8 %), and other rhythms in 6 cases (4 %). The initial ECG rhythm was unknown in 2 cases. Data from right heart catheterization within 3 months before CPR were available for 80 patients (61 %). The hemodynamic variables confirmed the presence of severe PAH in these patients but did not show any significant differences between survivors and non-survivors. Except for one patient, all long-term survivors had identifiable causes of circulatory arrest that were rapidly reversible. Moreover, in approximately 50 % of the patients in this study, an intercurrent illness contributed to death. These conditions were often minor abnormalities such as respiratory or gastrointestinal tract infections, which underscores the notion that patients with PAH are clinically fragile with little or no compensatory reserve in the setting of concomitant illnesses. The authors hypothesized that poor results of CPR in patients with PAH may be explained by the underlying hemodynamic condition. In fact, the mean pulmonary vascular resistance in the study population was 1,694 dyn * s * cm^{-5}, which is more than eight times above the upper normal limit of 200 dyn * s * cm^{-5}. Under these conditions, it is extremely difficult to achieve effective pulmonary blood flow and LV filling with chest compression. These data indicate that CPR for circulatory arrest in patients with PAH is rarely successful unless the cause of cardiopulmonary decompensation can be corrected.

On the basis of these pathophysiological considerations, measures to improve the results of CPR in PAH patients should aim at optimizing PAH-specific therapy to lower pulmonary vascular resistance. In this context, it is noteworthy that three of the successful CPR attempts included the intravenous bolus administration of iloprost, a prostacyclin analogue.

Given the lower incidence of VT/VF in patients experiencing cardiac arrest in the setting of PAH compared to patients with advanced left heart disease, the clinical role of implantable cardioverter-defibrillators in PAH patients remains unclear. Furthermore, the relative paucity of patients with such end-stage arrhythmias in the field of PAH makes systematic research difficult to track.

At present, no prospective clinical trial has been conducted to establish the true incidence of SCD in different subgroups of PAH. Prophylactic

antiarrhythmic therapy is not indicated for primary prevention of SCD in patients with PAH [74]. In the absence of clinical trials showing the benefit of prophylactic antiarrhythmic therapy in these patients, a "tailored therapy" based on clinical judgment may be considered in the management of asymptomatic arrhythmias such as non-sustained VT, taking into account the pros and cons of antiarrhythmic agents (antiarrhythmic benefit vs potential pro-arrhythmic risk and side effects). Otherwise, implantable cardioverter-defibrillators should be offered as a treatment option to PAH patients who manifest either syncope or cardiac arrest in the setting of documented VT/VF.

The role of pacing in PAH patients for relative bradycardia is not well established, highlighting the intrinsic difficulty in clinical management of PAH patients during cardiac arrest.

At present, there are not enough data supporting the role of cardiac resynchronization therapy in this setting. From a pathophysiological viewpoint, it is known that RV pressure overload may induce electrophysiological remodeling, with conduction slowing and APD prolongation, contributing to the loss of left and right ventricular synchrony. Moreover, delayed left ventricle-to-right ventricle peak shortening results in decreased cardiac output in patients with CTEPH and PAH.

Right heart failure in PAH is associated with mechanical ventricular dyssynchrony, which leads to impaired RV function and, by adverse diastolic interaction, to impaired LV function as well. However, therapies aiming to restore synchrony by pacing are currently not available and the role of cardiac resynchronization therapy in these patients remains undefined.

In an experimental model of PAH and right heart failure induced in rats by injection of monocrotaline, Handoko et al. [75] found that preexcitation of the RV free wall obtained by RV pacing improved RV function and reduced adverse LV diastolic interaction.

Hardziyenka et al. [76] conducted epicardial mapping during pulmonary endarterectomy placing a multielectrode grid on the epicardium of the RV free wall and LV lateral wall in 26 patients with CTEPH and compared these findings with clinical, hemodynamic, and echocardiographic variables. They found that the onset of diastolic relaxation of RV free wall with respect to LV lateral wall (diastolic interventricular delay) was delayed by 38 ± 31 ms in patients with CTEPH vs -12 ± 13 ms in control subjects ($p < 0.001$), because in patients with CTEPH the right ventricle completed electrical activation later than the left ventricle (65 ± 20 vs 44 ± 7 ms, $p < 0.001$) and epicardial APD duration, as assessed by activation-recovery interval measurement, was longer in RV free wall than in LV lateral wall (253 ± 29 vs 240 ± 22 ms, $p < 0.001$). They concluded that additive effects of electrophysiological changes in the right ventricle, in particular conduction slowing and APD prolongation as assessed by epicardial activation-recovery interval, may contribute to diastolic interventricular delay in patients with CTEPH.

More recently, the same group [77] evaluated 14 CTEPH patients with right heart failure and significant ventricular dyssynchrony (≥ 60 ms right-to-left ventricle delay in the onset of diastolic relaxation), showing that resynchronization therapy acutely reduced ventricular dyssynchrony and enhanced RV contractility, LV diastolic filling, and stroke volume. These findings provide a strong rationale for further investigations on cardiac resynchronization therapy and RV pacing as a novel treatment for right heart failure secondary to PAH.

Conclusion

Electro-anatomical remodeling of the right ventricle and right atrium in response to longstanding pressure and volume overload, due to altered autonomics, repolarization abnormalities, and ischemia, may be the underlying substrate predisposing to enhanced arrhythmogenicity in patients with right heart failure and PAH.

Supraventricular arrhythmias, namely AFl and AF, are common findings in patients with PAH, and are often associated with worsening heart failure and a decline in patient clinical status. Given the significant potential side effects of antiarrhythmic drugs, percutaneous

catheter ablation represents a safe and reliable alternative approach in this patient population. VT is less common, and relative bradycardia is a threatening sign, with bradyarrhythmias frequently observed in the setting of cardiopulmonary arrest. The role of pacing in PAH patients for relative bradycardia is not well established, highlighting the intrinsic difficulty in clinical management of PAH patients during cardiac arrest. Finally, the exact role of cardiac resynchronization therapy in these patients remains to be elucidated.

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Cardiac and Lung Transplantation

18

Robert P. Frantz

Abstract

Pulmonary hypertension and right heart dysfunction commonly accompanies advanced left sided cardiac failure, and has important implications for prognosis and management. A consistent, stepwise approach to the interpretation and modulation of hemodynamics is necessary in order to optimize decision making and outcome in patients being considered for cardiac transplantation. For patients with pulmonary arterial hypertension who are being considered for lung or heart-lung transplantation, multiple critical factors relating to timing of transplantation, optimal perioperative management, and the particular lung allocation scheme in a given country, must be carefully considered in order to optimize outcome for these patients.

Abbreviations

ARDS	Acute respiratory distress syndrome
ASD	Atrial septal defect
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
DLCO	Diffusion capacity for carbon monoxide
dPpa	Diastolic pulmonary artery pressure
ECMO	Extracorporeal membrane oxygenation
IPF	Idiopathic pulmonary fibrosis
ISHLT	International Society for Heart and Lung Transplantation
LAS	Lung Allocation Score
LV	Left ventricle
mPpa	Mean pulmonary artery pressure
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
Ppw	Pulmonary capillary wedge pressure
PVR	Pulmonary vascular resistance
RV	Right ventricle
RVAD	Right ventricular assist device
SRTR	Scientific Registry of Transplant Recipients
TPG	Transpulmonary gradient
UNOS	United National Organ System
VSD	Ventricular septal defect

Introduction

The right heart is a consistent source of consternation in patients being considered for, and undergoing, cardiac or lung transplantation.

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Donor right ventricular failure is a feared complication in cardiac transplantation. Decisions regarding timing of lung transplantation in pulmonary hypertension, and whether to perform lung or combined heart-lung transplant, often revolve around considerations of right heart failure and whether it can be successfully managed. Cardiac failure in patients with pulmonary hypertension undergoing lung transplantation can contribute to lung allograft failure, multiorgan failure, and perioperative death. This chapter will discuss these varied dilemmas that hinge on a common theme: right ventricular (RV) failure.

Donor Right Ventricular Failure in Cardiac Transplantation

The presence of pulmonary hypertension in patients with left ventricular (LV) failure is associated with a worse prognosis [1]. A study of patients with LV systolic failure who had ambulatory right ventricular pressure monitors implanted demonstrated that those patients who had subsequent clinical events had higher pulmonary artery systolic pressures, estimated pulmonary artery diastolic pressures, and right ventricular end-diastolic pressures [2]. Accordingly it is common that patients being considered for cardiac transplantation have significant pulmonary hypertension, and often substantial right ventricular failure. In the process of evaluating the prospective cardiac transplant candidate, it is incumbent upon the transplant team to make a determination regarding the risk of donor right ventricular failure following transplantation. The risk of RV failure following cardiac transplantation has multiple components that are summarized in Table 18.1. These include factors related to contractile state of the freshly transplanted heart, donor/recipient size discrepancies, and recipient preload and afterload properties, which are highly dynamic in the immediate postoperative period. We will focus on the aspects of the prediction of risk of RV failure in the cardiac transplant candidate.

Table 18.1 Factors influencing risk of donor RV failure following cardiac transplantation

Afterload	Persistence of elevated pulmonary vascular resistance and impaired pulmonary artery compliance
	Pulmonary vasculopathy
	Hypoxemia
	Acidosis
	Positive pressure ventilation
	Possible elevation of LV filling pressures
	Volume expansion
	Myocardial stunning
	Donor heart diastolic dysfunction (e.g., left ventricular hypertrophy)
Preload	Insufficient preload
	Bleeding for which inadequate volume is provided
	Excessive preload
	Intraoperative transfusion requirements (redo surgery, VAD removal, coagulopathy)
	Recipient vasoplegia for which excess volume expansion may be administered (preferred approach is vasoconstrictor administration)
Contractile dysfunction	Ischemic time
	Adequacy of donor heart preservation
	RV contusion
	Myocardial stunning
	Catecholamine surge from donor brain death
	Inotropic requirements of the donor
	Donor-recipient size mismatch

Prediction of Risk of RV Failure in a Cardiac Transplant Candidate

This process essentially involves a mind game: "If this patient went to the operating room today for a heart transplant, what would the pulmonary hemodynamics look like immediately following the operation?" This question can be addressed via a process that may involve several steps, contingent upon initial observations. Firstly, the initial hemodynamics at the time of transplant referral are assessed. Secondly, an acute effort to modulate the

hemodynamics may be made, essentially in an effort to mimic the immediate post-transplant state. Thirdly, subacute manipulation of hemodynamics while maintaining a pulmonary artery catheter to guide interventions can be performed. This may include use of diuretic, inotropes, vasodilators, and if necessary support devices such as an intra-aortic balloon pump. All of these are in an effort to optimize hemodynamics in order to predict the post-transplant state, and also potentially serving to maintain the patient in stable condition while awaiting transplant. Fourthly, longer term mechanical circulatory support devices may be implanted as a "bridge to decision". We will discuss these elements in sequential fashion.

Interpretation of Initial Hemodynamics

Hemodynamics must be performed and interpreted by physicians who are expert in this regard. Relatively common errors include failure to visually inspect the tracings to avoid confounders such as respiratory variability, and failure to achieve a true representation of the pulmonary capillary wedge pressure (Ppw). Such errors can cause major inaccuracy of the pressure measurements, leading to serious misinterpretation. Historically, the pulmonary artery pressure, the transpulmonary gradient (TPG), defined as the mean pulmonary artery pressure (mPpa) -Ppw, and the pulmonary vascular resistance (PVR), defined as (PAm – Ppw)/Cardiac output, have been the most widely used parameters for consideration of the risk for RV failure with transplantation [3]. In the 2012 ISHLT registry, preoperative pulmonary artery pressure and serum bilirubin were among the independent predictors of 1-year post-transplant mortality. A mean pulmonary artery pressure of <27 mmHg was associated with somewhat superior outcome (Fig. 18.1a). The mean pulmonary vascular resistance in patients undergoing cardiac transplantation was 2.1 Wood units, with the 95th percentile equal to 5.4 Wood units. Survival was somewhat superior for patients with PVR of 1 to <3 Wood units compared to those with PVR of 3–5 Wood units, with most of the difference occurring in the early postoperative period (Fig. 18.1b). Pulmonary vascular resistance and bilirubin were among predictors of 5-year survival (Fig. 18.1c), with a completely normal pre-transplant PVR being protective of outcome [4]. A pre-transplant transpulmonary gradient of less than 9 mmHg was associated with somewhat superior 5-year survival contingent upon 1-year survival.

Pulmonary Artery Diastolic Pressure to Pulmonary Capillary Wedge Gradient

The concept of utilizing the diastolic pulmonary artery pressure (dPpa) to Ppw gradient as a marker of pulmonary vasculopathy is not new, but has recently been discussed with renewed enthusiasm [5]. This parameter has advantages over transpulmonary gradient since it may be more informative across a range of cardiac outputs including high output states, although that aspect is less relevant in the context of candidates for cardiac transplantation where cardiac output is generally low. However, even in the setting of a low cardiac output, if the Ppw is elevated, it may disproportionately elevate the mPpa and accordingly transpulmonary gradient. This is because elevation in Ppw will increase pulmonary artery stiffening (reduced compliance) [6]. A dPpa to Ppw gradient >7 mmHg performs better than TPG >12 mmHg in predicting outcome of heart failure in patients with elevated left heart filling pressures [7], consistent with the concept that it may be a superior marker of pulmonary arteriopathy. However, this parameter has not been widely examined as an alternative marker of risk of RV failure following cardiac transplantation, and accordingly additional analyses of transplant databases in this regard is under way.

Acute Modulation of Hemodynamics

Acute Vasoreactivity Testing

Acute vasoreactivity testing with nitroprusside is often effective in dropping the pulmonary artery

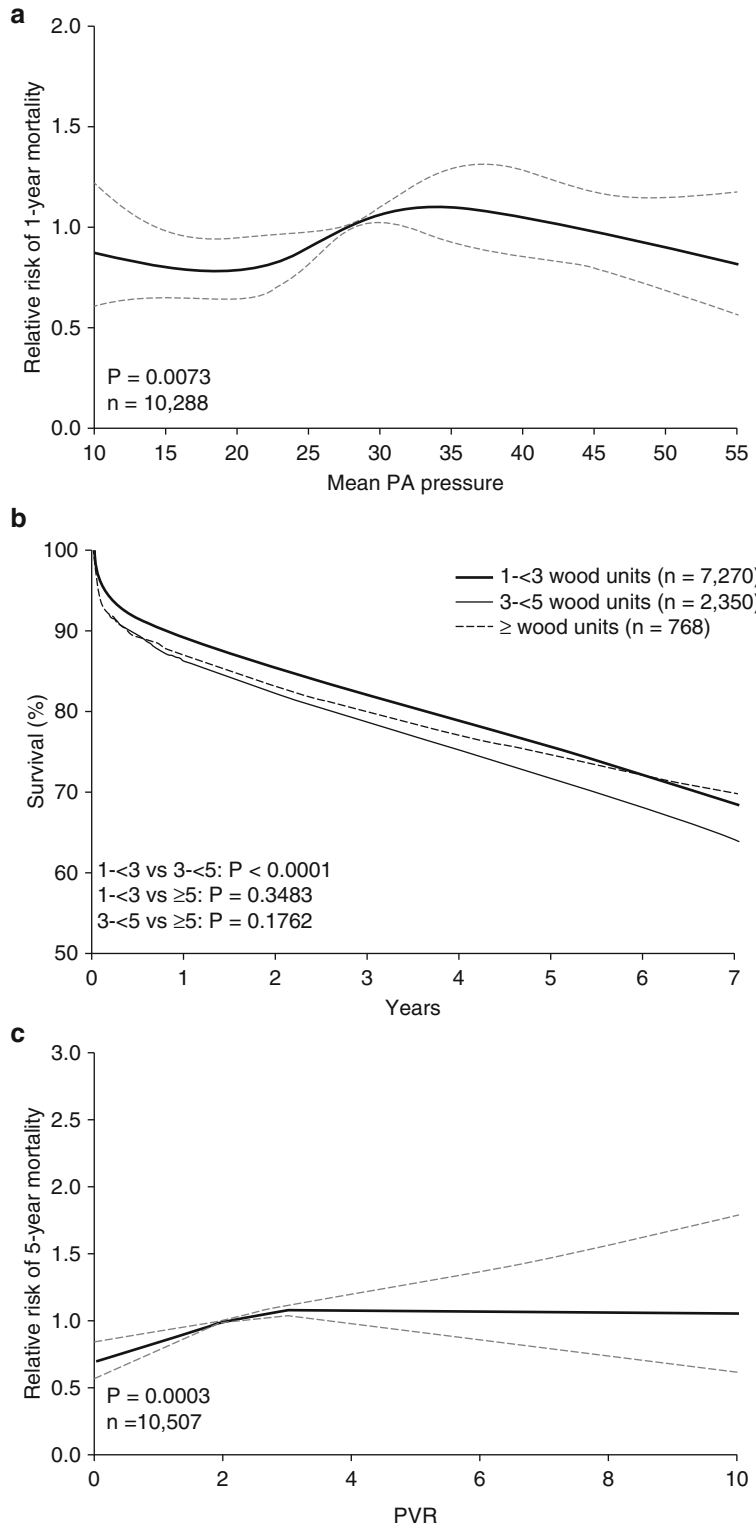

Fig. 18.1 (**a**) Relationship between pre-transplant mean pulmonary artery pressure and risk of 1-year mortality in adult heart transplant recipients in ISHLT registry between 2005 and June 2010. *Dashed lines* represent 95 % confidence intervals. (**b**) Kaplan-Meier survival curves based upon pre-transplant PVR for adult heart transplant recipients in ISHLT registry between 2003 and June 2010. (**c**) Relative risk of mortality by preoperative pulmonary vascular resistance for adult heart transplant recipients in ISHLT registry between 2005 and 2010

pressure and pulmonary capillary wedge, increasing cardiac output, and improving the pulmonary vascular resistance, particularly in patients with LV systolic failure [1]. If the pulmonary vascular resistance can be lowered to less than 2.5 Wood units, this has been associated with a low risk of donor RV failure at the time of transplant.

Subacute Efforts to Improve Pulmonary Hemodynamics

Transferring a patient to the intensive care unit, administering diuretics and inotropes, and if necessary placing an intra-aortic balloon pump, can be useful in improving hemodynamics and assessing reversibility of pulmonary hypertension.

Left Ventricular Assist Devices to Improve Pulmonary Hemodynamics

In the presence of intractable concern about pulmonary hypertension, placement of a left ventricular assist device as a "bridge to decision" about candidacy for heart transplant is often a reasonable approach. Frequently the pulmonary artery pressure improves within 24 h, but sometimes several months may be necessary in order presumably to allow for pulmonary vascular reverse remodeling to occur [8].

Lung and Heart-Lung Transplantation in Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) patients being considered for lung transplantation often have an advanced stage of cardiac dysfunction. This is inevitable given the young age of these patients, the availability of PAH therapy that has substantially improved outcome, concern regarding perioperative risk, and uncertainty regarding whether a patient has truly reached a point where transplantation is likely to result in a better outcome than persisting with medical therapy. Three month mortality in PAH patients undergoing lung transplantation as reported in the International Society for Heart and Lung Transplantation (ISHLT) Registry is 23 %, compared with 9 % for patients with chronic obstructive pulmonary disease (COPD), despite the much younger age of the PAH patients. In the ISHLT Registry, median survival of PAH patients undergoing lung transplant is only 5.0 years, with greater hazard for perioperative death than most other diagnoses. Nonetheless, conditional survival (assuming survival to 1 year) is among the very best, with a half-life of 10.0 years versus 6.8 years for COPD or idiopathic pulmonary fibrosis (IPF) [9]. (Fig. 18.2a, b) This stark contrast encapsulates the need to better understand and manage this perioperative risk. In this section, we will discuss factors that impact transplant waiting time, perioperative decision-making, management and outcome of these compelling patients.

The advanced stage of right ventricular dysfunction in PAH patients undergoing transplantation in the United States is driven in part by a United Network for Organ Sharing (UNOS) Lung Allocation Scoring (LAS) system, implemented in 2005. This scoring system does not yield scores likely to result in donor offers in the absence of profound cardiac failure despite maximal PAH therapy including iv prostanoids. However, PH patients, with factors such as a high oxygen requirement, can see their score driven by this, and indeed, may not have classical PAH in any case. Implementation of the LAS resulted in improved wait list mortality for all diagnostic groups except PAH [10]. In addition, the higher wait list mortality for PAH was despite having lower lung allocation scores than patients in other diagnostic groups, suggesting that the LAS system is not adequately capturing prognostic factors relevant to PAH. The impact of the LAS system on the phenotype of patients being listed under the PH category is well demonstrated in a recent analysis of temporal trends captured within the UNOS Scientific Registry of Transplant Recipients (SRTR) database of PH patients listed and undergoing transplantation in the United States [11]. Since implementation of the LAS system, patients listed for transplantation under the PH category have had more severely abnormal pulmonary function tests, greater oxygen requirements, shorter 6 min walk distances

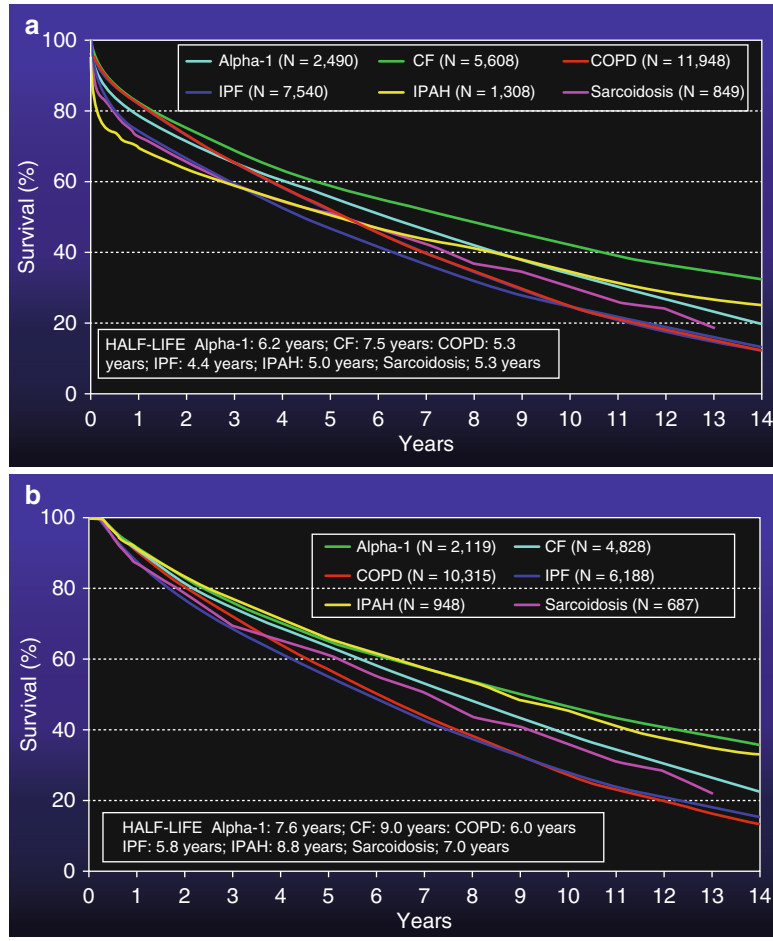

Fig. 18.2 (**a**) Kaplan-Meier survival curves for lung transplant recipients by diagnosis as reported to ISHLT registry between January 1990 and June 2010. Note the disproportionate early mortality in the pulmonary hypertension cohort. (**b**) Kaplan-Meier survival curves for lung transplant recipients contingent on 1-year survival by diagnosis as reported to ISHLT registry between January 1990 and June 2010. Note that the contingent survival for the pulmonary hypertension cohort is among the best of all diagnostic categories

and better preserved cardiac output. This likely largely reflects the parameters that result in a high lung allocation score, and may be skewing the PH category toward patients with more parenchymal lung disease than is generally seen in PAH. While these patients undoubtedly are in need of transplant, those patients with severely deranged hemodynamics are not readily receiving LAS scores that will facilitate transplantation. For PAH patients whose pathophysiology primarily revolves around impaired hemodynamics, and awaiting transplant in the United States, the LAS score will usually be too low to obtain organs, unless the patient receives a waiver from the UNOS Thoracic Organ Allocation Committee. This requires that the right atrial pressure be greater than 15 mmHg or the cardiac index be less than 1.8 L/min/m^2 despite maximal medical therapy, which is usually understood to include parenteral prostanoid therapy. Such parameters create a situation of worrisome risk for death while waiting, may result in increased perioperative risk, and increased hazard of requiring extracorporeal membrane oxygenation (ECMO) support as a shaky bridge to transplant.

Patient and, at times, physician preference to avoid lung transplant as long as possible may also play a role in delay of transplant referral and listing. Such patients are often young, and are hoping to live decades. Given that the long-term survival of lung transplant recipients remains uncertain, it is often tempting to delay transplant until such advanced disease is present that survival to transplant, and recovery thereafter, become more problematic.

Double lung transplant has clearly been associated with superior outcome to single lung transplant, so is definitely preferred. Nonetheless, lung transplantation in patients with advanced (PAH) has historically been associated with

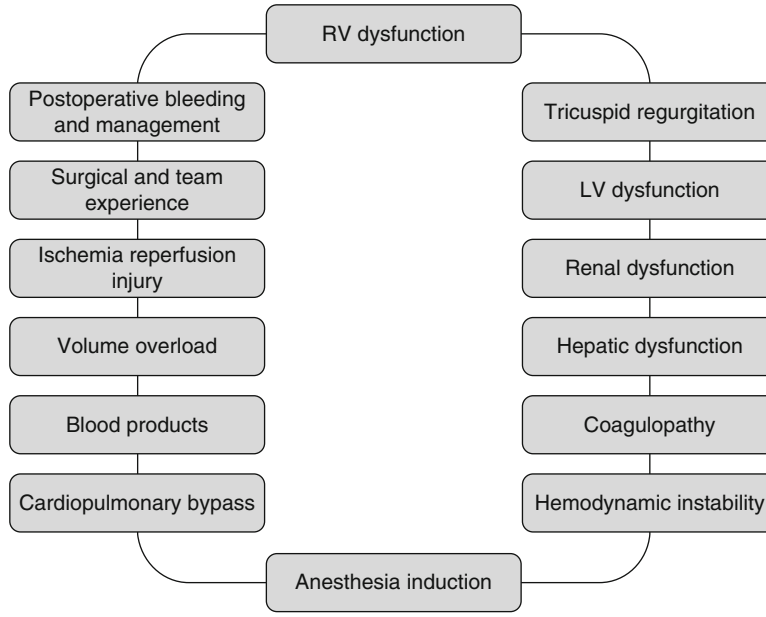

Fig. 18.3 Multiple factors influencing outcome of lung transplantation in pulmonary hypertension

greater perioperative mortality than lung transplantation performed for other indications [9]. This has resulted in debate regarding the relative role of combined heart-lung transplant and double lung transplant. Traditionally heart-lung blocks were often utilized in patients with pulmonary hypertension, and the hearts from such recipients were then used in domino fashion in patients requiring heart transplant who had elevated pulmonary vascular resistance [12, 13]. The hearts being used in domino fashion were hypertrophied and generally had well preserved function, but it appears less common in the current era that pulmonary arterial hypertension patients undergo transplant at a time when their right ventricles are still functioning well, so this option of domino transplant is less relevant.

Registries and case series have generally not shown a mortality difference in outcome between double lung and heart-lung transplant operations for pulmonary hypertension, but differing patient selection (e.g., potentially a decision to perform heart-lung in those patients with the most severe right ventricular failure) may obscure such differences. It is generally accepted that the perioperative course is less fraught with heart-lung transplantation, but proof of superior outcome is lacking, heart-lung organ blocks are quite scarce, and double lung transplantation will surely remain a much more common transplant operation for PAH.

Cardiac and Non-cardiac Pathophysiology of the Advanced PAH Patient

Transplantation for PH patients for whom transplant is actively considered most often fall under two different scenarios:

1. Gradually progressive RV failure despite chronic therapy with vasodilators
2. Abrupt deterioration precipitated by an acute insult in an otherwise previously compensated patient

In the first instance, the patient may have adapted over a prolonged period to quite low cardiac output, and have developed severe right ventricular dilation, often accompanied by moderate to severe tricuspid regurgitation. These patients may finally reach a point where exertional intolerance is severe, manifested by dyspnea, chest tightness, and syncope or near-syncope. The peri-transplant period in such a setting involves a complex interplay of patient, procedural, and provider-specific factors that ultimately determine outcome, as illustrated in Fig. 18.3. Hemodynamics typically include elevation of right atrial pressure and low cardiac index. Systemic saturation may also be low, reflecting impaired gas exchange, and/or opening of a patent foramen ovale as right atrial pressure rises. End-organ function may become compromised due to a combination of inadequate

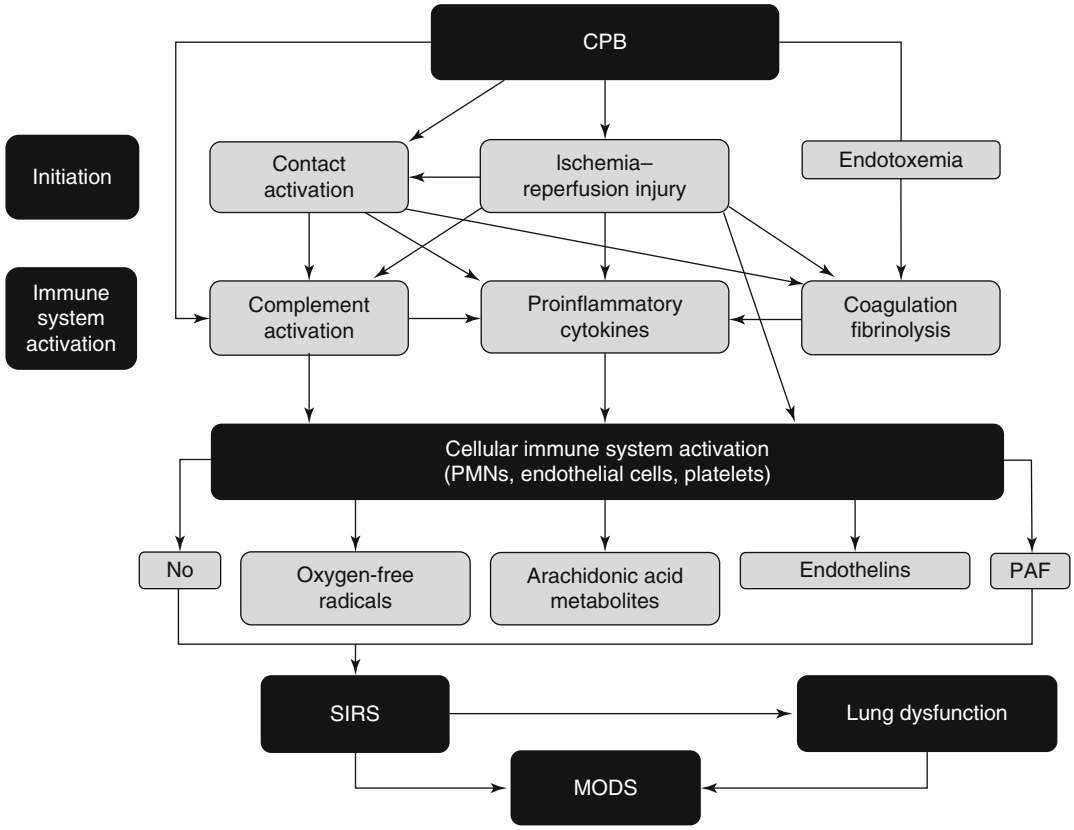

Fig. 18.4 A schematic representation by which cardiopulmonary (*CPB*) may lead to systemic inflammatory response syndrome (*SIRS*), lung dysfunction, and multiple organ dysfunction syndrome (*MODS*). *PMNs* polymorphonuclear cells, *NO* nitric oxide, *PAF* platelet-activating factor (Reprinted from Apostolakis et al. [19]. With permission from John Wiley & Sons, Inc.)

oxygen delivery and impaired perfusion. The impaired perfusion may represent a combination of systemic hypotension, low cardiac output, and elevated venous pressure. Ascites with increased intra-abdominal pressure can further compromise renal perfusion. Hepatic dysfunction with elevated transaminases and bilirubin further compounds the picture. For PH patients on warfarin, labile prothrombin times are common, with risk of hemorrhage either while awaiting transplantation or at the time of transplantation. Efforts to support cardiac output with inotropes can be useful, but also predispose to arrhythmia, or in the case of milrinone, possible exacerbation of hypotension or aggravation of prostanoid-related thrombocytopenia. Induction of anesthesia and the potential for worsening hypoxemia, hypoventilation, acidosis, and hemodynamic effects of positive pressure ventilation can make the induction period hazardous [14, 15]. Rapid requirement for institution of cardiopulmonary bypass may prolong cardiopulmonary bypass duration in the context of complex donor organ logistics.

The very need to institute cardiopulmonary bypass in order to proceed with lung transplant in PH immediately increases the complexity of the procedure compared to lung transplant performed for lung conditions without substantial accompanying pulmonary hypertension [16].

Cardiopulmonary bypass results in release of cytokines that increase potential for vascular permeability in the transplanted lung, leading to allograft injury, hypoxemia, and increased ventilatory requirements [17–19]. The wide-ranging effects of cardiopulmonary bypass are nicely illustrated in Fig. 18.4 [19]. Intraoperative

bleeding risk is exacerbated by pre-existing thrombocytopenia, platelet dysfunction related to prostanoid use, acquired von Willebrands disease related to shear stress in the pulmonary vasculature [20], effects of cardiopulmonary bypass, and coagulopathy related to preoperative warfarin use and hepatopathy. Cessation of anticoagulation at the time of transplant listing should be considered in order to reduce perioperative bleeding risk. In patients with PAH related to prior VSD or ASD who have had prior cardiac surgery, scarring in the chest further complicates operative complexity, duration, and bleeding risk. Volume overload related to administration of blood products and crystalloid in response to hypotension and bleeding, in the context of renal dysfunction reflecting preoperative factors, further exacerbates congestion and dysfunction of the allograft. Adding this scenario to a severely dysfunctional right ventricle makes it easy to understand why perioperative risk is higher in PAH patients undergoing transplant compared to, e.g., a pulmonary fibrosis patient without coagulopathy, hepatic dysfunction, RV failure, renal dysfunction, or need for cardiopulmonary bypass.

Surgical expertise in management of such a patient may also play a role. Lung transplant most commonly does not involve cardiopulmonary bypass, and transplant for PAH remains relatively uncommon. In the context of thoracic transplant surgeons, the need for cardiopulmonary bypass may also be an uncommon part of their practice. Center-specific outcomes vary, and to some extent reflect the number of transplants performed [9]. Anesthesiology awareness of the fragile nature of the PAH patient and need for judicious induction and avoidance of volume overload may also be variable.

Distention of the RV by the volume excess can further compromise LV filling by virtue of RV/LV interaction, impaired RV performance, and persistence of tricuspid regurgitation. In contexts where RV function is better preserved at the time of transplant, which seems increasingly rare, a hyper-contractile right ventricle "suicide RV" may develop, aggravated by perioperative use of inotropes.

The left ventricle also has an important role to play in perioperative hazards [21, 22]. Given the typically very low cardiac output state of the PAH patient at the time of transplant, the LV has been chronically under-filled, becomes small in size, and possesses diastolic filling abnormalities [23]. If the RV is severely dysfunctional in the immediate postoperative phase, septal shift and pericardial constraint may contribute to the difficulty that the LV faces in adapting to an abrupt increase in LV filling when coming off cardiopulmonary bypass. This may result in a rise in left atrial pressure, which will aggravate tendency toward edema of the recently ischemic, cytokine stressed, freshly transplanted lung. Monitoring of the pulmonary capillary wedge pressure or placement of a left atrial pressure monitoring line at the time of lung transplant may be helpful in avoiding excess rise in left atrial pressure following the transplant, by facilitating more aggressive volume management if LA pressure begins to rise. In some cases, continuous veno-venous hemodialysis or ultrafiltration can be useful to facilitate volume management in the face of inadequate urine output despite diuretics. Occasionally, LV systolic failure is observed, and may improve with appropriate supportive measures. These complex, interacting processes are summarized in Table 18.2.

Timing of Lung Transplantation in PAH

Ideally, lung transplantation should occur electively prior to development of end-stage RV failure and ensuing end-organ dysfunction and while the patient still has reasonable peripheral muscle preservation. Unfortunately there are multiple barriers to this timing. In the United States, the most severe barrier is the current LAS system. Further revision of this system is under active consideration.

Factors Relevant to a Previously Compensated Patient Who Suffers Abrupt Deterioration

Compensated PAH patients can rapidly decompensate in the face of a variety of stressors.

Table 18.2 Factors influencing outcome of lung transplantation in pulmonary hypertension

Right heart issues	Contractile dysfunction
	Tricuspid regurgitation
	Pulmonic regurgitation
	Distention related to volume overload
Left heart issues	Chronically under-filled
	Diastolic dysfunction
	RV/LV interaction
	Pericardial constraint
	Volume overload
Renal issues	Pre-existing renal dysfunction
	Elevated venous pressure
	Systemic hypotension reducing perfusion pressure
	Compromised cardiac output
	Ascites with renal vein compression
	Impact of vasoconstrictors
Coagulation issues	Preoperative warfarin
	Preoperative thrombocytopenia
	Platelet dysfunction (prostanoids, aspirin, cardiopulmonary bypass)
	Hepatic dysfunction
Anesthesia and intraoperative issues	Risk of hemodynamic collapse with induction
	Hemodynamic effects of positive pressure ventilation
	Low systemic pressure and resistance when coming off bypass
	Potential for metabolic acidosis related to hemodynamic compromise after bypass weaning
	Atrial arrhythmias
	Surgical and team experience
Lung allograft issues	Cytokine effects secondary to cardiopulmonary bypass
	Vascular permeability related to above and ischemia
	Impact of elevated LV filling pressures with sudden filling of chronically underfilled LV
	Effects of blood product administration (volume, transfusion related acute lung injury TRALI)

These include sepsis related to indwelling lines or other factors, pneumonia, pulmonary hemorrhage, GI hemorrhage related to anticoagulation, intra-abdominal processes, and trauma. Detailed discussion of the management of these varied scenarios is beyond the scope of this document. Advanced RV failure despite maximal vasodilator therapy can sometimes be mitigated by use of inotropes. Dopamine, milrinone, or norepinephrine may be of some benefit but there is risk of tachyarrhythmia, which is often poorly tolerated, and milrinone can cause hypotension or aggravate thrombocytopenia. Phenylephrine can help support systemic pressure. Atrial septostomy is sometimes utilized as a way to improve systemic blood flow, thereby delivering more oxygen to peripheral tissue, at the expense of systemic hypoxemia, and can be used as a bridge to lung transplantation [24–26]. This has the benefit of improving LV filling which may facilitate LV adaptation at the time of transplantation. However, atrial septostomy is best performed prior to the development of end-stage RV failure, since marked right atrial pressure elevation and markedly reduced cardiac output are risk factors for mortality with the septostomy procedure [27]. Patients with advanced RV failure can in principle be managed with mechanical circulatory support either as a bridge to recovery or a bridge to transplantation [28]. The wisdom of such an approach depends on the probability of recovery for non-transplant candidates, and on the probability that organs will be identified within an acceptable time frame in order to avoid the support approach being a stressful bridge to nowhere. Options for circulatory support theoretically include right ventricular assist devices (RVADs) and ECMO. RVADs have generally not been particularly successful, since the sudden high flow into the pulmonary hypertensive pulmonary bed poses risk of intrapulmonary hemorrhage or edema. Development of RVADs with more readily titratable flow characteristics would be a useful advance. Case reports of successful biventricular bridging in patients with biventricular failure with devices such as the HeartWare™ are available [29]. Advances in ECMO technology have created both new opportunity and new dilemmas for critically ill PAH patients. Veno-venous ECMO with right internal jugular vein cannulation can mitigate issues of hypoxemia in the event of

pneumonia, intrapulmonary hemorrhage, acute respiratory distress syndrome (ARDS) or other forms of acute lung injury. In the event of hemodynamic instability, which is a more common scenario in PAH, Veno-arterial ECMO can be employed, utilizing a variety of support systems and cannulation sites [30]. Avoidance of femoral cannulation is important in situations where support is expected to be prolonged, since the impact of immobility, and risk of line-related infection, can rapidly lead to an unsustainable scenario. Right internal jugular vein cannulation and right subclavian or axillary arterial cannulation can be successful, generally employing a cut-down to the artery with use of a chimney graft. This allows patient mobilization, and has been successfully utilized as a bridge to transplant or recovery in a variety of situations. However, there is significant risk of injury to the brachial plexus, posing risk of longstanding upper extremity problems.

Central cannulation with the arterial return coming back to the aorta, and use of an oxygenator and a centrifugal pump, has allowed mobilization and successful bridge to transplant [31]. This leaves the left ventricle potentially underfilled, which may compromise its adjustment at the time of transplant. Leaving the patient on ECMO for a few days post lung transplant, with gradual reduction in ECMO flows, can facilitate LV adaptation to the normalization of cardiac output. An alternative is the Novalung™ system, connecting from the pulmonary artery to the left atrium, and utilizing the patient's own RV as the pump, which has been remarkably successful [32–35]. The unloaded RV will improve its function and geometry, a potential advantage at the time of transplant. This system also has the advantage of avoiding need for a centrifugal pump with its attendant issues, and allows the LV to become accommodated to at least a somewhat higher cardiac output, potentially facilitating the perioperative hemodynamic course. A Quadrox™ system can also be utilized in such a fashion; the Quadrox iD™ system can be utilized for neonatal support [36].

Use of support systems as a bridge to lung transplant is dependent on waiting times that are not excessively long, and careful assessment of probability of survival if lung transplant is undertaken [37]. With the advent of support systems that allow patient mobilization, support for months is possible, but is an enormous commitment of resources, fraught with risks of sepsis, bleeding, coagulation issues such as thrombocytopenia related to the support system or related to prolonged use of heparin, and an emotional roller coaster for all involved.

Conclusions

Pulmonary hypertension is extremely common in patients with advanced cardiac failure, and has substantial prognostic and management implications. Pulmonary hypertension in patients being considered for cardiac transplantation requires careful evaluation with regard to reversibility. A consistent, step-wise approach will optimize ability to assess the risk of postoperative RV failure, and to take steps to mitigate that risk.

Lung transplantation in pulmonary hypertension patients is more complex than for most other lung transplant candidates, related to the wide range of issues described in this manuscript. A successful transplant requires a well-functioning team with expertise in identifying proper timing of transplant, pro-actively preparing the patient for transplant, bridging to transplant as needed with inotropes, atrial septostomy, or ECMO, optimal anesthesia support, skilled surgical teams fully comfortable with cardiopulmonary bypass and complex hemodynamic management, and judicious postoperative ventilatory, volume, renal, coagulation, and hemodynamic management. In skilled hands, pulmonary hypertension patients can do very well with transplant, and once clear of the perioperative period, have some of the best intermediate and long-term outcomes of any of the indications for lung transplantation.

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Atrial Septostomy

19

Adam Torbicki and Julio Sandoval

Abstract

In some forms of pulmonary hypertension progression of pulmonary vascular disease may be too fast to be matched by the right ventricle (RV). Indeed, RV failure is the leading cause of high mortality in patients with pulmonary aterial hypertension (PAH), except for those with Eisenmenger syndrome, who can maintain systemic cardiac output through central right to left shunt. Consequently, atrial septostomy (AS) has been proposed to improve left heart filling, systemic flow and outcome in non-Eisenmenger patients with severe pulmonary hypertension. At present, published series provide data on about 350 precedures performed in over 300 patients. The published evidence indicate 6.8 % peri-procedural and 10.8 % cumulative mortality at 1 month, while another 11.5 % patients who were submitted to atrial septostomy could be transplanted. Hemodynamic effects of AS for 104 procedures for which complete hemodynamic data sets were available showed immediate improvement of left heart filling, and systemic flow at a cost of fall of systemic oxygen saturation, most marked in patients with right atrial pressure (RAP) >20 mmHg at baseline. Despite clinically relevant 37 % increase in systemic cardiac index the peri-procedural mortality in this subgroup was very high, with 11 death after 26 procedures (42 %) contrasting with two periprocedural death in patients with RAP below 10 mmHg (2.5 %). No randomized trial have ever been performed to assess the long term effects of AS. Balloon dilatations not supported by stents or fenestrated devices do not protect from elastic recoil and small orifices often close. Therefore septostomies should be made earlier – before severe RV failure with high RAP develops – but larger. New

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technical developments, including remote controlled devices with modifiable shunt fractions and preventing from re-occlusion of the septostomy orifice should improve safety and long term effects of atrial septostomy.

Introduction

Lowering pulmonary input impedance is the obvious therapeutic target in right ventricular failure (RVF), if RVF has been caused by increased afterload. However, potential clinical gain can be also expected from attempts to unload the right heart by redistribution of blood to underfilled left heart chambers or directly to the aorta. Atrial septostomy and the pulmonary-aortic shunt (Potts anastomosis) represent clinically recognised methods serving this purpose at a cost of systemic desaturation. A more instrumentalized but physiologically appealing way of achieving similar hemodynamic goal, but with enriching the shunted blood with oxygen is represented by venous-arterial extracorporeal membrane oxygenators. The current chapter will present the physiological background and clinical value of atrial septostomy in the context of current management algorithms for patients with pulmonary hypertension.

Rationale

Right ventricular systolic failure is the leading cause of death in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH): two pulmonary vascular diseases characterized by progressive increase in RV afterload. There is convincing evidence that absolute RV elastance, reflecting its contractility, is increasing in PAH. However, the progression of pulmonary vascular disease (PVD) usually is too fast to be matched by appropriate functional remodeling of the RV. Moreover, although there is an initially beneficial stretch of the RV wall resulting in compensatory increase of RV performance – known as the Frank-Starling effect – this initiates a chain of unfavorable morphological and functional consequences starting a vicious circle, leading to uncoupling of the RV and pulmonary arterial bed. This, in turn, leads to progressive functional deterioration and ultimately to death. Indeed, the natural history of patients with PAH or CTEPH and chronic RV failure evidenced by a cardiac index (CI) below 2.0 L/min/m^2, and/or mean right atrial pressure (RAP) above 20 mmHg is grim [1]. Moreover, any additional "second hit" leading to exacerbation of chronic RV dysfunction represents a life-threatennig situation with in-hospital mortality 25–60 % despite advanced ICU management. Taken together, RV failure is responsible for about 3/4th of death within the 10 % annual mortality among PAH and non-operable CTEPH patients.

All this clearly suggests urgent need for effective and safe prevention of end-stage RV failure, if necessary, using interventional methods suitable for clinical application.

Theoretical Background

Atrial septostomy has been proposed as a treatment of RV failure secondary to pulmonary hypertension based on the reasoning derived from comparison of the outcome of two subgroups of PAH patients: with idiopathic PAH and those in whom PAH was associated with congenital shunts ultimately resulting in Eisenmenger syndrome.

Despite similar elevation of pulmonary artery pressure and resistance the patients with Eisenmenger syndrome were found to have much better life expectancy than those with idiopathic PAH [2, 3] (Fig. 19.1). Not only was overall mortality lower, but in 30–55 % it was due to sudden death and not end-stage RV failure [4–6].

Indeed, in most patients with Eisenmenger syndrome RV function and systemic perfusion are preserved, as evidenced by near-normal RA pressures and systemic cardiac output found at right heart catheterization (Fig. 19.2). If the mechanisms of such adaptation of the cardiovascular

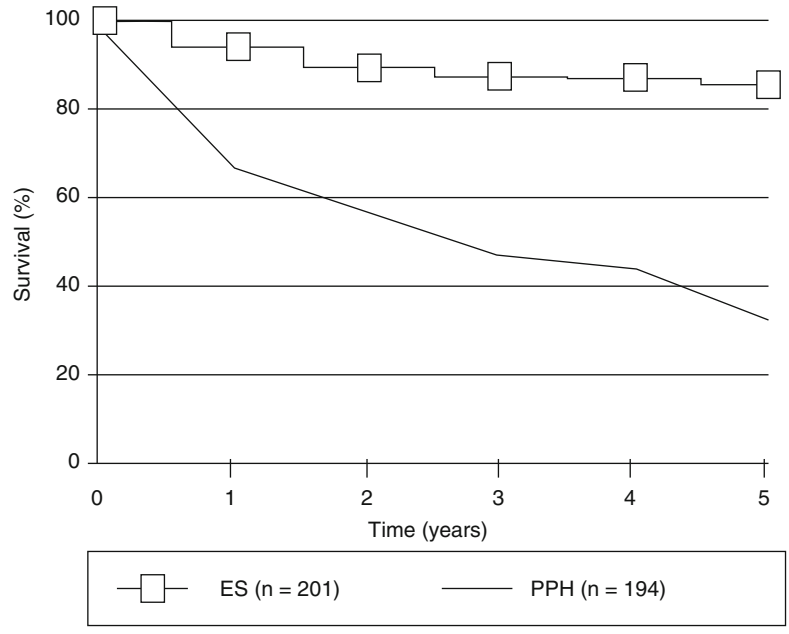

Fig. 19.1 Comparison of survival of patients with idiopathic pulmonary arterial hypertension and Eisenmenger Syndrome. *ES* patients with Eisenmenger Syndrome, *PPH* patients with idiopathic pulmonary arterial hypertension (Based on data from Ref. [2])

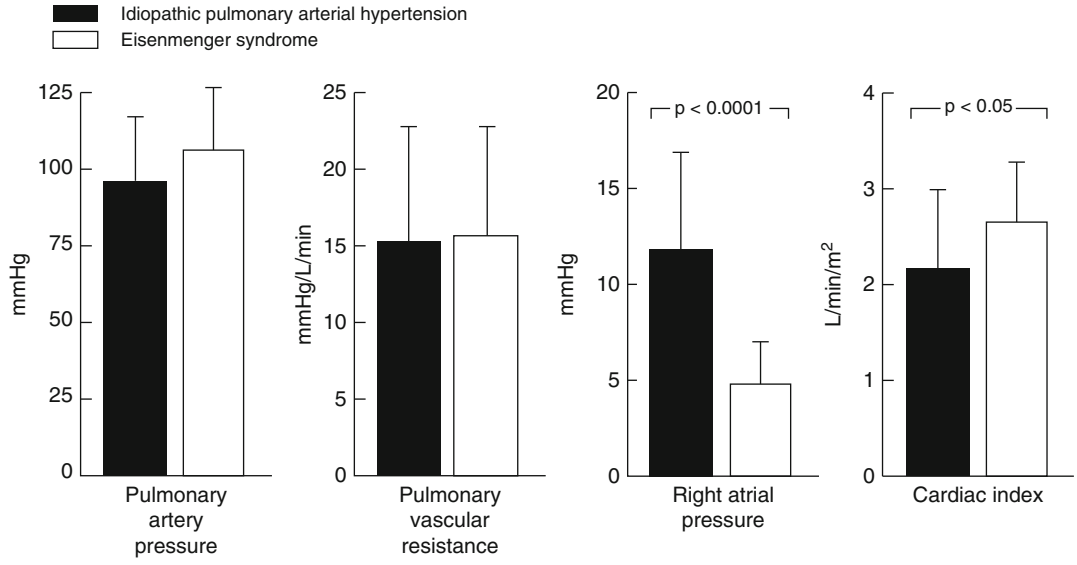

Fig. 19.2 Comparison of the hemodynamics of adults with severe idiopathic pulmonary arterial hypertension and Eisenmenger syndrome (Based on data from Ref. [2])

system to extremely elevated RV afterload could be understood this might offer the chance of using them as new therapeutic approaches for patients with other forms of PAH.

Out of several adaptive mechanism which have been suggested, including:

- preservation of a "fetal" phenotype of RV myocytes
- appropriate RV hypertrophy
- preserved, more dense RV coronary network
- reversed shunt feeding the systemic circuit through a persisting defect

the latter could potentially be reproduced in non-Eisenmenger patients suffering from PAH. Opening a shunt between the atria has been practiced since the times of Rashkind, though for other indications.

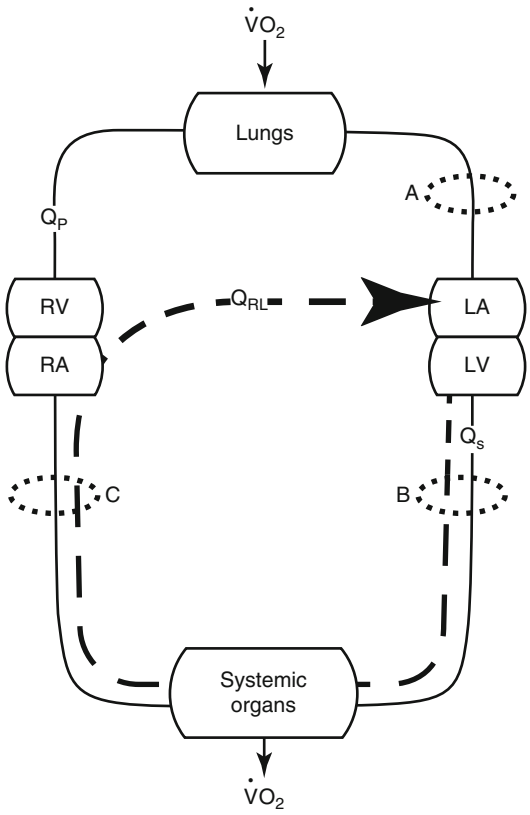

Fig. 19.3 Schematic representation of circulation with a right to left shunt through atrial septostomy. *LA* left atrium, *RA* right atrium, *RV* right ventricle, *Qs* systemic blood flow, *Qp* pulmonary blood flow, *QRL* right-to-left shunt through atrial septostomy, VO_2 total oxygen consumption by the body. In contrast to carbon dioxide removal and oxygen delivery that are determined by the effective Qp (*location A*) the delivery of nutrients (*location B*) and the removal of waste products (*location C*) are determined by systemic flow. Part of the venous return is redirected through atrial septostomy directly to the LA, thereby bypassing the pulmonary circulation (Modified from Koeken et al. [8]. With permission from The American Physiological Society)

Shunting blood from the right to left heart at the level of interatrial septum (Fig. 19.3) could potentially result in beneficial consequences such as

- increase in systemic output by improving LV filling
- decompression of the RV alleviating its failure

potentially leading to further improvements, such as e.g. better right ventricular coronary perfusion, less tendency for RV remodeling and functional tricuspid regurgitation, decreased kidney congestion and their improved perfusion.

Table 19.1 Factors predicting life expectancy in primary pulmonary hypertension, including the presence of patent foramen ovale (PFO)

	Survival		p
	<5 years (n	>5 years (n =	
Family	1	1	NS
CTD	3	0	NS
Pregnancy	0	5	<0.02
PFO	0	4	<0.05
RHF any	18	10	<0.05

According to Rozkovec et al. [7]. (Reprinted from Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. Br Heart J 1986;55:449–58. With permission from BMJ Publishing Ltd)
CTD connective tissue disease, *Pregnancy* disease diagnosed during or after pregnancy, *RHF* right heart failure

A price to pay would be systemic oxygen desaturation, particularly on exercise, with an unclear net result regarding tissue oxygen delivery and utilization.

Even more importantly, it is not clear whether and to what extent atrial septostomy alone would improve clinical outcome of patients with PAH if not accompanied by other adaptive mechanisms operating in patients born with congenital heart disease and steadily developing Eisenmenger syndrome. The evidence, that such an isolated shunt at the atrial level could be beneficial even if functionally opened only after development of PAH in the adult life is based on a higher prevalence of patent foramen ovale in long-term survivors of PAH as reported by Rozkovec et al. [7] (Table 19.1).

Computational Models

Mathematical modeling of the effects of complex hemodynamic interventions, such as atrial septostomy in a setting of chronic PH is tempting, particularly with increasing availability of advanced computational hardware and software. In a recent trial of Koeken et al., a Dutch group involving biomedical engineers assessed consequences of atrial septostomy with a multiscale

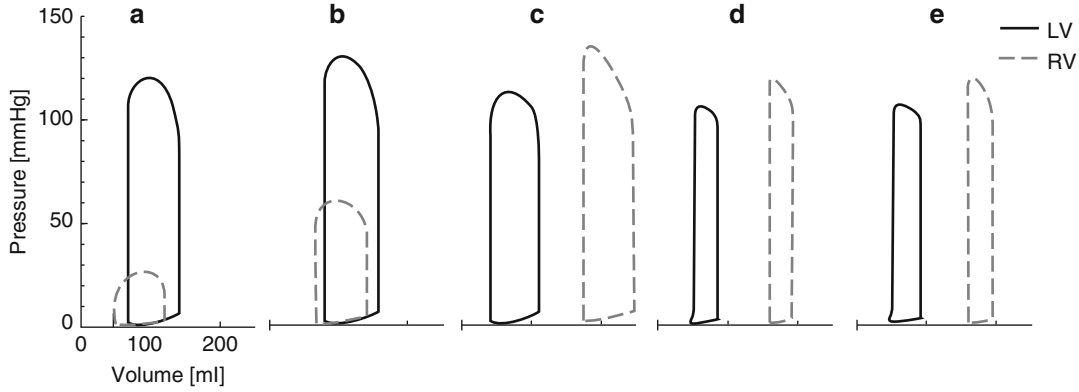

Fig. 19.4 Pressure-volume loops of the right (*dashed lines*) and left (*solid lines*) ventricle. *A* normal, *B* compensated pulmonary hypertension, *C* decompensated pulmonary hypertension, *D* severely decompensated pulmonary hypertension with decreased cardiac output, *E* same as D but after atrial septostomy of 14 mm in diameter. Note increased stroke volume of the left ventricle compared to D (Modified from Koeken et al. [8]. With permission from The American Physiological Society)

computational model of cardiovascular system [8]. They suggested that atrial septostomy could improve symptoms of right heart failure in patients with severe PH if net right-to-left shunt flow occurs during exercise. While their model confirmed that septostomy improves left ventricular filling and stroke volume (Fig. 19.4) and stabilizes systemic blood pressure, the expected beneficial effect on peripheral tissue oxygen delivery could not be found. The increase in systemic oxygen delivery after atrial septostomy has been examined by computer modelling, suggesting that the clinically observed beneficial effects of atrial septostomy may be more related to improved flow rather than oxygen delivery to perfused tissues [9].

Experimental Models

Experimental evidence suggesting that atrial septostomy may be beneficial in chronic PH dates back to the work of Austen et al. [10] (Fig. 19.5). After inducing chronic RV pressure overload by pulmonary artery banding ten dogs were submitted to a second surgical intervention. Five had an ASD and the remaining five had a sham operation. Dogs with ASD were able to perform moderate and severe exercise on a treadmill, whereas dogs who had the sham operation couldn't tolerate it.

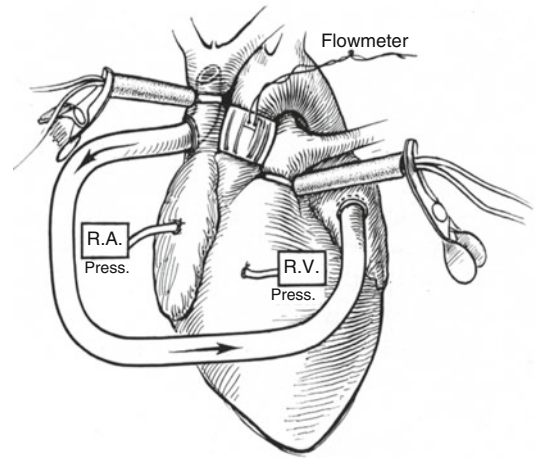

Fig. 19.5 Animal model used for assessing the acute effects of right to left atrial shunting, as described by Austen et al. in 1964. *RA* right atrium, *LV* left ventricle. *Arrow* indicates pulmonary artery banding used to chronically increase right ventricular afterload

Other authors have also shown beneficial effects of similar interventions in canine models [11, 12].

The effect of an inter-atrial shunt on right atrial (RA) and right ventricular mechanics was re-assessed by Zierer et al. [11]. After banding the pulmonary artery they used an 8 mm cannula to connect both atria. The model permitted controlled closing and opening of the shunt to assess

potential hemodynamic effects of septostomy. Also, by changing the venous return two levels of shunting could be compared – 15 and 30 % of the total cardiac output, respectively. Comprehensive analysis based on assessment of ventricular and atrial pressure/volume loops revealed that after "septostomy" RV and RA contractility did not change. Some changes were found in compliance of the right atrium, which increased especially at lower shunt flows. There was also a significant shift from the reservoir to the conduit function ratio in this chamber. While the experiment confirmed that cardiac output and systemic oxygen delivery increased after septostomy, this effect was present only with right to left shunting corresponding to 15 % of cardiac output. At higher shunt flow beneficial effects on systemic oxygen delivery were lost.

Similar message was conveyed by Weimar T et al. [12], who found a right-to-left shunt flow of 11 % of baseline cadiac output at the atrial level to be an optimal therapeutic target in severe RV pressure overload, The authors suggested, that atrial septostomy was not of significant hemodynamic benefit in moderate RV pressure overload. However, in contrast to previously discussed models, in the latter trial banding was done acutely, and thus the results and conclusions may not be fully representative for chronic pulmonary hypertension.

Clinical Evidence

The evidence regarding hemodynamic effects of atrial septostomy in patients with right ventricular dysfunction caused by increased RV afterload is limited, when compared to data regarding pharmacological treatment of pulmonary arterial hypertension. This limitation is a consequence of relatively low number of patients submitted so far to AS as well as to the insufficient quality of data due to the design of trials. At best the information comes from short case series. At present published series provide data on about 350 procedures performed in over 300 patients [13–32]. No randomized trial have ever been performed to assess the long term effects of AS. In some reports the outcome was compared to that of matched historical controls followed earlier by the same clinical team. The dynamic changes in medical care and availability of pharmacological therapy of PAH over time make such comparisons questionable.

Nevertheless, the published evidence, as well as our personal observations permit analysis of hemodynamic effects, clinical benefits and safety of AS. To allow generally applicable conclusions we decided to exclude single case reports from such analysis, which are more likely to be affected by favourable publication bias.

Characteristics of Patients Submitted to Atrial Septostomy

Out of 304 patients in whom AS was performed at least once, 76 were pediatric patients, 201 (71.6 %) were female, 277 (91 %) suffered from PAH. All the patients were either in 3rd or 4th WHO functional class with almost 50 % reporting syncope [13–32].

In vast majority of cases balloon atrial septostomy was performed (see below for explanation). But, out of 79 procedures in which blade balloon septostomy was used as either the main or contributing method, 32 were performed before year 2000 and those performed afterwards – almost entirely (41/42) in young children.

Safety, Clinical and Hemodynamic Effects of Atrial Septostomy

There were 24 death within the first 24 h after the procedure, resulting in 6.8 % peri-procedural mortality. Cumulative mortality at 1 month was 10.8 %. Interestingly, 11.5 % (35/304) patients could be transplanted.

Hemodynamic effects of AS could be analyzed for 104 procedures for which complete hemodynamic data sets were available. In order to provide some practical guidance regarding indication for AS in various stages of RV dysfunction we report the results according to the level of mean right atrial pressure before the procedure (Table 19.2).

Table 19.2 Hemodynamic effects of atrial septostomy according to the level of right atrial pressure prior to the procedure [13–32]

Variable	Baseline RAP < 10 mmHg (N = 27)			Baseline RAP 10–20 mmHg (N = 51)			Baseline RAP > 20 mmHg (N = 26)		
	Before	After	p <	Before	After	p <	Before	After	P <
RAP, mmHg	5.8 ± 1.96	5.48 ± 3.1	NS	14.1 ± 3.2	11.4 ± 3.8	0.001	25.8 ± 4.9	19.2 ± 4.4	0.001
LAP, mmHg	4.9 ± 2.47	6.5 ± 2.5	0.05	5.3 ± 3.6	7.9 ± 4.2	0.001	7.9 ± 3	10.4 ± 3.7	0.02
R-L atrial pressure, mmHg	1.17 ± 3.2	−1.32 ± 3.2	0.02	8.4 ± 4.1	3.3 ± 5.5	0.001	17.3 ± 5	7.7 ± 5.3	0.001
Mean PAP, mmHg	62.8 ± 17	64 ± 19.6	NS	64.9 ± 16.7	65.6 ± 16.7	NS	64.8 ± 23	69.9 ± 24.7	NS
Cardiac Index, L/min/m^2	2.37 ± 0.61	2.80 ± 0.7	0.001	2.10 ± 0.70	2.7 ± 0.9	0.001	1.6 ± 0.5	2.2 ± 0.6	0.001
SaO_2%	93.5 ± 4.1	87.2 ± 7.4	0.001	92.9 ± 4.1	82.8 ± 7.4	0.001	92.2 ± 4.5	78.3 ± 9.7	0.001

RAP mean right atrial pressure, *LAP* mean left atrial pressure, *R-L* right to left, *SaO_2* systemic oxygen saturation

Table 19.3 Clinical characteristics and procedure related mortality according to right atrial pressure before the operation

	Baseline RAP < 10 mmHg (N = 27)	Baseline RAP 10–20 mmHg (N = 51)	Baseline RAP > 20 mmHg (N = 26)
Age, years	23 ± 14	28 ± 14	27.5 ± 12
Syncope (%)	73.9 %	66.7 %	36 %
RVF (%)	34.7 %	73.8 %	88 %
Procedure-related mortality 1-month	0/27 (0 %)	2/51 (4 %)	11/26 (42.3 %)

RAP mean right atrial pressure, *RVF* right ventricular failure

Based on this analysis AS appears to result in immediate improvement of left heart filling, and systemic flow regardless the baseline level of RA pressure. In patients with RAP elevated at baseline its significant decrease immediately after the procedure was noted. Those beneficial effects occurred at a cost of fall of systemic oxygen saturation, most marked in patients with RAP > 20 mmHg at baseline (Table 19.3). Despite clinically relevant increase in systemic CI (from 1.6 to 2.2 L/min/m^2, i.e. 37 %) the peri-procedural mortality in this subgroup was very high, with 11 death after 26 procedures (42 %) contrasting with two periprocedural death in patients with RAP below 20 mmHg (2.5 %) (Table 19.3).

There is hardly any information on hemodynamic effects of septostomy during exercise. While many series reported increased exercise tolerance [19, 24, 31], particularly increased distance covered during 6 min walk test it is difficult to judge the contribution of psychological factor in patients who were submitted to septostomy. The assessment of long term effects of septostomy on exercise capacity is complicated by common tendency of the created orifice to shrink or close.

Late Effects of Septostomy on Right Ventricular Function

Improved left ventricular filling and reduced preload of the right ventricle in patients in whom it had been severely increased before septostomy should lead to improved right ventricular function and – hopefully – to its reversed remodeling. Indeed, better LV filling may improve RV systolic performance by direct support through interventricular septum. Also, reduced RV wall stress could mitigate increased RV myocardial

oxygen demand and potential ischemia, particularly during exercise. Decrease in BNP plasma levels reported after septostomy support reduced diastolic wall stretch and reduced RV afterload [29]. Moreover, in some reports improvement in hemodynamics after septostomy, as evidenced by RAP and CI, was even more marked at long term follow-up than immediately after the procedure [15, 28]. Also echocardiographic follow-up demonstrated reduction of RA and RV dimensions up to 6 months after septostomy suggesting persistent beneficial effects of this intervention on right heart remodeling [33].

Such effects may be also induced by restoration of more physiological autonomic system balance. It has been demonstrated that sympathetic overdrive may be one of the mechanisms involved in pathophysiology of RV failure in patients with PAH. Ciarka and coworkers, showed a significant decrease in initially elevated muscle sympathetic nerve activity after the procedure [27]. Less sympathetic drive can reduce myocardial oxygen demand, ischemia and tendency to arrhythmia. Of note, heart rate did not increase despite a significant systemic oxygen desaturation following septostomy

Effects on Blood Gases and Oxygen Transport

The effects of septostomy on systemic oxygen transport (SOT) and its tissue delivery are unclear. An increase in SOT resulting from the increase in CI despite the drop in SaO_2% has been suggested in some clinical studies [34] but seems unlikely and has not been confirmed when tested in recently developed computational models addressing this issue [8, 9]. Whether better perfusion of peripheral tissues improve local utilization of oxygen even if delivered in similar quantities remains unclear.

A potential adverse effect induced by acute systemic desaturation on pulmonary hemodynamic has been suggested by Kurzyna et al. Within an hour after successful septostomy and despite intially stable and well controlled degree of SaO_2 they noticed unexpected "secondary" significant drop in oxygen saturation [26]. It occurred in patients who were not receiving chronic targeted therapy and could be effectively reversed by inhalation of a prostanoid (iloprost). The authors linked this observation with an increase in PVR seen in some of their patients soon after completion of atrial septostomy [26]. This increase correlated in turn with the degree of desaturation of mixed venous blood entering pulmonary arterial bed, which was a direct consequence of acutely reduced systemic SaO_2. Hypoxemic constriction of pulmonary arterioles as a reaction to profound sudden reduction in SvO_2 despite alveolar normoxia has been suggested, but could't be proved. We generally think that it is alveolar hypoxia rather than hypoxaemia that causes pulmonary vasocionstriction so this a surprising conclusion. Interestingly, the hemodynamic data collected from 104 patients indeed show a trend towards increase of PAP after septostomy (Table 19.2). An alternative explanation of such trend might however come from improved RV output supported through interventricular septum by a better filled LV. In view of protection of patients from potential pulmonary hypoxic/hypoxemic vasoconstriction by powerful vasodilating drugs the clinical relevance of this potential side effect of septostomy was abrogated [32].

Risks and Limitation of Atrial Septostomy

Atrial septostomy is not an easy procedure. There is an important difference between puncturing interatrial septum to perform mitral annuloplasty or ablation in the left heart and atrial septostomy in severe pulmonary hypertension. The remodeling of the heart, and particularly reduced distance between interatrial septum and left atrial free wall as well as disturbed topography of the ascending aorta increase risk of perforation with potentially immediate fatal consequences. Fluoroscopy alone is used to guide the procedure in some experienced centers. However, with less experience more comprehensive imaging is needed to monitor the procedure. Parallel use of fluoroscopy and transesophageal imaging of the

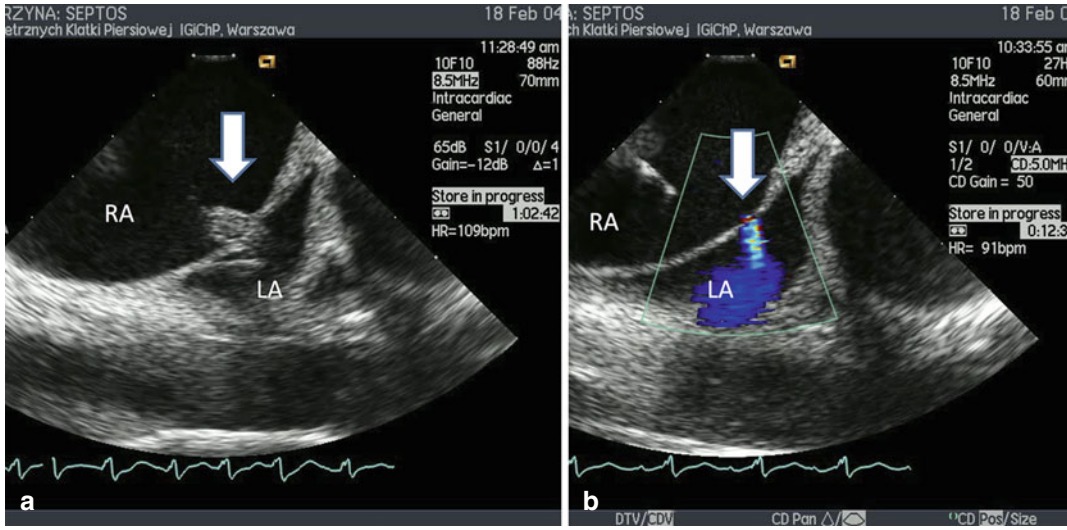

Fig. 19.6 Intracardiac echocardiographic monitoring of (**a**): balloon inflation (*arrow*) and (**b**): right to left shunt after puncturing interatrial septum. *RA* right atrium, *LA* left atrium. The intracardiac echocardiographic transducer is introduced via jugular vein and placed in high right atrium

interatrial septum is probably the best choice. Prolonged insertion of TEE probe however requires general anesthaesia, which is not without risks in severe pulmonary hypertension. Good collaboration of anaesthesiologist, interventionist and PAH expert is crucial to avoid problems. Transthoracic echocardiography offers some support during the procedure but is far less informative then TEE. Intracardiac ultrasound is an acceptable alternative (Fig. 19.6). While not as versatile as TEE, it can be performed without discomfort to the patient without anaesthesia.

Once the septum is punctured the next important step is to select the optimal orifice size. This is difficult with the blade balloon technique, which has been gradually abandoned because of the risk of creating tears in the septum which may result in oversized shunts with uncontrollable and life-threatening hypoxemia. Stepwise balloon technique is now used by most active centers. It allows precise control over the size of created orifice.

As an example, the procedure used in the Institute of Cardiology in Mexico is the following: baseline right and left heart pressures are recorded simultaneously with a pig-tail catheter in the ascending aorta just over the aortic valve to serve as an additional marker lowering the risk of aortic puncture. Cardiac output is calculated by the Fick method. Following trans-septal puncture using standard technique, the septostomy orifice is balloon-dilated in a carefully graded step-by-step approach, beginning at a diameter of 4 mm, and followed by 6-, 8-, 12- and 16-mm dilatations, as appropriate. Between each step and after 3-min allowed for stabilization of hemodynamics, left ventricular end-diastolic pressure (LVEDP) recordings and arterial oxygen saturation (SaO_2) are obtained. The final size of the defect is individualized in each patient and limited by the time at which any of the following first occurred: (1) an LVEDP increase of $\geq$18 mmHg; (2) a SaO_2 reduction to 80 %; or (3) a 10 % SaO_2 decrease from baseline. Follow-up of the patients is done in the intensive care area for the first 48 h, where continuous supplementary oxygen is administrated and appropriate anticoagulation is started. All patients are followed at outpatient clinic with particular care to maintain correct oral anticoagulation and appropriate hemoglobin levels [32].

The stepwise approach is safer but tedious, time consuming and expensive, as many balloons have to be used. Moreover, balloon dilatation, does not protect from elastic recoil and closure

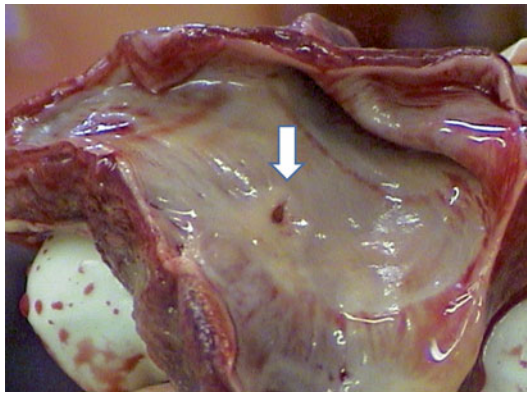

Fig. 19.7 Residual, hemodynamically non-effective orifice (*arrow*) seen post-mortem at the interatrial septum 6 months after atrial septostomy

(Fig. 19.7). Therefore, some teams aim at a predefined single-size orifice but protected from closure with a butterfly stent [35, 36] or fenestrated occluding device [25]. However, follow-up revealed occlusion of this device in four out of nine patients despite chronic anticoagulation or antiplatelet therapy [30] making such approach questionable. Butterfly stents seem to be more effective, but they have to be prepared and positioned on a septostomy ballon on-site by the operator during the procedure. This again significantly increases procedural time, and requires dedicated personel and a long time-slot of the hemodynamic laboratory . Recently a new concept of cryo-ablation to septostomy borders has been also applied with a good long term result after the second septostomy, which was performed because the first one closed (J. Sandoval, personal communication, 2014). In our experience and not unexpectedly the small orifices closed most often suggesting that septostomies should be made earlier – in patients with no more than mildly eleveated RAP – but larger.

Closing of septostomy can be suspected if at pulsoxymetry check-ups SaO_2 gradually returns towards baseline values. In such a case an attempt to push the leader across a still patent orifice avoiding risky puncture and limiting the procedure to balloon dilatation is tempting. However finding the residual hole may be very difficult and usually a new puncture is needed.

Atrial Septostomy and Therapeutic Strategy in Pulmonary Hypertension

Based on available evidence as well as our personal experience regarding the efficacy and safety of atrial septostomy it seems that this procedure has both a place and – even more importantly – a potential to play more prominent role in management of patients with PAH and right ventricular dysfunction. This is justified by

- sound pathophysiological background
- experimental and computational evidence consistent with clinical findings
- convincing data on increased systemic output due to improved left ventricular preload and resulting in clinical improvement
- lack of clinically significant consequences of systemic desaturation
- better understanding of peri-procedural risk and optimal patients selection

Those characteristics permit considering atrial septostomy particularly in patients who are suboptimally controlled by modern medical therapy. Syncope and fluid retention may be relieved by septostomy and time can be gained increasing the chance to survive on the lung transplantation list. If septostomy is considered in a patient it is of paramount importance not to miss the optimal moment characterized by still preserved acceptable oxygen saturation without prohibitive levels of RAP.

Septostomy may be particularly useful in countries/centers who have suboptimal access to lung transplantation programs or to expensive double and triple targeted therapy

Following actions are urgently needed

- identification and implementation of the best method to prevent re-occlusion of atrial septostomy
- designation of referral septostomy teams with appropriate experience and perspectives to create a high volume/high quality environment with appropriate quality monitoring
- preparation of a properly designed interactive registry offering standardized management suggestions and at the same time collecting evidence with a goal of using the results for

future optimization of patient selection and methodology of procedure. Such registry – if extended to centers not performing septostomy – would also allow comparison of long term outcome between matched groups of patients to whom septomy was or was not offered.

To optimize the risk/benefit ratio of atrial septostomy as well as introduce this procedure as a preventive measure which delays failure of the right ventricle despite progressive pulmonary vascular disease new data are needed. This includes a prospective trial to verify whether atrial septostomy may be effective in the setting of moderate right ventricular hypertension. Such an early intervention has been recently suggested by a clinical retrospective study but seems not to be supported by experimental data [12, 32].

In view of great achievements regarding assessment of efficacy and safety of modern pharmacotherapy of PAH and continuing problems with availability of donors for lung transplantation programs the community caring for patients with PH and the patients themselves have to mobilize resources and enthusiasm to arrange a landmark trial identifying optimal positioning of atrial septostomy in the future management strategy. New technical developments, including remote controlled devices with modifiable shunt fractions and preventing from re-occlusion of the septostomy orifice should encourage industry to support our effors, hopefully in the near future

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Index

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