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FOCUS ON THE RIGHT HEART (S. ROSENKRANZ, SECTION EDITOR)

The Right Ventricle: From Embryologic Development to RV Failure

Matthew R. Lippmann[1] · Bradley A. Maron[1,2]

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Abstract

Purpose of Review The right ventricle (RV) and left ventricle (LV) have different developmental origins, which likely plays a role in their chamber-specific response to physiological and pathological stress. RV dysfunction is encountered frequently in patients with congenital heart disease (CHD) and right heart abnormalities emerge from different causes than increased afterload alone as is observed in RV dysfunction due to pulmonary hypertension (PH). In this review, we describe the developmental, structural, and functional differences between ventricles while highlighting emerging therapies for RV dysfunction.

Recent Findings There are new insights into the role of fibrosis, inflammation, myocyte contraction, and mitochondrial dynamics in the pathogenesis of RV dysfunction. We discuss the current state of therapies that may potentially improve RV function in both experimental and clinical trials.

Summary A clearer understanding of the differences in molecular alterations in the RV compared to the LV may allow for the development of better therapies that treat RV dysfunction.

Keywords Right ventricle · Left ventricle · Adult congenital heart disease · Congenital heart disease · Pulmonary hypertension · Right ventricular failure

Introduction

The right ventricle (RV) and left ventricle (LV) have different embryologic origins, and each responds differently to stress. Specifically, pressure and volume overload contribute to RV dysfunction, which are encountered commonly in congenital heart disease (CHD). RV failure is an important predictor of morbidity and mortality in CHD; therefore, understanding the pathophysiology of pressure and volume overload in this disease spectrum is imperative.

The pathogenesis of RV failure includes myocardial stress, cytokine and neurohormonal activation, fibrosis, inflammation, and reduced contractility. Treatment of RV failure is largely extrapolated from treatment of LV failure; however, there are gaps with this management strategy because each ventricle exerts variable response patterns to stress. Emerging evidence shows that targeting molecular parameters implicated in the pathogenesis of RV dysfunction may become a novel therapeutic approach in the treatment of right heart failure.

Embryological, Anatomical, and Physiological Differences Between the RV and LV

This section contrasts the developmental biology, structure, and function of the RV and LV.

Embryological Differences Between Ventricles

Embryonic development of the cardiovascular system in humans occurs between the third and eighth weeks of gestation [1•]. The LV myocardium derives from the primary heart field and the RV myocardium derives from the anterior (secondary) heart field [1•]. These events develop

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✉ Bradley A. Maron
bmaron@bwh.harvard.edu

Matthew R. Lippmann
mlippmann@bwh.harvard.edu

[1] Division of Cardiovascular Medicine, Brigham and Women's Hospital, 77 Ave. Louis Pasteur, NRB 0630-N, Boston, MA 02115, USA

[2] Department of Cardiology, VA Boston Healthcare System, West Roxbury, MA, USA

successively and are driven by preprogrammed genetic signals. Basic helix-loop-helix transcription factors are important regulators of embryonic development [2]. Specifically, after cardiac looping, cardiomyocyte differentiation is dependent on basic helix-loop-helix transcription factors expressed in the RV (driven by dHAND) and the LV (driven by eHAND) [2, 3]. It has been demonstrated that deletion of dHAND in a murine model resulted in hypoplasia of the RV [2]. Identification of dHAND and eHAND was important as it provides a pathway through which molecular signaling controlling cardiogenesis may be further elucidated [3].

Anatomical and Physiological Differences Between Ventricles

In utero, the RV contributes to 60% of overall cardiac output with both ventricles having equal wall thickness [4, 5•]. Functionally, poorly oxygenated blood from the vena cava travels across the tricuspid valve to the RV into the pulmonary artery (PA) with minimal amounts of blood entering the lung due to elevated pulmonary vascular resistance (PVR) [4]. The low PA saturation maintains a state of high PVR and blood shunts through the foramen ovale and ductus arteriosus, largely bypassing the lungs [6]. There are many physiological transitions that occur at birth with important structural and functional changes.

The placental circulation in utero is under high PVR and there is a rapid decrease in PVR once the umbilical cord is clamped at birth [7]. As a result, RV wall thickness decreases and LV mass increases [6]. In the face of a lower impedance pulmonary circuit, the normal postnatal RV maintains a cardiac output equal to the LV (in the absence of intracardiac shunting) at one-sixth the energy expenditure of the LV [8].

The RV can be divided into three anatomical sections: inlet (including tricuspid valve), trabeculated apex, and outflow tract (infundibulum, a muscular structure that supports pulmonary valve leaflets) (Fig. 1A). The crista supraventricularis separates the tricuspid valve and pulmonary valve, which is different from the aortomitral continuity of the LV. Structurally, the normal adult RV is thin-walled and crescent-shaped (Fig. 1B), whereas the LV is thick-walled and bullet-shaped. As previously mentioned, myocyte differentiation is directed by chamber-specific expression of basic transcription factors that likely alters the plane of myocyte contractility for the respective chamber. Although the LV has three distinct myocardial fibers, the RV consists of superficial (circumferential) fibers and deep (longitudinal) fibers with contraction from inlet to outlet and from free wall to septum; the RV relies more on longitudinal shortening compared to the LV and is heavily influenced by loading conditions [6]. Some embryological, physiological, and anatomical differences between ventricles are summarized below (Table 1).

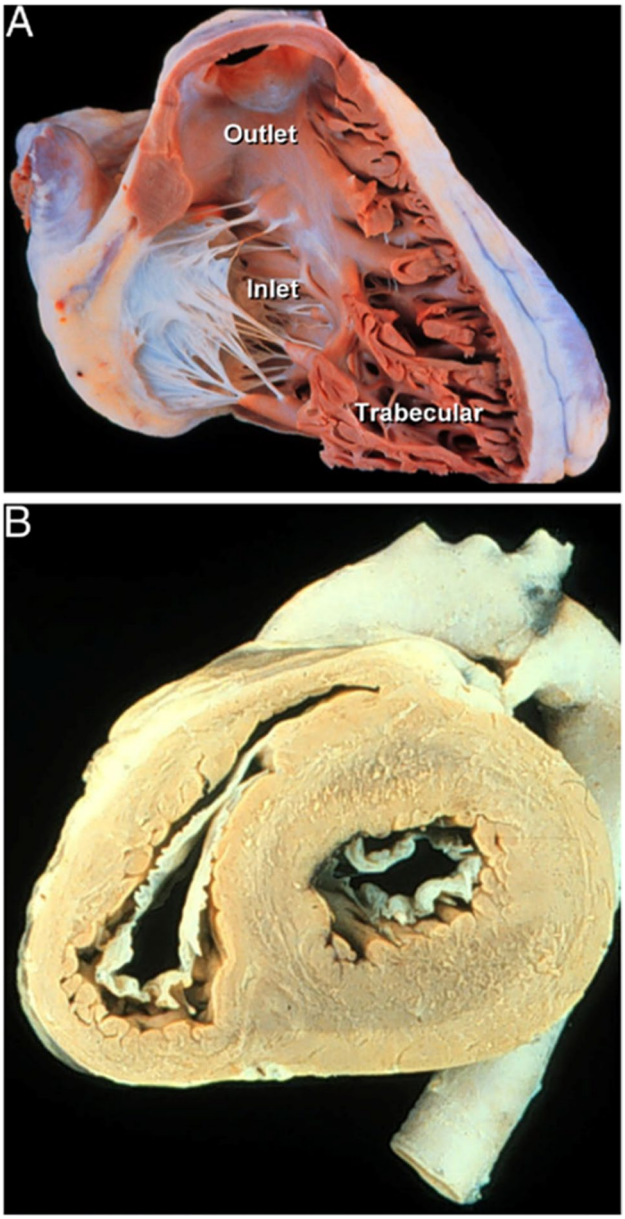

Fig. 1 Pathologic specimens. **A** Pathologic specimen of the right ventricle with the free wall removed to demonstrate the 3 anatomic regions [9]. **B** Pathologic specimen of the heart cut transversely demonstrating the crescent shape of the right ventricle [9]. Image from Warnes [9] reproduced with permission. Please remove Photo courtesy of Dr. W. D. Edwards, consultant in pathology, Mayo Clinic

RV-PA Coupling

The RV is coupled with the compliant PA, leading to a pressure–volume relationship distinct from the LV. Specifically, the RV is trapezoidal-shaped with few isovolumic periods, whereas the LV is rectangular-shaped with distinct isovolumic periods [10]. Functionally, the

Table 1 Embryological, physiological, and anatomical differences between ventricles

Embryological, anatomical, and functional comparisons of LV and RV	Left ventricle	Right ventricle
Embryologic origins	Primary heart field	Anterior heart field
Helix-loop helix transcription factors	eHAND	dHAND
Myocardium	Thick walls; fine trabeculations	Thin walls; coarse trabeculations
Wall thickness (mm)	7–11	2–3
Morphological features	Bullet shape; ellipsoid	Crescentic shape
Papillary muscles	Two large	Several small
Contraction properties	Concentric	Peristaltic
Response to pathologic load	Responds better to pressure overload	Responds better to volume overload
Coronary supply	Two coronary arteries	One coronary artery

LV continues to generate pressure until the aortic valve closes, whereas the RV pressure falls prior to pulmonary valve closure, but RV output continues in the face of low pulmonary resistance [10]. The RV takes advantage by producing a similar output to the LV with reduced stroke work but remains sensitive to afterload. RV-PA coupling is a measure of RV performance and refers to the relationship between RV afterload and contractility [11, 12]. More specifically, both RV and PA are "coupled" where the RV contractility should "match" the afterload [12]. If RV afterload decreases, RV contractility should decrease; if RV afterload increases, RV contractility should increase to maintain RV performance and preserve RV-PA coupling [12].

Difference between RV dysfunction and RV Failure

Difference Between RV Dysfunction and RV Failure

RV dysfunction is any abnormality of filling or contraction without clinical heart failure (HF), whereas RV failure results in clinical HF from a structural or functional impairment of the RV [13].

Causes of RV Failure

RV failure can be categorized by its mechanism of injury and chronicity. The RV may fail from pressure or volume overload, inflow obstruction, myocardial disease, pericardial disease, or myocardial ischemia.

This review focuses on pressure and volume overload, specifically as it relates to CHD; however, it is worth highlighting the spectrum of diseases that impact RV function (Table 2).

RV Pressure Overload Overview

There are many causes of RV failure from non-physiologic pressure overload, such as PH, pulmonary embolism (PE), congenital pulmonary valve stenosis, systemic RV dysfunction, double-chambered RV, and peripheral pulmonary stenosis [13]. The RV fails from both acute and chronic pressure overload but in different ways, and it is important to understand how.

Acute RV Pressure Overload

Acute PE causes pulmonary obstruction resulting in increased RV afterload and pulmonary arterial vasoconstriction. The rapid rise in afterload increases RV wall tension leading to RV dilatation and systolic dysfunction [14]. As the RV pressure increases, the septum shifts into the LV thereby reducing LV filling and compromising LV output [14]. Furthermore, coronary perfusion is restricted by elevated RV wall stress. The final event in this death spiral is worsening systemic hypotension and sudden cardiac arrest. The RV does not respond well to acute changes in afterload but responds better to long-term pressure overload through a hypertrophic adaptive response and expansion of extracellular matrix [15].

Chronic RV Pressure Overload

The adaptation to chronic pressure overload becomes maladaptive for the RV, resulting in dilation, decreased systolic performance, and reduced output [16]. RV pressure overload leads to concentric hypertrophy (sarcomeres are in parallel) thereby increasing myocardial thickness and reducing chamber diameter [17].

Table 2 The spectrum of diseases that impact RV function

Causes of RV failure	Pressure overload	Volume overload
Acute	Pulmonary embolism	Sepsis
	Acute respiratory distress syndrome	Excessive blood or saline transfusion
	Myocarditis	
	Hypoxia	
Chronic	Congenital pulmonary valve stenosis	Transposition of the great arteries
	Pulmonary hypertension*	Pulmonary regurgitation
	Double-chambered RV	Tricuspid regurgitation
	Systemic RV	Ebstein anomaly
		Atrial septal defect
		Partial anomalous pulmonary venous drainage

ASD indicates atrial septal defect; ARDS, acute respiratory distress syndrome; DCRV. *Includes pulmonary arterial hypertension (PAH)

Concentric hypertrophy is a remodeling process that helps defend cardiac output, but remodeling progresses from adaptive to maladaptive leading to cardiac failure. RV pressure overload generates oxidant stress and capillary rarefaction, leading to fibrosis, cardiomyocyte dysfunction, and cardiomyocyte loss [18]. It is unclear what triggers this transition from adaptive to maladaptive, but genetics, neurohormonal over-activation, and ischemia play roles [19].

Congenital PS and systemic RV are pressure overload conditions seen in CHD. Congenital PS is one of the most common congenital heart defects and the degree of RV hypertrophy varies with the severity of obstruction [20]. The RV is the systemic ventricle in D-loop transposition of the great arteries (D-TGA) post atrial switch (Fig. 2A-C) and L-loop transposition of the great arteries (L-TGA) or congenitally corrected TGA. In these defects, the aorta arises from the RV and PA from the LV. The chronic increase in afterload causes the systemic RV to assume a pressure–volume loop like the LV where ejection of blood during RV pressure decline no longer occurs [21]. This results in compensatory RV dilation to maintain stroke volume; these series of events lead to increase in myocardial wall stress and oxygen demand [21]. Lack of contractile reserve is another concern in systemic RVs [22]. Because of this exposure to systemic pressures, RV failure is the most clinically important problem we see in patients with TGA. In D-loop TGA post atrial switch, systemic AV valve (AVV) (tricuspid valve) regurgitation contributes to progressive decline in RV function [23]. In L-loop TGA, systemic AVV (tricuspid valve) regurgitation and RV failure are associated with increased mortality [20]. Therefore, the tricuspid valve function should be closely monitored in patients with TGA and a decline in RV systemic function should prompt a search for worsening AV valve regurgitation. The pathophysiological

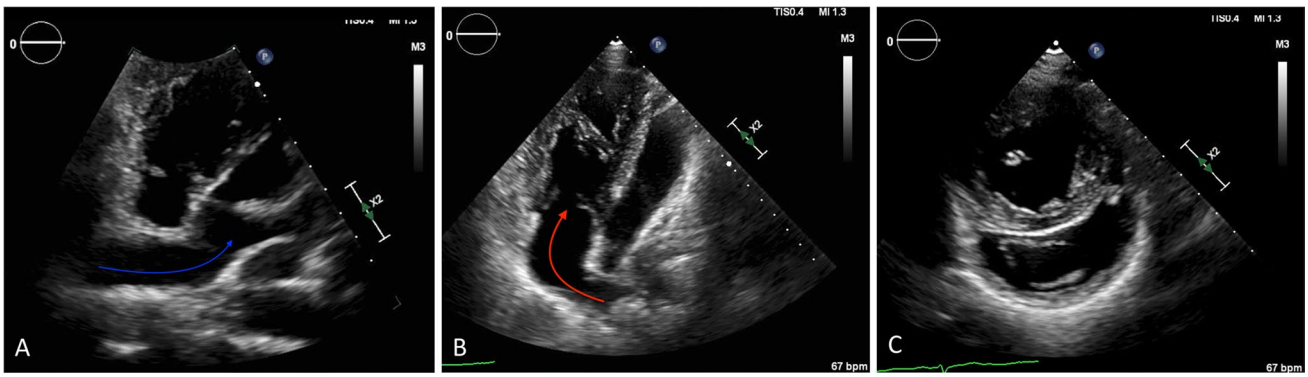

Fig. 2 Four-chamber view on a transthoracic echocardiogram shows the intra-atrial baffles seen in a patient with D-loop TGA post atrial switch where baffles are used to restore physiological circulation. **A** An atrial baffle diverts blood from both vena cava across to the mitral valve and LV (*blue arrow* is in the systemic venous baffle), which ejects blood to the PA. **B** The oxygenated pulmonary venous blood returns to the tricuspid valve and systemic RV (*red arrow* is in the pulmonary venous baffle), which ejects blood to the aorta. **C** Apical short-axis view on a transthoracic echocardiogram shows a dilated and hypertrophied systemic RV where the interventricular septum bulges into the "banana" shaped—a finding expected in a patient with systemic RV post atrial switch repair

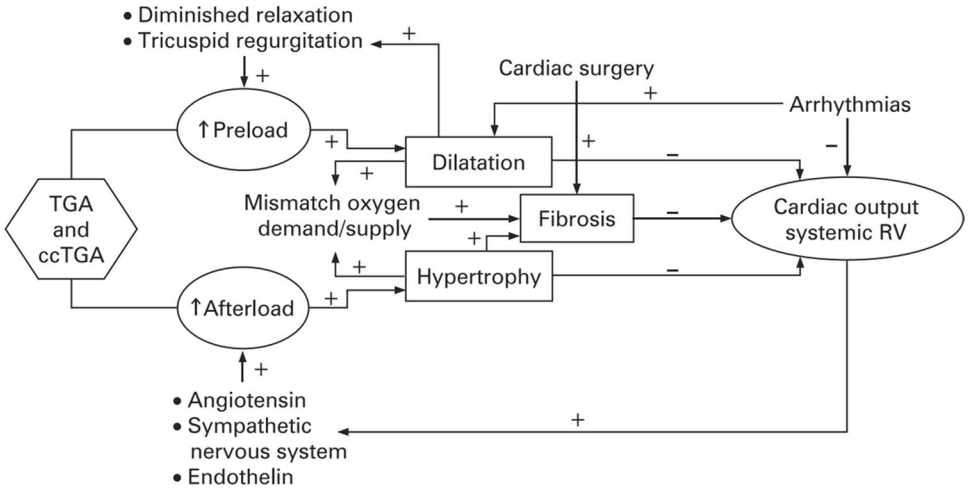

Fig. 3 Pathophysiological pathways of systemic right ventricular (RV) dysfunction from Winter [24]. The pathophysiology of systemic RV dysfunction is multifactorial and includes arrhythmias, tricuspid valve regurgitation, myocar-dial fibrosis, and myocardial ischemia. Image from Winter [24] reproduced with permission

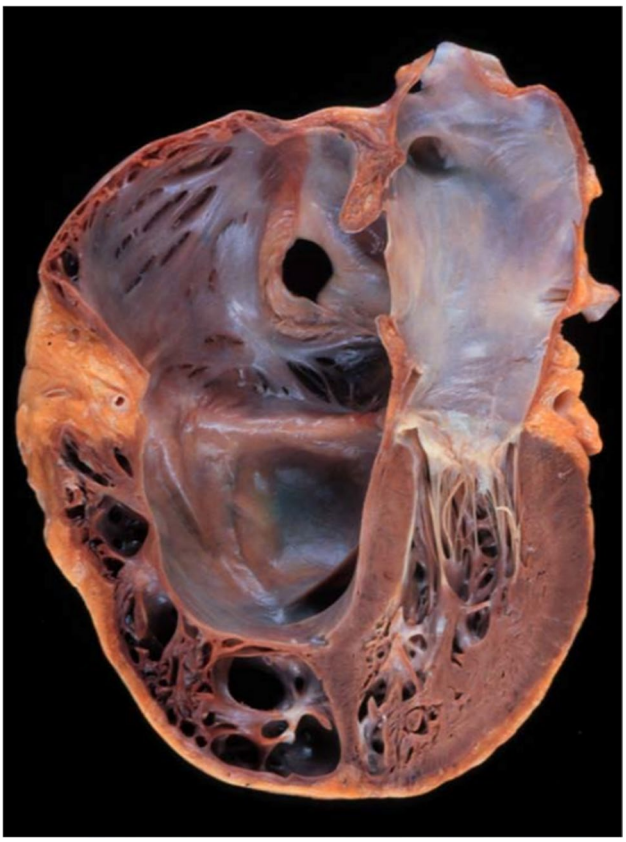

Fig. 4 Pathologic specimen cut in the 4-chamber plane from a patient with Ebstein anomaly from Warnes [9]. The tricuspid valve is displaced markedly inferiorly, and the right ventricular wall is extremely thin. Image from Warnes [9] reproduced with permission. Please remove Photo courtesy of Dr. W. D. Edwards, consultant in pathology, Mayo Clinic

mechanisms of systemic RV failure are multifactorial involving issues with preload and afterload (Fig. 3).

Ebstein anomaly (EA) is a congenital heart defect that imposes a significant RV volume load. EA has an accompanying RV myopathy and involves failure of delamination of the septal leaflet (sometimes posterior) of the tricuspid valve where the valve is apically displaced with an "atrialized" RV and a true RV below (Fig. 4).

Pathogenesis of Chronic RV Pressure Overload: Summary

The key pathophysiological principle in RV failure from chronic pressure overload is the prolonged exposure to increased afterload. RV pressure overload is associated with myocardial ischemia caused by reduced right coronary perfusion that promotes cardiomyocyte injury [25, 26]. Due to these changes, there is an increase in mitochondrial reactive oxygen species (ROS) accumulation, resulting in hypoxia-induced factor-1α (HIF-1α) inhibition and p53 activation [27]. These events lead to further reduction in angiogenesis. Furthermore, vascular endothelial growth factor (VEGF) and apelin are downregulated, contributing to impaired capillary growth [28].

Chronic RV Volume Overload

The RV adapts more favorably to volume overload compared to pressure overload. The thin RV wall permits it to accommodate changes in preload without significant changes in pressure. States of chronic volume overload, such as an ASD or PR after repair of tetralogy of Fallot (TOF), can persist many years prior to the development of RV failure.

ASDs are commonly diagnosed initially in adulthood and result in a net left-to-right shunt with direction and magnitude of blood flow determined largely by the size of the defect and ventricular compliance [29]. The shunt poses a volume load on the RV and pulmonary vessels. RV volume overload is associated with LV dysfunction due to altered ventricular geometry and reduced myofiber preload [30]. In long-standing ASDs (in the

absence of Eisenmenger physiology), an increased rate of morbidity is driven by the increased net left-to-right shunt because of progressive LV stiffness from systemic hypertension or aging [20].

TOF is the most common cyanotic CHD and obstruction along the RV outflow tract is a key element of its pathophysiology, but surgical mitigation of obstruction frequently results in PR, which leads to RV dilatation [31].

Pathogenesis of Chronic RV Volume Overload: Summary

The key pathophysiological principle in RV failure from chronic volume overload is a dilated tricuspid annulus that permits TR, exacerbating the volume load on the RV and septal shift. There is significant septal shift because the pericardium is unable to distend and, thus, cannot geometrically accommodate changes in end-diastolic volume manifest by RV dilation. The septal shift impairs LV filling that impairs LV end-diastolic filling, increases left atrial pressure, and often promotes pulmonary hypertension [31]. In volume overload, the RV is more prone than the LV to developing fibrosis, as demonstrated in an experimental high-flow porcine model [32]. Furthermore, patients with post-surgical repair of TOF and PR can develop RV fibrosis, even at areas remote from surgical incision sites, which is clinically relevant owing to the effect of replacement and interstitial collagen deposition on electromechanical stability and susceptibility to RV failure [33, 34].

The molecular mechanisms underlying RV volume overload in humans remain elusive, but some recent animal studies have shown the detrimental effects of volume overload on the RV, such as hypertrophy and angiogenesis [35]. Volume overload was shown recently to induce an immune response in the RV during the neonatal period in vivo [36]. Moreover, immune responses may be an initiating factor for RV remodeling and, therefore, immune modulating therapies have been proposed as one potential path forward to prevent potential deleterious effects of volume overload in neonatal right heart failure syndromes [36]. More data are needed before immunosuppressants should be considered for use under clinical circumstances, however, owing to the pathogenic effects reported for these therapies on myocardial tone and structural integrity.

Diagnosis and Assessment of RV Failure

A thorough history and physical examination is required. The symptoms of RV failure may be extremity swelling, early satiety, shortness of breath, and exercise intolerance [13]. The physical examination may reveal elevated jugular venous pressure with prominent V wave, RV heave, right-sided S3 gallop, ascites, and peripheral edema. A prominent pulmonic component of the second heart sound (P2) indicates the presence of PH. The pulmonic component is defined as loud if it is greater than the aortic component in the second left intercostal space or if audible at the cardiac apex [37].

The electrocardiogram may show right axis deviation and right atrial enlargement (p-wave amplitude > 2.5 mm in leads II, III, and aVF) [8]. RV hypertrophy may be identified as a dominant R wave in V1 (> 7 mm tall or R/S ratio > 1) [38].

Ideally, using serum biomarkers to help guide therapy is prudent. The serum N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker that may be useful in management of patients with HF due to RV dysfunction, but is not specific to RV heart failure per se [39].

The chest radiograph may demonstrate RV enlargement as manifest by a globular appearance of the cardiac silhouette and loss of the retrosternal airspace on the lateral projection.

Two-dimensional echocardiography aids in the diagnosis of RV dysfunction; however, there are limitations to the quantification of RV function. Tricuspid annular systolic velocity, tricuspid annular plane systolic excursion (TAPSE), and functional area change (FAC) are standard parameters used for the quantitative assessment of RV function but are load dependent [40]. RV strain is less load dependent and has high predictive value in patients with CHD and PH. Importantly, it enables detection of subclinical RV dysfunction even when TAPSE, FAC, or annular velocities are in the normal range but have not been used routinely in clinical practice [41].

Cardiac MRI provides a full unimpeded examination of the heart's structure and function. It is the gold standard for quantitative measurement of mass, EF, and volumes. It provides delayed gadolinium enhancement aiding in identifying fibrosis and velocity-encoded methods to measure blood flow. Multidetector computed tomography provides information about RV size and function. A hemodynamic catheterization is informative if the volume status is uncertain, worsening renal function in response to therapy, or hemodynamic instability [8].

Management of RV Failure

Management should focus on identifying the underlying cause while focusing on afterload reduction, preload optimization, and myocardial contractility support with pharmacotherapy. Advanced mechanical circulatory support may be utilized in select cases, if needed.

Despite the increase in mortality from RV failure in patients with CHD, there are no adequately powered trials to assess the role of pharmacotherapy in this group. Moreover, patients with CHD have historically been excluded from left-sided HF clinical trials. Therefore, it is important to understand that the guideline-directed medical therapies (GDMT) in HF should be regarded as LV-centric. Small series suggest a potential benefit of β-blockade in patients with systemic

RV, including improvement in symptoms; however, in a large clinical trial, carvedilol did not improve HF outcomes [42]. Some reports suggest mixed results but overall, there have been no demonstrable benefits of angiotensin-converting enzyme inhibitor or angiotensin-2 receptor blocker use in systemic RV dysfunction [43].

Patients with RV failure and CHD should be referred to a center specializing in the care of CHD to potentially correct any reversible anatomical or physiological lesions contributing to RV failure. Patients with a systemic RV routinely have systemic ventricular dysfunction, which is commonly associated with systemic AVV (tricuspid) regurgitation. AVV repair or replacement can improve the course of disease, if performed before a reduction in systemic ventricular function [44]. Cardiac resynchronization therapy may be considered in patients with CHD and reduced systemic RV function [45].

The current data do not recommend GDMT used for left-sided HF to patients with a systemic RV. A more comprehensive management strategy for RV dysfunction in CHD can be found in the newest iteration of the adult congenital heart disease guidelines [46]. Some patients may require consideration for heart only or heart–lung transplantation [46].

Novel Clinical and Experimental Therapeutic Approaches to RV Dysfunction

Clinical trials have been constructed to better understand PAH treatment, but most assessed cardiac improvement secondary to reduced PA pressure instead of assessing it as a primary objective. In other words, most clinical trials focused on improving RV function as a consequence of reduction in PA pressures; however, there are recent studies aimed at assessing RV function by measuring various structural and functional parameters.

Some clinical trials report improvements in RV ejection fraction at varying degrees: ~ 3.9% after 3 months of trimetazidine (NCT03273387 [47]), 10.1% after 6 months of macitentan (NCT02310672 [48]), and 10.4% after 6 months of carvedilol (NCT00964678 at clinical trials.gov [49]) suggesting an overall improvement in RV function. Changes in RV volumes have also been demonstrated. For instance, 6 months of carvedilol therapy caused a change of 22.6 mL in RVESV (NCT00964678 [49]) and 6 months of macitentan therapy caused changes in RVEDV of − 6.22 mL, and RVESV of 16.39 mL (NCT02310672 [48]). Reductions in RV mass have been observed. Macitentan therapy for 6 months caused a reduction of 10.10 g in RV mass (NCT02310672 [48]), suggesting an improvement in RV remodeling. These clinical trials reported improvement in RV function using imaging-related metrics; however, they did not focus on molecular parameters such as fibrosis, myocyte contraction, inflammation, and mitochondrial content, which could be possible novel therapeutic targets to address RV dysfunction. For example, current antifibrotic therapies effective in LV do not reverse RV fibrosis, which may be explained by the differences in extracellular matrix composition [50]. RV has more dendritic and macrophage cells, suggesting that inflammation plays a more important role [51]. Protein kinases A activators have been shown to improve sarcomere function as RV myofilaments have lower calcium sensitivity [52]. The RV has less mitochondrial content and lower rate of oxidation; therefore, preservation of mitochondrial integrity improves RV performance [53, 54]. These are potential molecular pathways to target in RV dysfunction, but they require further investigation.

Summary

Both ventricles are different in respect to their development, structure, and function. Acknowledging the differences in molecular alterations in both ventricles may facilitate the development of novel therapies. This is especially important for the RV because the mechanisms related to its dysfunction remain unclear. Advances in therapeutics for RV dysfunction are needed to improve morbidity and mortality, and though there are promising new pathways to target, they require further investigation.

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Declarations

Conflict of Interest B.A.M., Deerfield Corporation (beyond the scope of this work); Actelion Sciences (beyond the scope of this work), Tenax Company (beyond the scope of this work), and Regeneron (beyond the scope of this work); patent or patent pending (beyond the scope of this work): patent 9,605,047; PCT/US2019/059890; PCT/US2020/066886.

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