Current Heart Failure Reports (2023) 20:471–483
https://doi.org/10.1007/s11897-023-00629-7

The Right Heart in Congenital Heart Disease

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Accepted: 17 September 2023 / Published online: 29 September 2023

Abstract

Purpose of Review To analyze the pathophysiologic importance of the right heart in different types of congenital heart disease (CHD), summarize current diagnostic modalities, and discuss treatment options.

Recent Findings The right ventricle (RV) plays a key role in disease progression and prognosis, either as the subpulmonary or as the systemic ventricle. Volume and/or pressure overload as well as intrinsic myocardial disease are the main factors for RV remodeling. Echocardiography and cardiac magnetic resonance imaging are important noninvasive modalities for assessing anatomy, size, and function of the right heart. Timely repair of related lesions is essential for preventing RV dysfunction. Few inconclusive data exist on conventional pharmacotherapy in CHD-related RV dysfunction. Cardiac resynchronization therapy and ventricular assist devices are an option in patients with advanced systemic RV failure.

Summary Right heart disease is highly related with adverse clinical outcomes in CHD. Research should focus on early identification of patients at risk and development of medical and interventional treatments that improve RV function.

Keywords Right heart · Right ventricle · Pathophysiology · Imaging techniques · Congenital heart disease

Abbreviations

ACHD	Adult congenital heart disease
ASD	Atrial septal defects
CHD	Congenital heart disease
CMR	Cardiac magnetic resonance imaging
cc-TGA	Congenitally corrected transposition of the great arteries
CRT	Cardiac resynchronization therapy
d-TGA	d-Transposition of the great arteries
ES	Eisenmenger syndrome
FAC	Fractional area change
GCS	Global circumferential strain
GDF-15	Growth-differentiation factor 15
GRS	Global radial strain
HF	Heart failure
HLHS	Hypoplastic left heart syndrome
HT	Heart transplantation
hs-TnT	High-sensitive troponin-T
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricle
NT-proBNP	N-terminal proB-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PR	Pulmonary regurgitation
PVR	Pulmonary valve replacement
RA	Right atrium
RHC	Right heart catheterization
RV	Right ventricle
RVEF	RV ejection fraction
RVOT	Right ventricular outflow tract
RVOTO	Right ventricular outflow tract obstruction
RVSP	Right Ventricular systolic pressure

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SAVVR	Systemic atrioventricular valve regurgitation
S-ICD	Subcutaneous ICD
SCD	Sudden cardiac death
STE	Speckle tracking echocardiography
SRV	Systemic right ventricle
SV	Systemic ventricle
TAPSE	Tricuspid annular plane systolic excursion
TOE	Transesophageal echocardiography
TOF	Tetralogy of Fallot
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiogram
TV	Tricuspid valve
VAD	Ventricular assist device
VT	Ventricular tachycardia
VSD	Ventricular septal defect

Introduction

In patients with congenital heart disease (CHD), the right ventricle (RV) plays a key role in disease progression and prognosis, either as the subpulmonary ventricle, mostly affected by volume or pressure overload in patients with atrial septal defects (ASD), tetralogy of Fallot (TOF), Ebstein's anomaly of the tricuspid valve, pulmonary stenosis, and pulmonary valve atresia or as the systemic ventricle encountered in congenitally corrected transposition of the great arteries (cc-TGA), d-transposition of the great arteries (TGA) with previous atrial switch repair, and hypoplastic left heart syndrome (HLHS) with Fontan palliation. In many of these patients, congenital malformations, palliations, residual defects, and their resultant physiology as well as the high-pressure pulmonary or systemic circulation impact the RV, and this relationship impacts morbidity and mortality [1]. Apart from the RV, the right atrium (RA) is also affected in many repaired or unrepaired defects, in which atrial arrhythmias, thrombi formation, and/or paradoxical emboli are frequently encountered [2]. The increased morbidity caused by right heart dysfunction is also related to re-interventions and lengthy hospitalizations posing a high economic burden on healthcare systems [3].

In this paper, we will review the pathophysiologic mechanisms of right heart dysfunction and related complications in different CHD entities, summarize current noninvasive diagnostic modalities and their role in risk stratification, and discuss treatment options.

Pathophysiological Mechanisms of Right Heart Disease

Basic pathophysiologic mechanisms that are primarily responsible for right heart disease in several patients with CHD are volume and/or pressure overload (Figure 1). The RV adapts better to chronic volume overload caused by chronic left-to-right shunt or pulmonary valve regurgitation than to pressure overload, encountered in severe pulmonary hypertension (PH) or presence of a systemic RV [2]. In addition, the RV tolerates better an excess volume than the left ventricle (LV) does [4]; therefore, RV systolic dysfunction manifests later than LV dysfunction owing to LV volume overload. Adaptation of the right heart to chronic volume overload entails progressive dilatation of a compliant thin-walled RV and RA, associated with an increased risk of atrial tachyarrhythmias, especially in patients with septal defects. Tricuspid regurgitation (TR) secondary to tricuspid annular dilatation may also lead to additional chamber dilatation and progression of right heart dysfunction. Moreover, a combination of RV pressure and volume overload, as observed in patients with ToF and mixed pulmonary stenosis and regurgitation, may contribute to a progressive right heart disease.

In patients with cc-TGA or surgical palliation of d-transposition of the great arteries with atrial switch and in patients with HLHS, the RV adopts the role of the systemic ventricle (SRV) and transforms itself from a low-resistance pulmonary pump to a high resistance systemic pump, with a long-term exposure to a high-pressure circuit, leading to a higher likelihood of RV dilatation, systemic atrioventricular valve regurgitation (SAVVR), and systemic RV failure [5]. In these patients, myocardial ischemia may also contribute to the progression of RV failure.

Moreover, diastolic RV dysfunction may be encountered in certain CHD groups, manifesting with increased RV filling pressures, ventricular relaxation or RV restrictive filling patterns. Evaluation of RV diastolic parameters may be challenging in the presence of significant TR.

Finally, it is acknowledged that any anatomical or functional abnormalities of the right heart may also affect the left heart, since both ventricles coexist in the same pericardial sack and share the circumferential layer of myocardial fibers (mechanical coupling). Adverse ventricular interdependence is prominent in all patients with CHD that affect primarily the right heart [6]. A diastolic and/or systolic movement of the interventricular septum to the left, as well as pericardial constraint caused by the RV volume overload, impairs LV geometry and thus affect LV preload. In addition, reduced distensibility of the shared myocardial fibers, caused by dilated RV, impairs the LV contractility according to the Frank-Starling law.

Subpulmonary Right Ventricle

Atrial Septal Defects

ASD is one of the most common CHD, with ostium secundum ASD accounting for 80% of all ASDs, followed by

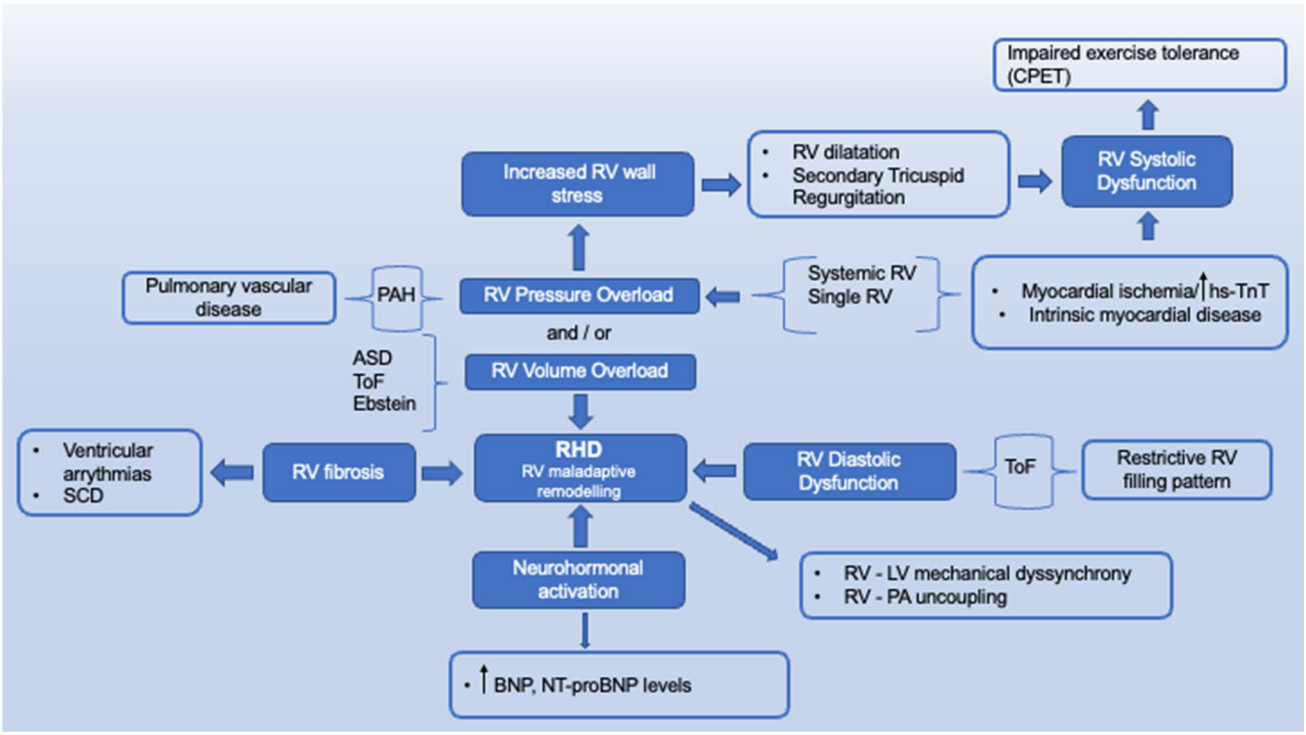

Fig. 1 Impact of different pathophysiologic mechanisms in the right heart disease. ASD: atrial septal defect, BNP: brain natriuretic peptide, CPET: cardiopulmonary exercise testing, EA: Ebstein's anomaly, hs-TnT: high-sensitive troponine T, RHD: right heart disease, RV: right ventricle, PA: pulmonary artery, SCD: sudden cardiac death, ToF: tetralogy of Fallot

ostium primum defect and sinus venosus ASD [7]. ASDs may be encountered as isolated lesions or in combination with anomalous pulmonary venous connections, persistent left superior vena cava, pulmonary stenosis, and mitral valve prolapse. The shunt volume depends on RV to LV compliance, defect size, and left atrium (LA) to right atrial (RA) pressure gradient. RV volume overload and pulmonary overcirculation occur initially in the setting of a significant left-to-right shunt. Aging decreases LV compliance (along with arterial hypertension and valvular or ischemic heart disease) and increases LA pressure, resulting in shunt increase and symptom worsening. If ASD is not timely closed, right heart volume overload leads to increased morbidity (exercise intolerance, HF, atrial arrhythmias, thromboembolic events, and PH) and mortality [8].

Transthoracic echocardiogram (TTE) is the first-line imaging modality to assess the location, size and shape of the defect, the degree and direction of shunting, and the hemodynamic impact on the size and shape of the right heart chambers [7]. Echocardiographic signs of RV volume overload are RV dilatation and interventricular septal flattening during diastole, indicative of a hemodynamic significant ASD that merits closure. The presence of RV hypertrophy, interventricular septal flattening during diastole and systole (D-shaped LV), short right ventricular outflow tract (RVOT) acceleration time of pulmonary ejection with midsystolic notching, and elevated RV systolic pressure (RVSP), determined from peak TR velocity by the simplified Bernoulli equation, are indicative of increased pulmonary vascular resistance that merits right heart catheterization (RHC) to guide optimal management. 3D echocardiography, especially with transoesophageal echocardiography (TOE), might provide incremental information on the rims of tissue surrounding the ASD and other technical aspects before transcatheter closure.

Cardiovascular magnetic resonance (CMR) can be used as a complementary method to assess hemodynamic and quantitative data. Noninvasive flow analysis is used to quantify shunt degree by measuring the ratio of the pulmonary flow over the systemic flow (Qp/Qs), and cine images enable accurate quantification of the volume and function of the dilated right heart chambers [9]. CMR can also detect partial anomalous pulmonary venous connections commonly associated with sinus venosus ASDs.

In general, RV volume overload is the most important parameter to guide ASD closure. Transcatheter device closure is the method of choice in secundum ASDs when technically feasible. After ASD closure, a marked decrease in RV volume is observed within the first year, with normalization of RV volume to be related with smaller preoperative RV volume [10]. A serial follow-up post-ASD closure is recommended, especially when defect closure occurs late

during adulthood, to early diagnose atrial arrythmias and signs of PAH after defect closure, which is encountered in 3% of these patients [11].

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly is a rare CHD of moderate or severe complexity characterized by abnormal formation and apical displacement of the septal and posterior leaflet of the tricuspid valve (TV), while the anterior leaflet is attached to the annulus, but is enlarged and sail-like in appearance. This apical displacement of the TV leaflets translates into an atrialized portion of the RV, a small remaining functional RV, and various degrees of tricuspid regurgitation [12]. Phenotypic expression and prognosis may vary and depend on the severity of the TV dysfunction, the degree of atrialization of the RV, the systolic function of the remaining RV, the degree of RA dilatation, and the arrhythmic burden [13]. Furthermore, mechanical dyssynchrony of the functional RV is associated with RV dysfunction and impaired exercise capacity [14].

Echocardiography sheds light on the anatomy and function of the TV (apical displacement of the septal or posterior leaflet (in adults $\geq$ 0.8 cm/m^2 BSA), size of the anterior leaflet, tethering of the septal, or posterior TV leaflet on the septum or ventricular wall) and size and function of the right heart structures (RA, atrialized RV, remaining functional RV, RVOTO, and associated lesions) (Figure 2).

Estimating the severity of TR and RV size and function is crucial for decision-making regarding the time of surgery. Significant right heart dysfunction is an independent predictor of early post-surgical mortality [15]. TV reconstruction should be performed timely before excess RV volume overload and function worsening to achieve reverse RV remodeling.

TR assessment may be challenging due to the absence of systolic flow reversal in the hepatic veins (equalization of pressures between the RA and RV) and the inability to calculate vena contracta and proximal isovelocity surface area (possibility of more than one color jet) [9]. TOE can aid in better visualizing the tricuspid leaflet anatomy and evaluating the color Doppler jet. CMR is unvaluable for pre- and

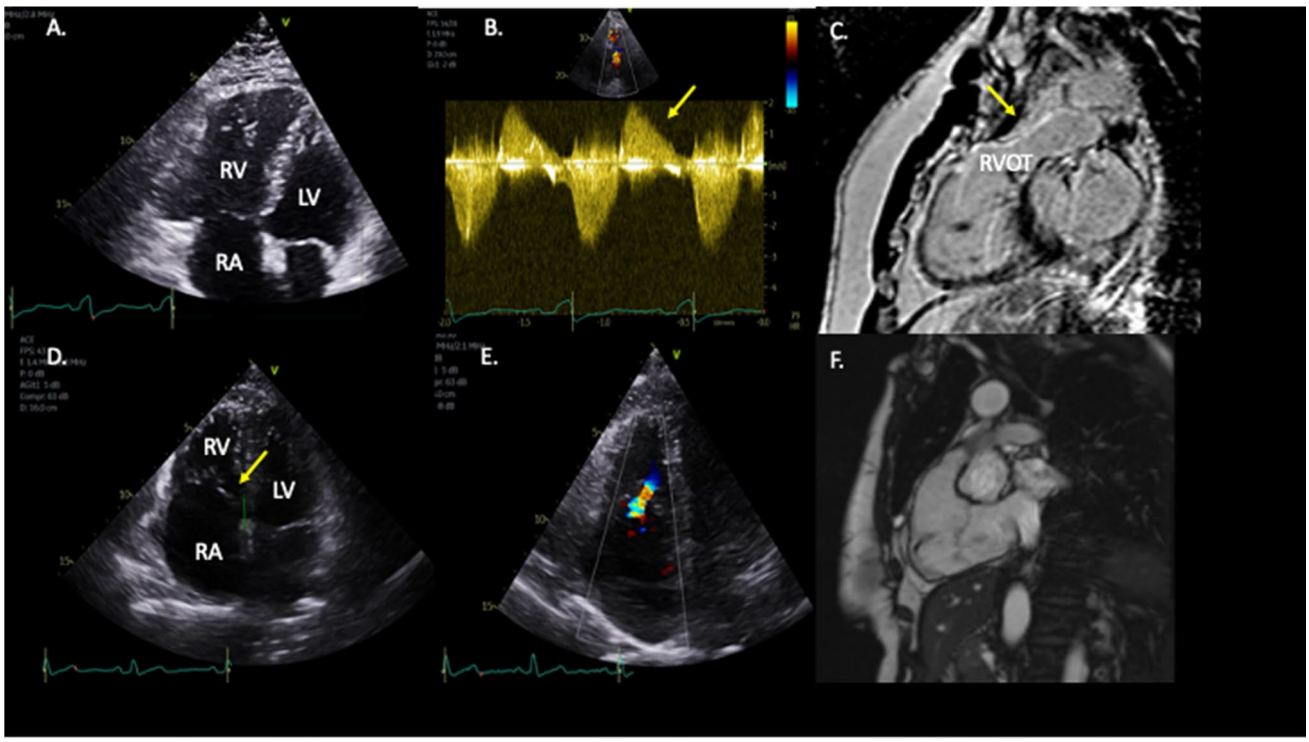

Fig. 2 Imaging assessment of lesions affecting the subpulmonary right ventricle (RV). A 40-year-old patient with repaired tetralogy of Fallot and severe pulmonary regurgitation. **A** Transthoracic echocardiographic 4-chamber view shows a dilated RV with bulging of interventricular septum towards the left ventricle. **B** Continuous wave doppler in the pulmonary valve of the same patient shows a triangular diastolic trace indicative of severe pulmonary regurgitation. **C** Late gadolinium enhancement (LGE) is depicted in the akinetic right ventricular outflow tract (RVOT) region in CMR. A 30-year-old patient with a "mild" unoperated Ebstein's anomaly. **D** Transthoracic echocardiographic 4 chamber view shows an apical displacement of the septal tricuspid valve leaflet (18mm), a dilated right atrium (RA) containing an atrialized portion of the RV and a quite sufficient remaining functional RV. **E** Color doppler shows a mild tricuspid regurgitation (yellow arrow). **F** CMR can be used to quantify the volume and function of the remaining functional RV as well as to better visualize the tricuspid valve anatomy

post-operative patient evaluation and risk stratification, as it enables high-quality views for quantification of the dilated right heart, RV function, and TV function. A CMR study showed impaired RV global radial strain (GRS) and global circumferential strain (GCS), with GRS being significantly compromised in patients with a severely displaced TV (>16 mm/m^2) [16]. CMR-assessed variables, such as RVEF, total R/L volume index, RV/LV end diastolic volume ratio, and apical septal leaflet displacement/total LV septal length, are able to predict first-onset atrial tachycardia in patients with Ebstein's anomaly of the tricuspid valve. In addition, RV and LV function assessed by CMR predicted major cardiovascular events [17].

Tetralogy of Fallot

TOF is the most common cyanotic CHD, consisting of a nonrestrictive subaortic ventricular septal defect (VSD) and varying degrees of RVOT obstruction (RVOTO), due to anterior deviation of the conal septum. Although early surgical TOF repair has significantly improved survival into late adulthood, even patients with a "well-repaired" TOF (r-TOF) may have residual hemodynamic and electrophysiological abnormalities, related primarily with right heart disease [18].

Severe chronic pulmonary regurgitation (PR) is the most common residual lesion in patients with a transannular patch repair; although well tolerated for years, it eventually leads to symptomatic RV dilation and dysfunction associated with a worse prognosis [19]. With advances in transcatheter and surgical pulmonary valve replacement (PVR), early detection of RV enlargement and dysfunction has become increasingly important to optimize time for intervention. RV function in ToF is affected by preload (RV volume overload due to PR), afterload (RVOTO), and contractility, as well as by synchrony of contraction and ventricular interdependence [20]. Significant PR, RV outflow tract aneurysm, and akinesia can decrease cardiac output [21]. Co-existing RVOTO or distal pulmonary arterial stenoses augment the deleterious effects of severe PR on RV. Elevated RV pressure and RV hypertrophy due to RVOTO have been described as independent risk factors for poor outcome and decreased exercise performance, despite smaller RV volumes [22].

Echocardiography is an easily available and cost-effective tool to evaluate patients with ToF pre- and post-operatively. Echocardiographic assessment of RV size and function is challenging because of the shape of the RV [1]. Indirect 2D measures of the RV function, easily obtainable from the RV-focused apical 4-chamber view, are fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). Moreover, speckle tracking echocardiography has been introduced as a sensitive technique to assess myocardial deformation. RV free wall longitudinal strain has been shown to be an independent predictor of adverse clinical outcomes in patients with repaired TOF [23,24]. When technically feasible, 3D evaluation of RV volumes and RV ejection fraction (RVEF) is recommended in centers with experience in 3D TTE [9].

RV dilatation and interventricular septal flattening during diastole are indicative of a severe PR ± RVOTO in repaired TOF that needs further assessment. Significant TR may occur secondary to RV dilatation. In patients with TOF, an elevated RVSP may be attributed to RVOTO and/or pulmonary stenosis or may be indicative of PH in the absence of the previous etiologies. Furthermore, the presence of pulmonary arterial end-diastolic forward flow as assessed with continuous wave Doppler is indicative of a restrictive RV physiology that despite being a negative prognostic marker, especially in the early post-operative period, may have a protective role, when it emerges late in the course of ToF, as a less compliant RV may be protected from further enlargement in the presence of severe PR [25]. CMR is considered the gold standard to assess RV volume and function as well as the location and degree of myocardial fibrosis in patients with TOF, while it allows accurate quantification of PR and measurement of size, shape, and expansion of the pulmonary arteries in these patients.

Optimal timing for PVR remains challenging. PVR improves symptoms and reduces RV volumes, but a survival benefit still needs to be shown [26]. In asymptomatic patients with severe PR and/or RVOTO, when CMR measured end-systolic index exceeds 80 mL/m^2 and/or the end-diastolic volume index exceeds 160 mL/m^2 and/or there is progression of TR or RV systolic dysfunction, PVR should be considered [1]. RV to pulmonary arterial (PA) coupling indices could be sensitive markers of a progressive maladaptive RV response to long-standing volume overload that could guide timely PVR, before the onset of clinical symptoms and RV systolic dysfunction [27]. RV acceleration isovolumic contraction correlates with PR severity, demonstrating a reduced contractile function in relation to the degree of PR, and may be another early, sensitive index for selecting patients for PVR [28]. Finally, worsening of cardiopulmonary exercise indices in asymptomatic patients is associated with impaired RV function and may guide decision for PVR [29].

Ventricular tachycardia (VT) and sudden cardiac death (SCD) may be encountered later in life post-TOF repair and are closely related to RV dilatation and dysfunction. The length of the RVOT akinetic region was found to be a predictor of ventricular arrhythmias in adult TOF patients [30]. RV late gadolinium enhancement (LGE) at surgical sites is common after RVOT patching and/or resection of infundibular stenosis and correlates with RV dysfunction, exercise intolerance, neurohormonal activation, and clinical arrhythmias in TOF (Figure 2) [31, 32]. A recent analysis among 550 consecutive

r-TOF patients that underwent CMR in an expert center demonstrated that the extent of RV LGE and a reduced RV ejection fraction ≤47%, along with the presence of LV LGE and LV dysfunction, were independent predictors of all-cause mortality together with an increased B-type natriuretic peptide, a reduced peak exercise oxygen uptake, prior sustained atrial arrhythmia, and age ≥50 years [33•]. Finally, T1 mapping as a novel technique to quantify diffuse RV myocardial fibrosis in ToF patients showed that the amount of diffuse RV myocardial fibrosis is associated with RV volume overload [34]. All these parameters should be taken into consideration, when selecting TOF patients at high risk for SCD that will benefit from the insertion of an implantable cardioverter defibrillator (ICD).

Pulmonary Arterial Hypertension/Eisenmenger Syndrome

The presence of a chronic systemic left-to-right shunt leads to pulmonary overcirculation that results in pulmonary vascular remodeling and a progressive increase in pulmonary vascular resistance. If the trigger factor persists, irreversible changes evolve to the development of PAH, which mainly affects RV size and function, related to a worse long-term prognosis [35]. With progression of the disease, bidirectional shunting occurs, which turns into a predominant right-to-left shunt with further worsening of the disease [36]. Maladaptation of the RV to the increased pulmonary artery pressures and resistance eventually results in progressive RV failure. Eisenmenger syndrome (ES) comprises the extreme end of PAH associated with CHD, which can occur in patients with large, unrepaired intracardiac or extracardiac shunts. RV is offloaded by the right-to-left shunt, sustaining cardiac output at the expense of cyanosis [37]. However, prognosis of ES is not as promising as previously thought due to immortal time bias [38]. In general, patients with a pre-tricuspid shunt tolerate the increase in pulmonary blood flow much better than patients with post-tricuspid shunts, and only a minority with an unrepaired pre-tricuspid shunt develops ES at an old age. In patients with ES, a mortality prediction model based on echocardiographic indices of right heart disease has been proposed, indicating the impact of right heart on the survival of these patients [39]. Unlike other patients with PAH, ES patients have an increased RV free wall transverse strain that correlates with a better survival compared to patients with idiopathic PAH [40].

Systemic Right Ventricle

Biventricular Systemic Right Ventricle Physiology

Patients with congenitally corrected TGA (ccTGA) and d-TGA after an atrial switch (Mustard or Senning) procedure have a biventricular circulation with a morphologic SRV supporting the systemic circulation. Major long-term complications encountered in these patients are systemic RV dysfunction and RV failure, severe secondary systemic atrioventricular valve regurgitation (SAVVR), and arrhythmias associated with increased morbidity and mortality [41].

RV dysfunction is attributed to multifactorial mechanisms and appears after the third decade of life (Figure 1) [4, 5, 41]; (1) chronic persistent pressure overload leads to RV hypertrophy, which initially compensates for systemic afterload, but in the long term, it is associated with a potential right coronary artery supply to RV demand mismatch; (2) neonatal perioperative hypoxia and potential myocardial ischemia could influence RV function later in life; (3) SRV shortening, as assessed with TTE and MRI speckle tracking, shifts from a predominant longitudinal to a circumferential one without torsion as normally found in the systemic LV; (4) RV fibrosis identified with CMR LGE and T1 mapping techniques is highly related to SRV dysfunction and ventricular arrhythmias; (5) neurohormonal activation similar to that seen in acquired left HF is related with SRV remodeling, myocardial apoptosis, and fibrosis; (6) there is impaired atrioventricular blood flow because of rigid atrial baffles in patients with TGA and atrial switch; (7) SAVVR is usually secondary to annular dilatation or due to an abnormal tricuspid valve observed in cc-TGA; and (8) associated cardiac defects are mostly in patients with a cc-TGA, such as severe pulmonary stenosis or ventricular septal defect.

Echocardiography is the first-line diagnostic modality, providing information on size and systolic function of the SRV, the subpulmonary LV and outflow tract obstruction, severity of SAVVR, and leakage or obstruction of the atrial baffles. CMR is widely used to thoroughly assess SRV volumes and function, SRV fibrosis, and potency or leakage of atrial baffles (Figure 3). Predicting HF events in patients with a SRV and a biventricular circulation is important for timely intensification of follow-up [42]. Estimation of RV GLS, measured with STE, in combination with RVEF%, as well as RV volumes and mass, determined with CMR can well identify patients at highest risk of advanced HF or death [42, 43•].

In asymptomatic patients with a severe SAVVR, quantification of progression of SRV dilatation and RV function is crucial to determine the time of surgery. Despite a preserved EF at rest, both ventricles are unable to increase stroke volume and EF in response to exercise associated with an impaired exercise capacity [44, 45].

A minority of patients with a systemic RV may present with PH as a consequence of pulmonary baffle obstruction or failing SRV. Signs of PH are often subtle including decreased flattening of the interventricular septum in systole, an abnormally wide PA, or elevated systolic pressure in the subpulmonary LV estimated from the mitral valve

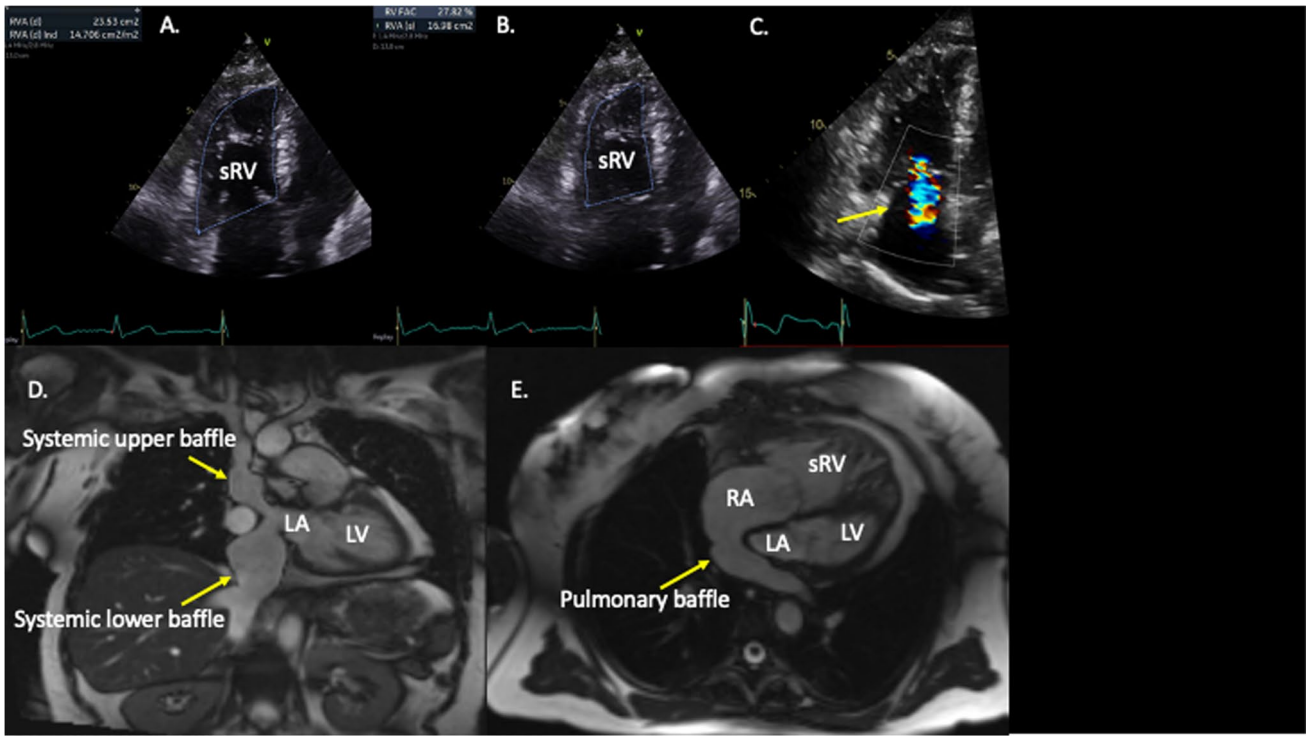

Fig. 3 Imaging assessment of a 38-year-old patient with a systemic right ventricle (sRV) after Mustard operation for d-transposition of the great arteries. Echocardiographic 4 chamber views in end-diastole (**A**) and end-systole (**B**) showing reduced function of the sRV as assessed by fractional area change (FAC) that is 27.8% (<35%). SRV is usually accompanied by various degrees of regurgitation of the systemic atrioventricular valve (yellow arrow), as assessed with color doppler (**C**). CMR has the advantage to provide high quality images of the atrial baffles in order to assess possible leakage or obstruction (**D, E**). LV: left ventricle, LA: left atrium, RA: right atrium

regurgitation in the absence of pulmonary stenosis and can be difficult to recognize [46]. Suspicion of PH dictates diagnostic heart catheterization to exclude/confirm PH as it impacts management and prognosis.

Single Right Ventricle Physiology

Patients with a hypoplastic left heart syndrome (HLHS) have a single functional RV and are palliated with the Fontan procedure in three stages. As a result, systemic venous return is passively directed to the pulmonary arteries (Figure 4). Long-term complications include thromboembolic events, arrhythmias, progressive SAVVR, RV dysfunction, HF symptoms, protein losing enteropathy, liver or renal insufficiency, and PH as a result of a chronic increase in the central venous pressure and a failing RV [47, 48]. Smaller RV size during the initial stages of palliation is related with better transplant free survival and higher likelihood of Fontan completion among children with HLHS [49]. Higher RV end-diastolic volumes are independently associated with a higher mortality risk in patients with a Fontan circulation. RV dominance has been associated with a greater increase in end-systolic volume index, a greater decrease in EF, and a higher rate of heart transplantation (HT), HT listing, or death [50]. CMR flow analysis provides accurate noninvasive hemodynamic data, including collateral flow and shunt through a fenestration if present.

Treatment Options

Prevention

Timely repair of right heart defects and related lesions that impact RV size and function is essential for preventing progressive RV failure and adverse clinical outcomes in patients with CHD. Close follow-up in asymptomatic patients, using noninvasive imaging modalities and blood biomarkers, is necessary to detect early signs of RV enlargement or dysfunction and timely guide interventional procedures or surgery [51]. Impaired RV function, increased RV volumes, and the presence and extent of myocardial fibrosis have been associated with increased risk of exercise intolerance, arrhythmias, all-cause mortality, and SCD in patients with a subpulmonary RV or SRV [10, 17, 24, 33•, 40, 42, 52–54] (Table 1). Cardiopulmonary exercise test (CPET) can be utilized as an objective measure of exercise capacity

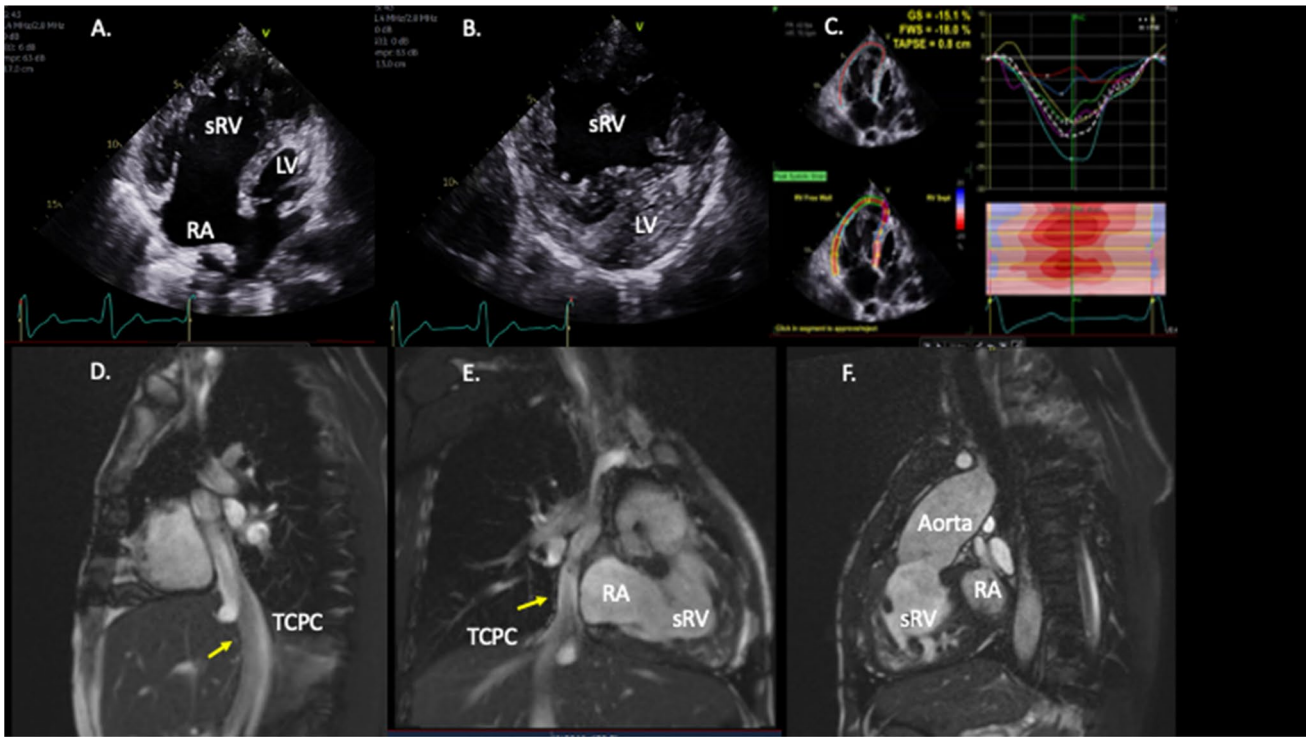

Fig. 4 Imaging assessment of a patient with hypoplastic left heart syndrome (HLHS) and a single right ventricle morphology (sRV). Echocardiographic 4-chammber (**A**) and parasternal short axis view (**B**) show a hypertrophied dilated sRV and a hypoplastic left ventricle (LV). Echocardiographic speckle tracking analysis of the sRV shows a reduced global longitudinal strain (GS=-15%) and a free wall strain (FWS=-18%). Tricuspid annular systolic excursion (TAPSE) is also reduced (**C**). CMR shows a patent extracardiac total cavopulmonary connection (TCPC) that directs the systemic venous blood to the pulmonary arteries (yellow arrows) (**D, E**). sRV volume and function as well as dimensions of the ascending aorta and aortic valve function can be also assessed (**F**). RA: right atrium

to unmask exercise intolerance in apparently asymptomatic patients. [55, 56].

Medical Therapy

Unlike pivotal clinical trials, establishing disease-modifying drugs in acquired left-sided HF, very few inconclusive data exist on conventional HF pharmacotherapy in ACHD, derived from small cohorts [57]. Guideline recommendations, mostly based on clinical experience or position statements, support the use of conventional HF treatment in patients with a biventricular circulation and impaired systemic LV function [1]. There are no robust data to support the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or aldosterone antagonists, alone or in combination, to improve outcome in patients with a failing SRV and a uni- or biventricular heart or in patients with subpulmonary RV dysfunction [58]. Recently, a few small prospective studies on the safety and efficacy of sacubitril/valsartan in patients with a systemic RV demonstrated significant improvement in NT-proBNP, ventricular function, and exercise capacity without serious adverse reactions [59, 60]. However, robust evidence regarding the use of this agent in ACHD is still lacking [61, 62]. Finally, no data exist about the use of sodium-glucose cotransporter 2 inhibitors in ACHD patients with a systemic RV. Diuretics may provide relief of symptoms if overt HF is present. Given the pre-load dependency of the Fontan patients, diuretics should be used with caution. The only evidence-based medical treatment of RV impairment in CHD is the target of PH with PAH drugs (endothelin receptor antagonists, phosphodiesterase type 2 inhibitors, prostanoid analogs, and soluble guanylate cyclase stimulators) which has been shown to improve symptoms, exercise capacity, right heart hemodynamics, RV size and function, quality of life, and survival [63, 64].

Devices and Procedures

On top of medical treatment, cardiac resynchronization therapy (CRT) may be considered in ACHD patients with HF, despite little evidence on indications and outcomes. Efficacy of CRT may vary with the underlying anatomy of the systemic ventricle (left, right, or functionally single), the presence and degree of structural SAVVR, primary myocardial disease or scarring, and type of electrical conduction

Table 1 Non-invasive markers of RV enlargement and dysfunction that predict clinical outcomes in patients with CHD.

CHD	Sample	Author, year	Method	RV and RA parameters	Endpoint	Cut-off points	AUC
ASD	*N*=52	Umemoto, S, 2020 [10]	CMR	Preoperative RVEDVI RVESVI RVEF	Normalization of RV volume post-ASD closure	Preoperative RVEDVI< 183mL/m^2 RVESVI < 75 mL/m^2 RVEF>56%	0.68 0.75 0.64
EA	*N*=79	Rydman R, 2018 [17]	CMR	RVEF total R/L volume index RV/LV EDV ratio Apical septal leaflet displacement/total LV septal length	First-onset AT	RV/LV EDV ratio >2.4 Apical septal leaflet displacement/LV septal length >67%	–
Repaired ToF	*N*=33 Moderate to severe PR	Arroyo-Rodriguez C, 2020 [24]	Echo	RVFWSL%	Functional capacity (exercise test)	RVFWSL < 17%	0.785
	N=100	Timóteo A, 2017 [52]	Echo	RVS RAS	Arrhythmias	RVS −15.3% RAS 23%	0.696 0.699
	N=550	Ghonim S, 2022 [33•]	CMR	RVLGE extent RVEF BNP Peak V0$_2$ prior sustained atrial arrhythmia	All-cause mortality	RVLGE extent, RVEF ≤47%, BNP ≥127 ng/L, peak V0$_2$ ≤17 mL/kg/min, prior sustained atrial arrhythmia	0.87
	N=550	Ghonim S, 2022 [33•]	CMR Echo	RVLGE extent RVEF BNP Peak V0$_2$ Akinetic RVOT RVSP	Ventricular arrhythmias	RVLGE extent, RVEF ≤47%, BNP ≥127 ng/L, peak V0$_2$ ≤17 mL/kg/min, Akinetic RVOT≥55mm RVSP≥47mmHg	0.79
PAH	ES *N*=43 Other PAH *n*=40	Mocceri P, 2016 [40]	Echo	RV free wall transverse strain	Survival	RVFWTS > 22%	0.76
	ES *N*=181	Mocceri P, 2012 [39]	Echo	TAPSE RV effective systolic to diastolic duration time RA area RA to LA area	Mortality	TAPSE <15mm RV effective systolic to diastolic duration time ≥ 1.5 RA area ≥ 25cm^2 RA to LA area ratio ≥ 1.5	0.90
	ES *N*=48	Jensen A, 2015 [54]	CMR	RVEF% LVEF% Oxygen saturation%	Mortality	RVEF <40% LVEF <50% Oxygen saturation 90%	-
Systemic RV							
	d-TGA (*n*=101)	Lewis M, 2022 [42]	CMR	RVEDVI RVESVIRRVEF RV mass	HT referral, VAD, or death	RVEDVI>132mL/m^2 RVESVI ≥ 81mL/m^2 RVEF <38% RV mass ≥ 115	0.93 0.90 0.73 0.84
	cc-TGA (*n*=57)	Lewis M, 2022 [42]	CMR	RVEDVI RVESVIRRVEF RV mass	HT referral, VAD, or death	RVEDVI>126mL/m^2 RVESVI ≥ 84mL/m^2 RVEF <39 % RV mass ≥ 112g	0.76 0.74 0.71 0.74

AUC area under the curve, *AT* atrial tachycardia, *cc* congenitally corrected, *BNP* brain natriuretic peptide, *CMR* cardiovascular magnetic resonance, *EDV* end diastolic volume, *HT* Heart Transplant, *LA* left atrium, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *PR* pulmonary regurgitation, *RAS* right atrial strain, *RVEDVI* right ventricular end-diastolic volume index, *RVESVI* right ventricular end-systolic volume index, *RVEF* right ventricular ejection fraction, *RV mass* right ventricular mass, *RVFWSL* right ventricular free wall longitudinal strain, *RVFWTS* right ventricular free wall transverse strain, *RVOT* right ventricular outflow tract, *RVS* right ventricular strain, *RVSP* right ventricular systolic pressure, *TAPSE* tricuspid annular systolic plain excursion, *TGA* transposition of the great arteries, *VAD* ventricular assist device

delay [65]. Resynchronization of systemic RVs, subpulmonary RVs, and LVs with RBBB is challenging but can yield beneficial results. Targeted multidisciplinary pacing strategies have been shown to improve ventricular function and symptoms in selected patients [66]. In addition, ACHD patients that require a pacemaker should be considered for biventricular pacing to avoid dyssynchrony.

The benefit of ICD therapy in primary prevention for single or systemic RVs is less well established [67]. According to the latest ACHD guidelines, ICD implantation may be considered

for primary prevention in patients with advanced single or systemic RV dysfunction (EF systemic RV <35%) in the presence of additional risk factors (HF symptoms, nonsustained VT, severe SAVVR, and wide QRS >140 ms) with a IIb recommendation [1]. In patients with a baffle leak who require a PM/ICD, closure of the baffle leak should be considered, when technically feasible, prior to insertion of transvenous leads. Subcutaneous ICD (S-ICD) is an alternative for patients with a complex anatomy and venous access problems (Fontan circuit) or at a high risk for infections needing ICD therapy or in patients with an ICD indication not requiring pacing for bradycardia, CRT, or antitachycardiac pacing [68•, 69].

Maintenance of sinus rhythm (SR) is a priority in patients with a systemic RV or ES, as arrhythmias are associated with symptom worsening and HF decompensation. Synchronized cardioversion should be performed in tertiary centers to restore SR. Catheter ablation is recommended as first-line therapy and preferred over long-term pharmacological treatment, in case of amenable, circumscribed substrates, as antiarrhythmic drugs are often associated with negative inotropic and/or dromotropic effects [1].

Mechanical Support and Heart Transplantation

Heart or heart-lung transplantation, although limited by donor shortage, may also be considered a therapeutic option for end-stage HF [65]. The number of ACHD recipients worldwide has increased over the decades. ACHD patients listed tend to be younger with less cardiovascular comorbidities than non-ACHD ones considered for transplantation; however, they may have multiorgan involvement that requires combined organ transplantation. Whereas early post-transplantation mortality appears increased in ACHD, long-term prognosis is better in ACHD than in other cohorts [70].

Ventricular assist devices (VAD) can bridge patients to transplantation, increasing the probability of a successful transplantation with prolongation of waiting time. In selected patients, it may be also a destination therapy. However, ACHD patients are not often considered for VAD support because of the complexity of the anatomy, paucity of VAD programs focused on ACHD, and the need for surgeons with expertise in ACHD. A systemic RV morphology is not a contraindication for a VAD, although coarse trabeculation may merit special approach, since it may block the inflow cannula; in this case, selective myomectomy should be considered [71].

Conclusions

Right heart dysfunction is highly related with adverse clinical outcomes in CHD. Thorough evaluation and management of right heart disease are a challenging task. Research should focus on early identification of patients at risk for RV dysfunction in order to timely repair the responsible lesion to prevent RV failure. To this direction, noninvasive imaging modalities with new software applications may help to early detect subtle signs of maladaptive RV remodeling. Clinical trials for the development of medications and devices that improve RV function are also warranted. Close follow-up of CHD patients in expert centers is important for the prevention and management of RHD.

Funding AA was the recipient of the International Training and Research Fellowship EMAH Stiftung Karla Voellm, Krefeld, Germany, between 2020 and 2022.

Declarations

Conflict of Interest Alexandra Arvanitaki declares no conflict of interest. Gerhard Diller declares no conflict of interest. George Giannakoulas declares lecture/consultant fees from Bayer HealthCare, Janssen, Ferrer, MSD, GSK, Elpen Pharmaceuticals, and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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