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Right ventricular failure in congenital heart disease

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Abstract

Purpose of review—We aim to review select literature pertaining to congenital heart disease (CHD)-induced right ventricular (RV) function and failure.

Recent findings—We review recent findings pertaining to children and adults with repaired tetralogy of Fallot (rTOF), systemic RV and hypoplastic left heart syndrome (HLHS). We emphasize pathophysiological mechanisms contributing to RV dysfunction in these conditions, the risk factors for adverse outcomes and the continuing challenges in treating these patients. We discuss how recent pathology findings, as well as developments in imaging and computer modeling have broadened our understanding of the pathophysiology of these conditions. We further review developments in the molecular and cellular basis of RV failure; and in particular, the RV molecular response to stress in repaired tetralogy of Fallot (rTOF). We highlight some of the genetic complexities in HLHS and how these may influence the long-term outcomes in these patients.

Summary—Recent literature has led to new understandings in the pathology, pathophysiology, risk factors for adverse outcomes, molecular and genetic basis for RV dysfunction and failure in CHD. Although these findings provide new therapeutic targets, the treatment of RV failure at this time remains limited.

Keywords

congenital heart disease; hypoplastic left heart syndrome; repaired tetralogy of Fallot; right ventricle; right ventricular failure

INTRODUCTION

A testament to the progress made in cardiology and cardiac surgery is the extraordinary improvement in survival in patients with congenital heart disease (CHD) with a nearly 30% reduction in mortality from the 1980s to the early 2000s. This is mostly attributed to improved outcomes in infants with severe forms of CHD, such as right-sided obstructive

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Conflicts of interest

There are no conflicts of interest.

lesions and single ventricles and a resulting dramatic increase in adults living with repaired CHD, now representing 1.4 million individuals in the United States alone. These improved outcomes have led to an increasing number of infants, children and adults with heart failure. In particular, right ventricular (RV) failure is an important determinant of clinical status and outcomes in children and adults with various types of CHD [1]. The RV is at risk for failure from a variety of causes including reduced contractile function (e.g. arrhythmogenic right ventricular cardiomyopathy and Ebstein anomaly), increased pressure-loading (e.g. RV-pulmonary artery conduit stenosis after repair of truncus arteriosus or pulmonary atresia), increased volume-loading [e.g. pulmonary regurgitation after repair of tetralogy of Fallot (rTOF)], electromechanical dyssynchrony (i.e. incoordinate contraction between different segments of the ventricle) induced by right bundle branch block (e.g. rTOF), increased myocardial fibrosis (e.g. rTOF), abnormal coronary perfusion (e.g. pulmonary atresia with intact ventricular septum), restricted filling capacity (e.g. Fontan circulation), inefficient energy transfer between the ventricle and the vasculature coupling (e.g. Fontan circulation) and adverse interactions between the RV and left ventricle (LV) [e.g. hypoplastic left heart syndrome (HLHS)]. In many instances, the co-existence of multiple factors may lead to RV failure, such as in the systemic RV with tricuspid regurgitation. In this manuscript, we will review recent literature from several examples of key CHD as it pertains to RV function and failure in these lesions.

TETRALOGY OF FALLOT

Long-term RV dysfunction and failure is most relevant in rTOF; however, RV function after surgical repair is also pertinent. The presence of a transannular patch across the pulmonary annulus and the associated severe pulmonary regurgitation and RV outflow dysfunction, important long-term considerations, continue to be of interest. Annavajjhala *et al.* [2] serially reviewed echocardiograms in 42 children after surgery for TOF, finding, not surprisingly, that children with a transannular patch had more RV dilatation versus those without transannular patch at all time-points, although RV and LV strain, reflective of myocardial function and the myocardium changing shape and dimensions during the cardiac cycle by echocardiography, improved postoperatively in both groups. Interestingly, LV strain at the last follow-up echocardiogram was lower in patients with significant pulmonary regurgitation, consistent with adverse interactions between the RV and LV that have been reported in long-term rTOF survivors.

Pulmonary regurgitation and resultant RV dilatation have been emphasized for many years as risk factors for RV failure. An older age at pulmonary valve replacement and prepulmonary valve replacement RV hypertrophy and dysfunction have also been found to be predictive of a shorter time to postoperative death and sustained ventricular tachycardia [3]. However, overall, studies have not conclusively demonstrated that pulmonary valve replacement, which reduces pulmonary regurgitation and RV volumes has improved survival or the incidence of ventricular tachyarthymias [4]. Thus, other factors, such as increased RV fibrosis and RV electromechanical dyssynchrony likely contribute to RV failure. Using computer models in combination with analysis of observed clinical data in children, our group showed that increasing QRS duration from right bundle branch block, and the resulting RV mechanical delay, had greater impact on RV remodeling, RV global function

and exercise capacity as compared with the severity of pulmonary regurgitation [5]. Moreover, RV electromechanical dyssynchrony (i.e. incoordinate contraction between different RV segments that stems from right bundle branch block) is related to RV dilatation and dysfunction [6]. Consequently, acutely pacing the RV in rTOF to resynchronize its contraction improves mechanical efficiency and hemodynamics [7]. The question remains whether long-term resynchronization therapy is warranted or effective in this population; and when it should implemented. Likewise, pulmonary valve replacement itself may reduce QRS duration by electrocardiogram, thereby addressing RV failure through a narrowing of the QRS duration as well as reduction of pulmonary regurgitation [8]. Heng *et al.* [9] found that right heart volumes decrease immediately after pulmonary valve replacement, followed by continuing further reduction in RV end-systolic volumes. They concluded from their results that pulmonary valve replacement before the indexed RV end-systolic volume reaches 82ml/m^2 confers optimal chances to normalize RV function [9]. Our group's aforementioned study also demonstrated that, regardless of pulmonary regurgitation or right bundle branch block induced electro-mechanical dyssynchrony, intrinsic myocardial contractility (i.e. the intrinsic ability of the muscle to generate force independent of its loading conditions) is a key determinant of RV function and exercise capacity [5]. Unfortunately, myocardial contractility remains very difficult to determine in clinical practice. Increased RV myocardial fibrosis in rTOF may be responsible in part for reduced contractility as well as decreased compliance; and linked to RV remodeling and adverse outcomes [10]. Using histological assessment from RV myocardial biopsies taken at time of pulmonary valve replacement, Yamamura *et al.* [11] found that the severity of fibrosis was associated with increased RV end-systolic volumes, RV mass and right atrial area after pulmonary valve replacement, and a trend towards increased heart failure events. These parameters have been found to be risk factors for adverse outcomes in this population [12,13]. Focal scarring and biventricular diffuse fibrosis can be detected by cardiac magnetic resonance (CMR) imaging after TOF repair. Cochet *et al.* [10] found that scar size relates to systolic dysfunction, and diffuse fibrosis to RV dilatation; and that both relate to the occurrence of ventricular arrhythmias. Interestingly, this study found that shorter CMR Tl values (an imaging marker of diffuse fibrosis) after pulmonary valve replacement may suggest that diffuse fibrosis is reversible with therapy [10]. Patient-specific modeling of myocardial stiffness using CMR may be an interesting approach to evaluate the impact of increased RV fibrosis and decreased RV compliance in rTOF [14]. The link between electrical and mechanical abnormalities, and their association with fibrosis are important in the pathophysiology of rTOF and QRS fragmentation (notching) may be related to the degree of RV fibrosis and dysfunction and may predict mortality in this population [15,16].

SYSTEMIC RIGHT VENTRICLES

Failure of the systemic RV in patients who have undergone an atrial switch operation for transposition of the great arteries (TGA) or who have con-genitally corrected transposition continues to underlie increased morbidity and mortality in these populations [17,18]. However, although these groups are often analyzed together, imaging studies suggest that caution should be exercised when evaluating pooled analyses of systemic RV patients, given differences in myocardial contraction patterns, septal extracellular volume by CMR (a

surrogate for fibrosis), and the exercise response of TGA – Mustard/Senning versus corrected TGA patients [19]. The Mustard/Senning procedures create two baffles in the upper chambers of the heart, the atria, to direct systemic venous blood to the LV from which arises the pulmonary artery and pulmonary venous blood to the RV from which arises the aorta. Global RV function, assessed by ejection fraction and tricuspid annular systolic plane excursion, which are echocardiography measurements, have been found to be lower in TGA versus corrected TGA, with regional differences [20]. Interestingly in both these types of systemic RVs, no relation was found between echocardiographic or CMR-derived RV systolic function parameters at rest and peak oxygen uptake during exercise [21]. Therefore, exercise imaging may be warranted to evaluate whether RV function limits exercise capacity.

As for rTOF, several mechanisms can underlie failure of the systemic RV including myocardial fibrosis [22,23]. Interestingly, one study found that diffuse fibrosis as assessed by CMR was common in the LV, but not RV, in patients after an atrial switch procedure and a systemic RV [24]. Likewise, myocardial ischemia has long been suspected to account for a portion of sudden death and/ or ventricular arrhythmias in this population. Chaix *et al.* [24] recently provided histopathological evidence in support of myocardial ischemia as a cause of sudden death in this patient population in a cohort of 140 adults with a systemic RV. Intriguingly, the study found in two of five patients who underwent autopsy, acute massive myocardial infarction of the hypertrophied systemic RV, alongside chronic subendocardial ischemie lesions. These findings occurred in the presence of normal proximal coronary arteries. Another autopsy study in four adults who had undergone an atrial switch procedure in childhood, and who had lived more than 30 years, found that compared with the LV, the systemic RV was much thicker, the myofibers much larger, and either grossly visible or microscopic-sized scars were present in association with abnormalities of the RV intramural coronary arteries including numerous and large vessels with thick walls and often narrowed lumens [25].

Despite some progress in understanding the pathophysiology, the literature remains frustratingly unclear on the efficacy of heart failure therapy for the failing systemic RV. A recent American College of Cardiology/American Heart Association Task Force systematic review/clinical Practice Guideline found that after at least 3 months of treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or aldosterone antagonists, there was no statistically significant change in mean ejection fraction, ventricular dimensions, or peak ventilatory equivalent of oxygen [26]. A concerning finding of this systematic review was that the methodological quality of the majority of included studies was low, because of a lack of a randomized and controlled design, small sample size and incomplete follow-up [26]. Consequently, the systematic review could not provide conclusive evidence with regard to a beneficial effect of medical therapy in adults with systemic RV dysfunction and concluded that sufficiently powered randomized controlled trials or comparative-effectiveness studies are needed to elucidate the efficacy of ACE inhibitors, ARBs, beta blockers and aldosterone antagonists in patients with systemic RVs [26,27]. Given the lack of evidence for the efficacy of medical treatment, these patients may require heart transplantation or other therapies. However, pulmonary arterial hypertension has been found to be common in systemic RV patients referred for heart transplantation [28]. Although precapillary pulmonary hypertension may exist in these

patients, systemic RV dysfunction increases the risk for postcapillary pulmonary hypertension. Despite management with pulmonary vasodilators and afterload reduction, criteria for listing patients for combined heart and lung transplant versus heart transplant alone are unclear [28]. A bridge to transplantation with a ventricular assist device may be a feasible and relatively well tolerated option in these patients [29].

The presence of tricuspid regurgitation, as the systemic atrioventricular valve, continues to be an important risk factor for adverse outcomes. Tricuspid valve surgery can stabilize RV function and improve heart failure status as expressed by New York Heart Association functional class for several years [30]. However, mortality after surgery can be substantial, in part because of existing comorbidities [31]. The authors of a relatively small series of 26 patients concluded that patients with significant tricuspid regurgitationa should be referred early for surgery to improve outcomes [30]. In the general adult population, tricuspid valve repair seems to result in better survival compared with tricuspid valve replacement without increased risk of reoperation [31].

RV pacing is associated with RV dysfunction and mortality in patients with a systemic RV [32]. In a portion of patients with systemic RV failure, cardiac resynchronization therapy of the systemic RV may improve heart failure symptoms, although some patients have recurrence of RV dysfunction [33]. The optimal location for lead placement remains an unanswered question and is responsible for a substantial proportion of nonresponse to cardiac resynchronization therapy [34]. Endocardial mapping followed by a limited surgical incision has been suggested to optimize lead placement [34]. Of note, almost half of patients with a systemic RV may suffer from atrial or ventricular arrhythmias, often related to RV dysfunction [17,35]. Consequently, expert arrhythmia management in a center experienced in the management of adults with congenital heart disease is paramount [36].

HYPOPLASTIC LEFT HEART SYNDROME

Although an example of a systemic RV, the pathophysiology, course, management and considerations for HLHS differ from other types of systemic RVs. The high-incidence of complications and mortality in these patients extends beyond RV failure to include factors, such as prematurity, low birth weight and end-organ function [37]. Nonetheless, whether as a result of HLHS or not, RV versus LV morphology was found to be a significant risk factor for heart transplantation or death, predominantly because of RV failure [38]. Here we will relate to some of the recent literature pertaining to RV function as a cause of heart failure in these patients, and an important determinant of survival. Even early in the course, patients with decreased RV function and larger RV end-diastolic and systolic volumes after the Norwood operation were more likely to fail a cavopulmonary connection at stage 2 of palliation [39]. Conversely, infants with preserved RV function had a shorter hospital length of stay and duration of intubation. Similarly, our group found that during serial follow-up of infants with HLHS, echo measures of RV function, and especially RV dilatation, were related to death or need for heart transplant [40]. In this cohort, during follow-up, RV dilation, dysfunction, and tricuspid regurgitation improved in transplant-free survivors but worsened in those transplanted or who died. Indeed, RV function, as measured by cardiac output, even in the immediate postnatal period is associated with later death or transplant

[41]. Tricuspid regurgitation is a risk factor for adverse outcome; however, although tricuspid valve repair reduces tricuspid regurgitation in most HLHS patients, their outcomes are limited by the short durability of repair and recurrent tricuspid regurgitation in a third of patients [42]. Moreover, RV dysfunction in this high-risk group was progressive and a major determinant of transplant-free survival. Increased ventricular end-diastolic pressure from RV dysfunction is a known risk factor for morbidity and mortality in patients and the echo-Doppler systolic to diastolic duration ratio has been found to correlate with ventricular end-diastolic pressure in these patients [43].

A more direct assessment of RV myocardial function via echocardiography strain imaging may also be beneficial in assessment of HLHS. In a small study of 35 infants with HLHS during the first 6 months of life, RV strain analysis was found to identify at-risk HLHS infants with interstage strain values being worse in infants with HLHS who had a poor cardiac outcome as defined by cardiac death, heart transplantation or persistent moderate or greater RV dysfunction [44]. Similarly, when assessed before the bidirectional cavopulmonary anastomosis, children with good RV function by echocardiographic measures, such as RV fractional area change (a surrogate for ejection fraction) and RV strain had a low likelihood of death or heart transplantation [45]. In patients with normal RV fractional area change values, reduced strain may improve prediction of clinical outcomes. Over the longer term, patients with HLHS continue to have a high incidence of complications and they represent a minority, albeit a growing minority, of patients reaching adulthood with a Fontan circulation [46]. This high rate of cardiovascular complications may differentiate patients with HLHS from other CHD needing a Fontan operation, although other studies have suggested excellent survival in those reaching the Fontan procedure [47].

THE MOLECULAR AND CELLULAR BASIS OF RIGHT VENTRICULAR FAILURE

The high incidence of RV failure, the lack of improvement in long-term outcomes following pulmonary valve replacement and the lack of response to standard heart failure therapies have raised the questions ‘Is heart failure the same across the spectrum of age and precipitating causes?’ and ‘How much is inherently programmed into the ventricle itself?’ We will summarize some of the myocardial remodeling events seen with RV failure.

THE RIGHT VENTRICULAR MOLECULAR RESPONSE TO STRESS IN REPAIRED TETRALOGY OF FALLOT

We and others have shown fundamental differences in the mechanisms of RV versus LV failure [48]. Data from animal models of RV stress mimicking residual lesions after repair of TOF have shown extracellular matrix and cytoskeletal remodeling, upregulation of genes regulating reactive oxygen species production and downregulation of antioxidant protection, angiogenesis, energy production and mitochondrial function more so than that seen in the LV under stress [49]. Right ventricular volume and pressure overload demonstrate similar changes; however, pressure overload shows a more severe phenotype at the molecular level. These differences could impact the effectiveness of the drugs used to treat heart failure. In

preclinical models of RV pressure loading, treatment with losartan led to an improvement in fibrosis and cardiac hypertrophy [50]. The REDEFINE trial in adults with repaired TOF suggest that renin–angiotensin–aldosterone inhibition using losartan is not beneficial for patients with mild RV failure [51]. However, the findings from this study may suggest that once RV fibrosis has developed, as the molecular correlate of restrictive physiology, it cannot be reversed with angiotensin receptor blockers, but that institution of angiotensin receptor blockers prior to the development of fibrosis might be beneficial. It is also possible that longer term administration of angiotensin receptor blockers might be required to limit the slow progression of RV fibrosis in these patients.

THE COMPLEX GENETICS OF HYPOPLASTIC LEFT HEART SYNDROME MAY INFLUENCE LONG-TERM OUTCOMES

Liu *et al.* [52] performed a remarkable screen of more than 100 000 murine fetuses and isolated several single ventricle variants. Using mouse forward genetics, they reported the first isolation of HLHS mutant mice and identified genes causing HLHS. Network analysis revealed seven interconnected modules involved in disturbances of the cell cycle (KIFC3 and CDK1); muscle differentiation (TRIM63); mitochondrial and Notch signaling (STAT3, EGFR and EP300); EGF, Wnt and cadherin signaling (EGFR and CTNNB1); chromatin regulation (EP300); and cardiac hypertrophy (TRIM63, EGFR and SLC4A1), which could predispose the heart to early energy failure, vascular dysfunction and premature aging. This article forms the basis of our understanding of the inherent programmed biology of HLHS. Furthermore, disruption in NOTCH signaling in HLHS demonstrates disorganized myofibrillar network, decreased sarcomeric proteins, which may lead to contractile dysfunction and deficiency in nitric oxide signalling, which may lead to altered vascular responsiveness and endothelial senescence [53,54]. Indeed, the addition of Sildenafil to plasma from patients with HLHS and RV failure reversed pathologic cardiomyocyte remodeling [55].

CONCLUSION

In summary, these data point to the inherent predisposition of HLHS and perhaps other systemic RV and TOF to RV failure both contractile and vascular over and above that induced by a lifetime of volume and pressure loading. These data also pave the way for targeting novel pathways to improve ventricular function and vascular health.

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of special interest

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KEY POINTS

Several mechanisms including abnormal loading, electromechanical dyssynchrony, valvar abnormalities, coronary abnormalities and myocardial fibrosis contribute to progressive RV dysfunction in CHD.

Upregulation of genes regulating reactive oxygen species production, extracellular matrix and cytoskeletal remodeling and downregulation of antioxidant protection, angiogenesis, energy production and mitochondrial function are more prominent in the stressed RV versus LV.

Despite the discovery of new genetic and molecular mechanisms, specific medical therapies for RV failure remain lacking.