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Novel Insights and Treatment Strategies for Right Heart Failure

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Abstract

Purpose of Review The function of the right ventricle (RV) is intimately linked to its preload (systemic volume status) and afterload (pulmonary vasculature). In this review, we explore current knowledge in RV physiology, RV function assessment, causes of right heart failure (RHF), and specific treatment strategies for RHF.

Recent Findings We examine the evidence behind new pharmacological therapies available, such as macitentan and riociguat in the treatment of specific etiologies of RHF. We will also focus on RHF in the setting of heart failure with preserved ejection fraction (HFpEF) and in the presence of left ventricular assist devices (LVAD), looking at current treatment recommendations, including mechanical circulatory support. Lastly, we will look to the horizon for the latest research on RHF, including the molecular basis of RHF and potential novel treatment methods for this old yet poorly understood syndrome.

Summary Disturbances in this complex relationship result in the clinical syndrome of RHF. Despite advances in the management of left heart diseases, much work remains to be done to understand and manage RHF.

Keywords Right heart failure · Pulmonary arterial hypertension · Pulmonary venous hypertension · Right heart failure post-LVAD · Pulmonary vasodilator · Mechanical circulatory support

Introduction

The right heart has traditionally been less understood compared to the left heart, due to its more restricted role in systemic diseases. Cardiovascular research has largely been focused on the left heart, and effective treatment strategies have been developed for left heart diseases. As we prolong the lives of patients with left heart and systemic diseases, we start to realize that right heart failure (RHF) can often be a source of morbidity and even mortality in this group of patients. It is thus important for us to review what we know about the heart, in particular, the long neglected right heart.

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Right Heart Anatomy and Function

The right ventricle (RV) has a complex geometry, consisting of the inlet and the outlet portions, separated by the crista supraventricularis [1•]. It has a shared wall with the left ventricle (LV), the interventricular septum, and a RV free wall which attaches to the anterior and posterior septum. It receives systemic venous return via the right atrium and delivers deoxygenated blood into the pulmonary circulation. In a normal heart, the RV has roughly the same cardiac output as the LV but faces a lower afterload, due to the lower resistance of the pulmonary vasculature. As such, the RV wall is thinner and more compliant than the LV.

Pathophysiology of Right Heart Failure

The right heart is intimately related to the pulmonary vasculature. Pathological processes leading to an increased pulmonary vascular resistance (PVR) will at first result in a corresponding increase in RV muscular contractility. This adaptive mechanism is known as 'coupling' of the RV and its load [2]. This increased RV contractility is initially maintained by an increased RV wall muscular thickness. However, as the disease progresses, the RV cavity dilates and the heart rate increases to maintain cardiac output. Eventually with the

increased RV myocardial metabolic demands and increased RV wall stress, the RV decompensates and 'uncoupling' occurs [3]. At this point, right heart failure occurs, with the consequential signs and symptoms, namely effort intolerance, jugular venous distension, abdominal ascites, and edema in the lower extremities.

Methods of Assessing Right Heart Function

Assessment of RV function is challenging for a few reasons. Firstly, the unique crescent shape of the RV makes quantification of its size and function difficult. More importantly, RV function is highly load dependent. Changes in preload and afterload conditions of the RV will result in fluctuations in the measured RV function. As such, multimodality cardiovascular imaging is recommended for a comprehensive assessment [4].

Echocardiography, despite its limitations, remains the most commonly used modality for assessment of the RV. A comprehensive study of the RV should be performed in all clinical echocardiography studies [5]. Two-dimensional (2D) assessment of RV dimensions can aid in the prognostication of certain disease states, including idiopathic pulmonary arterial hypertension [6] and acute pulmonary embolism [7]. The estimation of ejection fraction of the RV, measured as fractional area change (FAC), can also be obtained from the echocardiogram. A decreased RV FAC has been shown as an independent predictor of death and cardiovascular events after myocardial infarction [8]. Tricuspid annular plane systolic excursion (TAPSE) can also be easily obtained from 2D echocardiogram, in combination with M-mode echocardiogram. A lower TAPSE is associated with higher mortality and need for emergency heart transplantation in patients with chronic heart failure with reduced ejection fraction (HFrEF) [9]. Besides 2D echocardiogram, Doppler-derived indices such as the RV myocardial performance index [10], dP/dT [11], and Doppler tissue imaging of the peak systolic tricuspid annular velocity [12] have been shown to provide prognostic information in patients with various cardiac conditions affecting the right heart.

Other imaging modalities are also important in the assessment of RV function. Computed tomographic (CT) assessment of the heart is particularly important in the assessment of the right heart in the setting of concomitant pulmonary pathology, such as pulmonary embolism (PE) [13, 14]. Cardiac magnetic resonance imaging (CMR), however, has emerged as the 'gold standard' modality for the evaluation of RV ejection fraction (EF) [4] and can prove a useful tool for prognostication [15]. CMR can also further characterize the RV myocardium and is useful in the diagnosis of conditions such as arrhythmogenic right ventricular cardiomyopathy (ARVC) [16].

Hemodynamic data have been used in RV function assessment. The ratio of right atrial pressure and pulmonary capillary wedge pressure, as well as the pulmonary artery pulsatility index (PAPi), has been used to describe RHF after LV assist device (LVAD) implantation and acute myocardial infarction [17–20]. RV stroke work index (RVSWI) has been found to be useful in predicting RV failure after LVAD implantation [17]. Pulmonary artery compliance was described as a strong predictor of RV failure and adverse outcomes in chronic heart failure [21]. Table 1 summarizes the common indices used.

Causes of Right Heart Failure

The causes of right heart failure are varied. RV mechanics and function can be altered in states of pressure or volume overload. It can also be caused by RV myocardial contractile failure [23]. These causes are summarized in Table 2.

An important cause of right heart failure is chronic RV pressure overload from pulmonary hypertension. The etiologies of pulmonary hypertension are varied and often represent end-stage remodeling of the pulmonary vasculature in various cardiac and pulmonary diseases. The 2015 ESC/ERS guideline has classified pulmonary hypertension into five groups according to etiology, as detailed in Table 3 [27].

Clinical Manifestations of Right Heart Failure

Clinical manifestations of RHF can be related to systemic congestion and low cardiac output state [28•]. Signs of systemic congestion include jugular venous distension, positive hepatojugular reflux, generalized edema, and hepato-splenomegaly. In the event of RV failure compromising cardiac output, signs of low output will include hypotension, tachycardia, cool extremities, altered mentation, and oliguria.

It has been shown that the abdominal compartment plays an important role in the disease progression of congestive heart failure [29]. Saturation of the splanchnic circulation and lymphatic efflux system with back pressure from the failing RV causes a disruption in intravascular fluid dynamics. The resultant fluid shift presents as interstitial edema and ascites. This increases the intra-abdominal pressure and is related to the development of cardiorenal syndrome [30].

Biochemical derangements are often seen in RHF. This is related to both systemic congestion and compromised cardiac output. Systemic congestion often manifests as hepatic and renal insufficiency. Blood tests will reveal elevated transaminases, abnormal coagulation profile, increased blood urea nitrogen, and elevated creatinine. Cardiac specific biomarkers such as the natriuretic peptide and troponin levels will be elevated as a result of RV myocardial stress. Serum lactate will also be elevated due to systemic tissue hypoperfusion

Table 1 Indices and formulas used in defining right heart dysfunction

Imaging indices		
2DE fractional area change (FAC), %	(RV end-diastolic area − RV end-systolic area) / RV end-diastolic area × 100	< 35 [5, 8]
Tricuspid annular plane systolic excursion (TAPSE), cm		< 1.7 [5, 9]
RV myocardial performance index (pulse Doppler)	(TCO − ET) / ET	> 0.43 [5]
RV myocardial performance index (tissue Doppler)	(IVRT + IVCT) / ET	> 0.54 [5]
Rate of RV pressure rise (dP/dT), mmHg/s	Time taken for TR velocity to increase from 1 m/s to 2 m/s	< 400 [11]
Tissue pulsed Doppler S wave (RV S′), cm/s		< 9.5 [5]
CMR derived ejection fraction, %		< 52 (men) < 51 (women) [22]
Hemodynamic indices		
Cardiac filling pressures	RAP / PCWP	> 0.63 (RHF after LVAD) [17] > 0.86 (RHF after LVAD) [18]
Pulmonary artery pulsatility index (PAPi)	(PASP − PADP) / RAP	< 1.85 (RHF after LVAD) [19] ≤ 0.9 (RHF in acute MI) [20]
RV stroke work index, mmHg mL m^{-2}	(mPAP − RAP) × SVI	< 300 [17]
Pulmonary artery compliance, mL/mmHg	SV / (PASP − PADP)	< 2.5 (RHF in chronic heart failure) [21]

2DE 2-dimensional echocardiography, *TCO* tricuspid valve closure-to-opening time, *ET* ejection time, *IVRT* isovolumic relaxation time, *IVCT* isovolumic contraction time, *TR* tricuspid regurgitation, *CMR* cardiac magnetic resonance imaging, *RAP* right atrial pressure, *PCWP* pulmonary capillary wedge pressure, *PASP* pulmonary artery systolic pressure, *PADP* pulmonary artery diastolic pressure, *mPAP* mean pulmonary arterial pressure, *SVI* stroke volume index

secondary to reduced cardiac output. Anemia is seen in up to a third of patients with chronic heart failure. It is often associated with iron deficiency as well as resistance to the endogenous hormone erythropoietin [31, 32].

Table 2 Causes of right heart failure

1. Primary RV myocardial dysfunction
   - RV myocardial ischemia/infarction
     1. Coronary thrombosis [24]
     2. Iatrogenic
        Postcoronary intervention [25]
        Postcardiac surgery
   - Myocarditis
   - Arrhythmogenic right ventricular cardiomyopathy (ARVC) [26]
2. Volume overload
   - Right-sided valvular insufficiency
     1. Tricuspid valve regurgitation
     2. Pulmonary valve regurgitation
   - Increased venous return and septal shift toward LV following LVAD placement
   - Congenital heart diseases
     1. Atrial septal defect
     2. Ebstein's anomaly
2. Pressure overload
   - Pulmonary hypertension
   - Acute LV failure
   - Pulmonary embolism
   - Acute lung injury/hypoxia
   - RV outflow tract (RVOT) obstruction
     1. Pulmonary valve stenosis
     2. Congenital defects (pulmonary atresia, tetralogy of Fallot)

Specific Etiologies and Novel Management Strategies

Right Heart Failure Secondary to Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH), or precapillary pulmonary hypertension, is a disease of the pulmonary vasculature. Chronic increase in pulmonary pressure results in RV pressure overload. Symptoms and mortality of idiopathic PAH have been shown to be closely related to the ability of the RV to adapt to the elevated pulmonary pressures [33, 34]. The key for management of PAH is thus the reduction of RV afterload.

Many classes of drugs have been shown to be beneficial in the treatment of PAH. In patients demonstrating vasoreactivity on cardiac catheterization, high-dose calcium channel blockers should be initiated [35]. Prostaglandin analogues such as iloprost and treprostinil have been shown to improve exercise tolerance and symptoms [36, 37], while epoprostenol was able to confer survival benefit in severe disease, according to one study [38]. Phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil and tadalafil have been shown to also improve symptoms and hemodynamic parameters of patients with PAH [39, 40].

Endothelin receptor antagonists (ERA) such as bosentan and ambrisentan have been previously shown to improve exercise capacity and hemodynamics [41–43]. The more recent SERAPHIN trial, studying macitentan in 250 patients with symptomatic PAH, incorporated for the first time clinical

Table 3 Classification of pulmonary hypertension

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic
   - 1.2 Heritable
     - 1.2.1 Bone morphogenetic protein receptor, type 2 (BMPR2) mutation
     - 1.2.2 Other mutations
   - 1.3 Drugs and toxins induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 Human immunodeficiency virus (HIV infection)
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   - 1′.1 Idiopathic
   - 1′.2 Heritable
     - 1′.2.1 Eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) mutation
     - 1′.2.2 Other mutations
   - 1′.3 Drugs, toxins and radiation induced
   - 1′.4 Associated with:
     - 1′.4.1 Connective tissue disease
     - 1′.4.2 Human immunodeficiency virus (HIV) infection

1″. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   - 2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
   - 4.1 Chronic thromboembolic pulmonary hypertension
   - 4.2 Other pulmonary artery obstructions
     - 4.2.1 Angiosarcoma
     - 4.2.2 Other intravascular tumors
     - 4.2.3 Arteritis
     - 4.2.4 Congenital pulmonary arteries stenosis
     - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   - 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

events as primary endpoints. It showed a reduced risk of a composite mortality and morbidity endpoint in the treatment arms compared to placebo. This was largely driven by reduced clinical worsening and was regardless of whether the patient was previously on therapy [44].

Newer classes of medications include the soluble guanylate cyclase (sGC) stimulator, riociguat. Similar to PDE-5 inhibitors, it works on the same nitric oxide-cyclic guanosine monophosphate (cGMP) pathway. Riociguat sensitizes and stimulates the nitric oxide-sGC-cGMP pathway, which leads to increased generation of cGMP and subsequent vasodilation. The recent randomized PATENT-1 study of 443 patients with PAH showed an improvement in exercise capacity, PVR, NT-proBNP levels, and time to clinical worsening in the riociguat treatment group [45].

Selexipag, the first selective oral prostacyclin IP receptor agonist, represents a new therapeutic class of drug. In the GRIPHON study, the selexipag group had a lower risk of the primary composite outcome of death or complications related to PAH, compared to the placebo group. This was mainly driven by reduced hospitalization and disease progression [46].

Beyond the choice of drugs, an important question in the drug treatment of PAH would be the strategy of initiating treatment. Studies have examined the advantage of upfront combination therapy. A small study of 23 patients with severe symptomatic PAH who were started upfront on epoprostenol and bosentan showed benefits in symptom and hemodynamic outcomes compared to those initiated on epoprostenol monotherapy [47]. Another group of 18 patients with severe PAH were started on upfront triple therapy of epoprostenol, bosentan, and sildenafil. All patients were alive at 3 years and showed sustained clinical and hemodynamic improvement [48]. The randomized prospective AMBITION trial compared initial combination of ambrisentan plus bosentan versus initial monotherapy with either ambrisentan or bosentan. The upfront combination group had a lower risk of clinical failure events compared to the initial monotherapy groups [49].

Current guidelines recommend risk stratifying by functional class. Low- and intermediate-risk patients can start with upfront combination therapy or initial monotherapy with sequential combination if necessary. For high-risk patients, upfront combination therapy is recommended [27]. Treatment should be goal oriented in order to achieve low-risk status for the patient.

Right Heart Failure in Congenital Heart Disease

With advancement in cardiac imaging and surgical management, we are seeing more adults living with congenital heart diseases, who may or may not have undergone surgical repair of the congenital defect. A main cause of morbidity and

mortality in this group of patients is the development of pulmonary arterial hypertension and subsequent right heart failure. Routine surveillance and timely surgical treatment remains the key in management [50].

Adult patients with unrepaired congenital heart diseases usually have simple shunts, deemed not necessary for repair in childhood, or only diagnosed as adults. They include atrial septal defects (ASD), ventricular septal defects (VSD), and patent ductus ateriosus (PDA). The left to right shunt of an ASD results in RV volume overload, and it has been recommended that ASD closure should be performed when signs of RV volume overload are present on imaging, regardless of symptoms [50, 51]. On the other hand, LV volume overload occurs in the presence of significant shunt through a VSD or PDA. Closure of VSD or PDA is indicated in the presence of symptoms, or with evidence of LV volume overload on imaging.

Chronic, significant shunting of blood through the above congenital defects results in pulmonary vasculature remodeling and PAH, with eventual shunt reversal. The patient develops progressive RHF and cyanosis, termed the Eisenmenger syndrome [52]. Patients with Eisenmenger syndrome are no longer eligible for defect closure, and medical therapy will be the mainstay of treatment. A single randomized-controlled trial compared bosentan against placebo in 54 Eisenmenger syndrome patients with World Health Organization (WHO) functional class III symptoms (BREATH-5 trial). There were improvements in 6-min walk distance and hemodynamic parameters in the bosentan arm over a 16-week treatment period [53]. An open-label extension of the BREATH-5 trial showed sustained improvement up to 40 weeks [54]. Other observational studies also showed improvements in functional capacity with the use of tadalafil and ambrisentan [55, 56]. Lastly, long-term epoprostenol use was reported in 20 patients with PAH associated with congenital heart diseases. There were improvements in functional status and hemodynamic parameters, though significant infusion line-related complications were encountered [57].

In patients with previously repaired complex congenital heart disease, regular surveillance of RV function is an important aspect of management. Tetralogy of Fallot (ToF) is the commonest cyanotic congenital heart disease [58]. In adult patients presenting with previously repaired ToF, abnormalities frequently encountered include pulmonary valve regurgitation, tricuspid regurgitation, residual atrial and/or ventricular septal defects, right ventricular outflow tract (RVOT) obstruction, and RVOT aneurysms [59]. They result in RV volume and/or pressure overload. If left uncorrected, this will lead to eventual RHF, a main cause of mortality and morbidity in this group of patients who otherwise have good postsurgical prognosis. It is currently recommended that patients with repaired ToF be assessed regularly with echocardiography or CMR for RV dysfunction at 2 to 3 yearly intervals [60]. Patients with evidence of RV dilation or decreased RV ejection fraction will warrant more frequent follow-up imaging.

Right Heart Failure Secondary to Left Heart Disease

Left heart disease is a very common cause of pulmonary hypertension and right heart failure. It has been shown that right heart failure is a highly reliable predictor of mortality and morbidity in patients with chronic heart failure [61, 62]. We are now only starting to understand the complex mechanism of how left heart disease affects the right heart. Chronic pulmonary congestion from left heart disease leads to morphological changes to the pulmonary vasculature, including muscularization of the pulmonary venules and intimal hypertrophy of the pulmonary arteries [63]. This results in pulmonary venous hypertension, which increases afterload for the RV. It also triggers multiple neurohormonal and molecular pathways, which eventually lead to RV modeling and subsequent failure [64]. Other important contributing factors include decreased RV coronary perfusion from poor LV function, ventricular interdependence due to septal dysfunction, and impairment of RV diastolic function due to LV dilation in a limited pericardial compartment [1•].

The current most important clinical classification of left heart failure would be based on LVEF. Stratifying heart failure into two distinct phenotypes of HFrEF and heart failure with preserved ejection fraction (HFpEF) allows us to examine the effect of RV dysfunction on each phenotype and vice versa.

Heart Failure with Reduced Ejection Fraction

In patients with HFrEF, it has been shown that decreased RV function is a strong predictor for morbidity and mortality [65, 66]. Although evidence-based medications (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone antagonists, beta-adrenergic blockers, and more recently, angiotensin receptor-neprilysin inhibitors) and implantable devices (defibrillators, resynchronization therapy) have long been associated with improved symptoms and decreased mortality [67], the effects of these treatment strategies on the RV remain inconclusive. Although two older studies demonstrated beneficial effects of captopril and carvedilol on RV function in heart failure patients [68, 69], long-term data on clinical effects of medication in this group of patients remains scarce.

The current recommendation for treatment of right heart failure in HFrEF remains closely tied to the treatment of left heart disease. Evidence-based medications and devices should always be used as part of the treatment strategy. The maintenance of euvolemia and reducing pulmonary venous hypertension are the key in right heart preservation [70].

Heart Failure with Preserved Ejection Fraction

Increasingly, we are seeing more patients with heart failure presenting with a normal ejection fraction, a clinical syndrome termed HFpEF. This syndrome is a complex interplay between endothelial dysfunction, inflammation, prohypertrophy signaling pathways, and comorbidities, resulting in diastolic dysfunction. The eventual outcome will be that of a clinical syndrome of heart failure, despite a preserved EF [71]. In a meta-analysis, RV dysfunction as measured using a variety of echocardiographic or invasive hemodynamic parameters is highly prevalent in the HFpEF population. The presence of RV dysfunction confers poor outcome in HFpEF patients, much like what was seen in the HFrEF cohort [72]. Melenovsky et al. found RV dysfunction to be the strongest predictor of death in a small HFpEF cohort, in a separate study [73].

With current evidence suggesting the importance of RV function in determining the outcomes of HFpEF patients, addressing RV dysfunction is logically the key in modifying the trajectory of the disease. Treatment strategies studied so far have targeted either the pulmonary vasculature in an attempt to reduce pulmonary hypertension or directly at the RV myocardium to improve contractility [64]. Results from trials using sildenafil to target the nitric oxide-cGMP pathway have largely been negative [74, 75]. However, a more recent phase 2 SOCRATES-PRESERVED trial studying the sGC stimulator vericiguat showed encouraging results at 12 weeks, in improving quality of life compared to placebo [76].

Strategies targeting the myocardium have largely studied the effects of neurohormonal inhibition pathways, namely the autonomic nervous system/adrenergic pathway and the renin-angiotensin-aldosterone (RAAS) system. A follow-up study of the SENIORS trial suggests that the beta-adrenergic blocker nebivolol might be effective in reducing all-cause mortality or cardiovascular hospitalization in its cohort of patients with LVEF > 35% [77]. However, studies on RASS blockage on HFpEF patients have so far proved inconclusive. In the CHARM-Preserved trial, candesartan appeared to reduced hospitalization compared to placebo, but irbesartan did not perform better than placebo in preventing death or cardiovascular events in the I-PRESERVE trial [78, 79]. In the more recent TOPCAT trial, spironolactone also did not reduce death, cardiac arrest, and HF hospitalization compared to placebo [80].

In the setting of acute decompensated HFpEF, two recent studies examined the utility of dopamine. In the ROSE-AHF study, a post hoc analysis suggested reduced efficacy of diuresis with low dopamine compared to placebo in the HFpEF population. There was also a suggestion of worse long-term outcome in the dopamine group, with significantly more deaths at 180 days and a higher incidence of death or HF rehospitalization at 60 days [81]. In the ROPA-DOP study, low-dose dopamine was studied against intermittent bolus and continuous infusion furosemide in decompensated HFpEF. In contrast to the ROSE-AHF HFpEF cohort, low-dose dopamine in conjunction with continuous infusion furosemide in this study enhanced the volume of diuresis significantly [82]. The verdict on dopamine in this setting remains open.

To date, guidelines do not recommend any specific treatment for RHF in HFpEF. Volume optimization remains the key in management of this group of patients.

Right Heart Failure Secondary to Pulmonary Disease

Chronic lung disease/chronic hypoxemia causes vasoconstriction of the pulmonary vasculature and remodeling of the pulmonary circulation. These result in pulmonary hypertension and eventual RHF, a syndrome described as ‘cor pulmonale.’ Management of patients with RHF secondary to pulmonary diseases would thus be focused on managing underlying lung disorder and domiciliary oxygen as appropriate [27].

Right Heart Failure Secondary to Chronic Thromboembolic Pulmonary Disease

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by obstructive remodeling of the pulmonary arteries as a result of major vessel thromboembolism. This causes increased afterload for the right heart and eventually leads to signs and symptoms of RHF. Surgical treatment with pulmonary artery endarterectomy is the treatment of choice for eligible patients [83]. Previous published data showed significant improvement of symptoms and hemodynamics following surgery [84]. In patients not eligible for surgery, percutaneous balloon angioplasty is potentially useful, based on nonrandomized, observational data [85].

With regards to medical treatment, a recent study examined the use of riociguat in patients with inoperable CTEPH or recurrent CTEPH after pulmonary artery endarterectomy. Riociguat was shown to improve exercise capacity and PVR as compared to placebo [86]. It has since been incorporated into the guidelines as a class I recommendation for patients with CTEPH who are deemed inoperable or who have recurrent disease after surgery [27].

Right Heart Failure Following Left Ventricular Assist Device Implant

With the expanding indications for LVAD and increasing expertise in LVAD surgery/management, we are seeing an exponential number of patients undergoing LVAD implantation in recent years [87]. RHF post-LVAD implantation is not uncommon. With this delicate population growing, management of RHF post-LVAD implant is an important area that requires additional attention.

Prior to LVAD implantation, patients with advanced heart failure are often faced with pulmonary hypertension (venous

or mixed pattern) and a certain degree of RV dysfunction. The stress of LVAD surgery can thus easily disrupt the delicate RV and pulmonary vasculature afterload coupling. Together with increased systemic venous return and/or excessive leftward shift of the interventricular septum, the RV can decompensate and fail (Fig. 1). Despite multiple risk stratification models and risk scores predicting RHF post-LVAD, this syndrome still complicates around 10–40% of all LVAD implants [88, 89].

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has defined RHF post-LVAD as elevated central venous pressure and resultant end-organ manifestation, as summarized in Table 4 [90].

Management of RHF post-LVAD implantation should be approached with a multipronged strategy. Preventive measures should be undertaken prior to and during LVAD surgery. Before the surgery, patients should have meticulous volume optimization through diuresis or ultrafiltration to lower CVP [91]. Intraoperatively, strategies such as minimizing transfusion and cardiopulmonary bypass times have been suggested to reduce the incidence or post-LVAD RHF [88, 92].

Postoperatively, RHF is associated with poorer outcomes and increased risks of complications [17, 93]. It should be promptly recognized and treated aggressively. Once diagnosed with RHF, inotropes such as milrinone or dobutamine should be considered [88, 91, 94].

The effects of postoperative inhaled pulmonary vasodilators have also been investigated [95]. Studies on nitric oxide in patients with pulmonary hypertension implanted with older pulsatile devices showed reduction in pulmonary arterial pressures and improved LVAD flows compared to placebo [96]. In a more recent study on patients with elevated PVR, there was a trend toward lower RHF rates in the nitric oxide-treated group [97]. With regards to inhaled prostaglandins, a retrospective study looking at a cohort of patients receiving HeartMate II LVADs, inhaled epoprostenol was found to be associated with decreased pulmonary arterial pressures but increased bleeding risks [98]. The use of inhaled iloprost, in conjunction with other vasodilators post-LVAD, was also reported to be associated with lower incidence of RHF [99].

Lastly, inhaled milrinone has been studied as well. It has been shown to reduce mean pulmonary arterial pressures from baseline, with no patients requiring right ventricular assist devices in the study cohort [100]. Patients failing medical therapy should then be considered for mechanical support.

Acute Right Heart Failure: Insights and Management

Medical Treatment of Acute Right Heart Failure

The RV myocardium does not cope with rapid changes in preload or afterload well. Sudden change in RV loading conditions or sudden impairment of RV myocardial contractility can tip the patient into a syndrome of acute RHF. As the RV acutely decompensates, the RV cavity dilates. This causes worsening of TR, leftward septal shift, and compression of the LV cavity within a nonpliable pericardium [28•]. The overall result is impaired LV loading and decreased LV stroke volume. Common causes include acute RV infarction, acute pulmonary embolism, exacerbation of pulmonary hypertension, acute LV failure, and postcardiac surgery. The first step in the management of acute RHF involves addressing any reversible, precipitating insult to the right heart, such as coronary intervention for RV myocardial infarction. Subsequent management strategies will involve optimization of RV preload and afterload, as well as augmenting RV contractility as necessary [23].

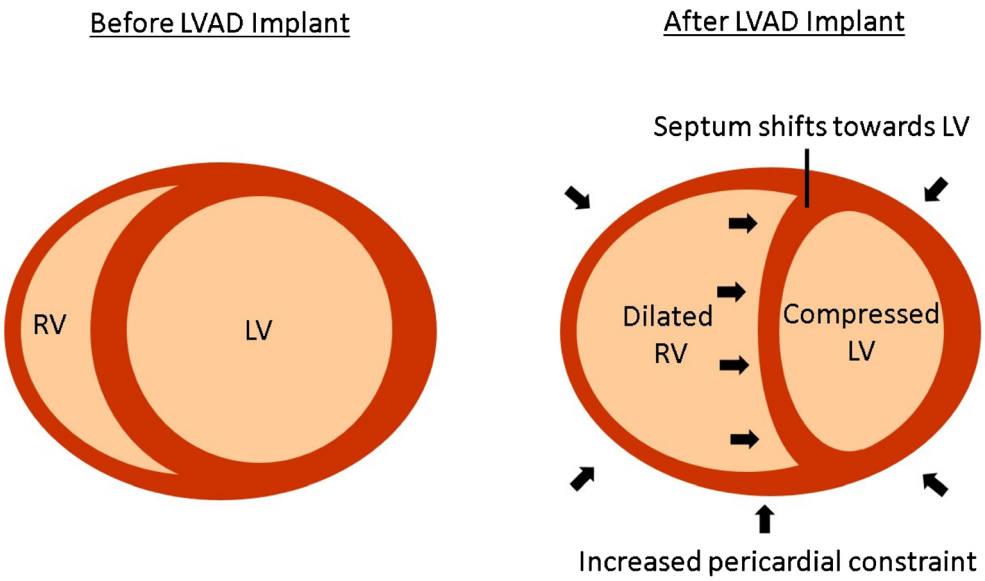

Fig. 1 Increased venous return into the RV after LVAD implant causes RV dilatation and septal-shift toward the LV. The combination of RV volume overload and decreased LV preload results in congestion and systemic hypotension

Table 4 INTERMACS definition of RHF post-LVAD

Definition

Symptoms or finding of persistent right ventricular failure characterized by both of the following:
- Documentation of elevated central venous pressure (CVP) by
  - Direct measurement (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg
  - Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography
  - Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient
- Manifestations of elevated central venous pressure characterized by
  - Clinical findings of peripheral edema (≥ 2+ either new or unresolved)
  - Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging
  - Laboratory evidence of worsening hepatic (total bilirubin > 2.0) or renal dysfunction (creatinine > 2.0)

Severity

Mild
- Patient meets both criteria for RHF plus
- Postimplant inotropes, inhaled nitric oxide, or intravenous vasodilators not continued beyond postop day 7 following VAD implant
  AND
- No inotropes continued beyond postop day 7 following VAD implant

Moderate
- Patient meets both criteria for RHF plus
- Postimplant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond postop day 7 and up to postop day 14 following VAD implant

Severe
- Patient meets both criteria for RHF plus
  - Central venous pressure or right atrial pressure greater than 16 mmHg
    AND
  - Prolonged postimplant inotropes, inhaled nitric oxide, or intravenous vasodilators continued beyond postop day 14 following VAD implant

Severe acute
- Patient meets both criteria for RHF plus
  - Central venous pressure or right atrial pressure greater than 16 mmHg
    AND
  - Need for right ventricular assist device at any time following VAD implant
    OR
  - Death during VAD implants hospitalization with RHF as the primary cause

Medical therapy for RHF starts with preload optimization. Invasive hemodynamic monitoring with a central venous or pulmonary artery catheter should be considered [28•]. Volume challenge with a crystalloid should be given in patients with a CVP < 10 mmHg [101]. However, care must be taken in fluid resuscitation to avoid overdistension of the RV, which might paradoxically result in LV compression and decreased systolic blood pressure. In a volume overloaded patient with CVP > 12–15 mmHg, diuretic therapy should be initiated [102].

In patients with persistent hemodynamic instability despite optimization of loading condition, inotropes and vasopressors are next in line. Commonly used inotropic agents in acute heart failure include dobutamine and milrinone. Dobutamine is an adrenergic inotrope which works by augmenting myocardial contractility, thus improving stroke volume and cardiac output. Milrinone, on the other hand, is a phosphodiesterase 3 inhibitor which increases cardiac contractility and, at the same time, decreases PVR [103, 104]. Both agents have potential side effects of hypotension and arrhythmogenicity. Concomitant use of a vasopressor is indicated in the event of systemic hypotension while on dobutamine or milrinone, to maintain end-organ perfusion pressure [23, 28•].

Mechanical Circulatory Support in Acute Right Heart Failure

In patients with refractory cardiogenic shock secondary to RHF despite maximal medical therapy, several options for mechanical circulatory support (MCS) are currently available. They can either be used as a bridge to RV recovery or to a definitive therapy, such as a heart transplant.

Extracorporeal membrane oxygenation (ECMO) has been the mainstay MCS for cardiogenic shock. In the veno-arterial (VA) configuration, it provides both pulmonary and circulatory support for biventricular heart failure [105]. However, this is more support than necessary for isolated RHF. Instead, a Rotaflow centrifugal pump (Marquet, Wayne, NJ) can be used in a pure RV assist device (RVAD) configuration, with the cannulation outflow at the femoral vein or the right atrium and inflow into the pulmonary artery via a surgical graft. The main advantage of this system is the low cost involved. However, insertion requires a sternotomy and the circuit can only provide support for 5 to 7 days. It has been used successfully as a bridge to RV recovery in a series of post-LVAD patients requiring mechanical RV support [106].

Longer duration of support can be provided by the CentriMag magnetically levitated pump (St Jude, Minneapolis, MN). Similar to the Rotaflow-ECMO circuit, the femoral venous or right atrial cannula provides the outflow for the CentriMag pump, while the inflow cannula is inserted into the pulmonary artery via a sternotomy. It can provide RV support for up to 4 weeks and has been successfully used in patients after cardiac surgery or myocardial infarction [107, 108]. As with the Rotaflow-ECMO, an oxygenator module can be added to the RVAD circuit for additional pulmonary support in the event of respiratory failure.

More recently, the Impella RP catheter-based, micro-axial pump (Abiomed, Danvers, MA) is available as a single catheter, percutaneous RVAD system. Inserted through the femoral vein under fluoroscopic guidance, it provides a direct RV bypass, drawing blood from the inferior vena cava and ejecting it into the pulmonary artery. In the RECOVER-RIGHT observational cohort, the Impella RP had comparable survival rates to a historic cohort of patients receiving the CentriMag RVAD system [109]. Table 5 summarizes the characteristics of the different MCS options available for the management of acute RHF.

Molecular Basis of Right Heart Failure and Novel Treatment Strategies

With the advances in molecular biology, we are also beginning to understand RHF at a subcellular level. Studies have revealed possible pathways involved in RHF [111]. Differences between the LV and RV in regulating energy production, mitochondrial function, reactive oxygen species (ROS) production, antioxidant protection, and angiogenesis could account for the different trajectories observed between LV and RV under stress, providing potential targets for the treatment of RHF [111, 112].

Dysregulation of Energy Production

In a pressure overloaded RV, the shift to glycolysis from free fatty acids for energy production occurs earlier than in the LV [110]. This shift is beneficial as less oxygen is required for adenosine triphosphate (ATP) production. However, as disease progresses, a steady decline in utilization of both free fatty acids and glucose is observed [113].

Metabolic modulating therapeutics aimed at increasing glucose utilization have been tested in animal models of pulmonary hypertension and in human clinical trials of LV failure/pulmonary hypertension-induced RHF, with varying success [114]. Trimetazidine, aside from metabolic modulating function, also inhibits cardiac fibrosis via reduction of collagen accumulation and reduced connective tissue growth factor (CTGF) expression [114]. Ranolazine, by inhibiting late inward sodium channels, may reduce contractile and electrophysiological disturbances, thus reducing myocardial oxygen consumption [114, 115]. In a small study, perhexiline improved peak oxygen consumption (VO_2 max), LV ejection fraction, symptoms, resting and peak stress myocardial function, and skeletal mass energetics [116].

Mitochondrial Dysfunction/ROS and Antioxidant Protection

Cardiac mitochondria are responsible for supplying energy to the heart. Factors affecting this process result in reduced energy to a failing RV. Mitochondrial membrane potential is normally lower in the RV compared to normal LV. However, in RV hypertrophy, membrane potential increases and becomes more hyperpolarized [117]. Inhibition of hyperpolarization has been shown to increase inotropy in the hypertrophied heart and might prove a potential area of therapy.

Mitochondrial biogenesis disruption has also been proposed [118]. Rosca et al. observed a decline in mitochondrial biogenesis in a decompensated heart failure state, but this was preserved in a compensated state [119].

Closely linked to mitochondrial function is the production of ROS. Increased ROS production is expected when the ventricles are subjected to afterload stress. Oxidative stress on the RV is made worse by the lack of antioxidant activity in the RV early in the disease process. Unlike the LV, antioxidant enzymes are not activated during the initial compensated stage which predisposes RV to increased ROS-related damage and apoptosis [120].

Elamipretide, a water-soluble tetrapeptide, stabilizes cardiolipin and selectively targets the electron transport chain to improve the efficiency of electron transport and restore

Table 5 Right ventricular assist devices

	Rotaflow ECMO	CentriMag	Impella RP
Outflow	Femoral vein/right atrium	Femoral vein/right atrium	Single catheter
Inflow	Pulmonary artery	Pulmonary artery	Single catheter
Insertion	Sternotomy	Sternotomy	Percutaneous
Maximum support	10 L/min	10 L/min	4 L/min
Duration of support	5–7 days	4 weeks	14 days

cellular bioenergetics [121]. Animal studies suggest that elamipretide is able to restore depleted cardiolipin in the mitochondria and decreases intracellular ROS by reducing production and assist in clearing excess ROS [122, 123].

Defective Angiogenesis

Tissue hypoxia is a potent stimulator of angiogenesis, mediated by hypoxia-induced factors (HIF) and vascular endothelial growth factor (VEGF) [124]. It has been observed in animal models that uncoupling of VEGF signaling and angiogenesis occurs in RV hypertrophy, resulting in lower capillary density in the myocardium [125]. This results in chronic ischemia of the RV wall, which eventually leads to fibrosis of the RV myocardium and eventual RHF [126]. This finding was also reported in a human autopsy study, where patients with HFpEF were found to have decreased microvascular density and increased myocardial fibrosis compared to controls [127]. Several strategies to enhance myocardial angiogenesis with different candidate angiogenic factors have been studied. However, the right combination of growth factors and optimal delivery method has yet to be determined [128].

Conclusion

Despite advances in modern science and medicine, we are only beginning to understand the complex syndrome of RHF. The RV is certainly very different from the LV, and many medications which are beneficial in LV failure have little, if any, effect in patients with RHF. Fortunately, with increased awareness of this condition, drugs and new treatment strategies are now starting to emerge, targeting the different causes of RHF. In addition, with the advent of molecular medicine, we are starting to gain new insights about the subcellular/molecular mechanisms of RV failure. Much effort is now focused on novel treatment strategies targeting these newly discovered mechanisms of RV failure, with the hope of developing effective therapies in the future for the treatment of RHF.

Compliance with Ethical Standards

Conflict of Interest Weiqin Lin and Ai-Ling Poh declare that they have no conflicts of interest. W.H. Wilson Tang reports personal fees from The Advisory Board Company, personal fees from Springer, and grants from the National Institutes of Health, outside the submitted work.

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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