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Right ventricular failure in left heart disease: from pathophysiology to clinical manifestations and prognosis

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Abstract

Right heart failure (RHF) is a clinical syndrome in which symptoms and signs are caused by dysfunction and/or overload of the right heart structures, predominantly the right ventricle (RV), resulting in systemic venous hypertension, peripheral oedema and finally, the impaired ability of the right heart to provide tissue perfusion. Pathogenesis of RHF includes the incompetence of the right heart to maintain systemic venous pressure sufficiently low to guarantee an optimal venous return and to preserve renal function. Virtually, all myocardial diseases involving the left heart may be responsible for RHF. This may result from coronary artery disease, hypertension, valvular heart disease, cardiomyopathies and myocarditis. The most prominent clinical signs of RHF comprise swelling of the neck veins with an elevation of jugular venous pressure and ankle oedema. As the situation worsens, fluid accumulation becomes generalised with extensive oedema of the legs, congestive hepatomegaly and eventually ascites. Diagnosis of RHF requires the presence of signs of elevated right atrial and venous pressures, including dilation of neck veins, with at least one of the following criteria: (1) compromised RV function; (2) pulmonary hypertension; (3) peripheral oedema and congestive hepatomegaly. Early recognition of RHF and identifying the underlying aetiology as well as triggering factors are crucial to treating patients and possibly reversing the clinical manifestations effectively and improving prognosis.

Keywords Heart failure · Right ventricular dysfunction · Pulmonary hypertension · Systemic venous pressure · Oedema

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Introduction

Right heart failure (RHF) is a clinical syndrome with signs and symptoms secondary to dysfunction and/or overload of the right heart structures, resulting in systemic venous hypertension (SVH) and peripheral oedema and, finally, reduced cardiac output (CO). RHF and right ventricular (RV) dysfunction (RVD) are not synonymous, as some patients have asymptomatic RVD, and RVD does not always cause RHF. Until recently, the mechanisms responsible for the syndrome have not been fully elucidated [1].

The RV has received little attention in the past, with cardiologists mainly dealing with the diseases of the left ventricle (LV), primarily because the contribution of the RV to overall cardiac hemodynamics was unclear. For this reason, the RV has been often termed the forgotten chamber, and it was considered little more than a passive conduit that passes the blood onto the pulmonary circulation.

The RV has been neglected because of its complex geometry, which is extremely difficult to characterise by two-dimensional imaging. Due to its peculiar shape and anatomy, RV volume cannot be measured using the approaches commonly used for LV. Similarly, RV contraction modalities are different and are characterised by prevalent longitudinal shortening, whereas the radial systolic function is less pronounced [2] (Fig. 1).

The physiological perspective

From a physiological perspective, the RV should be considered a high-volume low-pressure pump that propels the same stroke volume (SV) as the LV but with approximately 25% of the stroke work [3, 4].

The RV is more compliant than the LV and better able to handle an increased volume but is thin-walled and, therefore, poorly designed to deal acutely with a pressure load [5]. Instead, it can accommodate a large amount of blood with minimal increases in pressure. One seminal work highlighted the response of the RV and LV to experimental increases in afterload [6] (Fig. 2). In LV, an afterload increase leads only to a slight decrease in SV; conversely, the same afterload in the RV can bring about a marked fall in SV [7]. A clinically relevant corollary of these observations is that the RV is less suited to counteract pressure overload than volume overload.

The RV ability to offset the afterload largely depends on the satisfactory coupling between the RV and the pulmonary circulation, known as RV pulmonary artery coupling, which results in an efficient energy transfer from the right heart to the pulmonary vessels [8, 9]. The close relationship between the RV and the LV, the so-called ventricular interdependence that results from the forces transmitted from one ventricle to the other through the interventricular septum, further modulates RV behaviour. Efficient CO and filling are achieved by synchronous contraction and relaxation of the two ventricles.

The ability to offset the load is not the only difference between the ventricles. The RV assignment is not solely to pump blood into the circulation with a certain degree of potential energy but also to lower right atrial (RA) pressure to maintain pressure in a very distensible venous system at the lower possible level, significantly below the plasmatic oncotic pressure, allowing drainage of blood from the veins [10]. This information enables us to understand the genesis of RHF as a result of the incompetence of the right heart to maintain systemic venous pressure sufficiently low to guarantee optimal venous return (equal to CO in steady-state) or to do so only with an abnormally elevated venous pressure

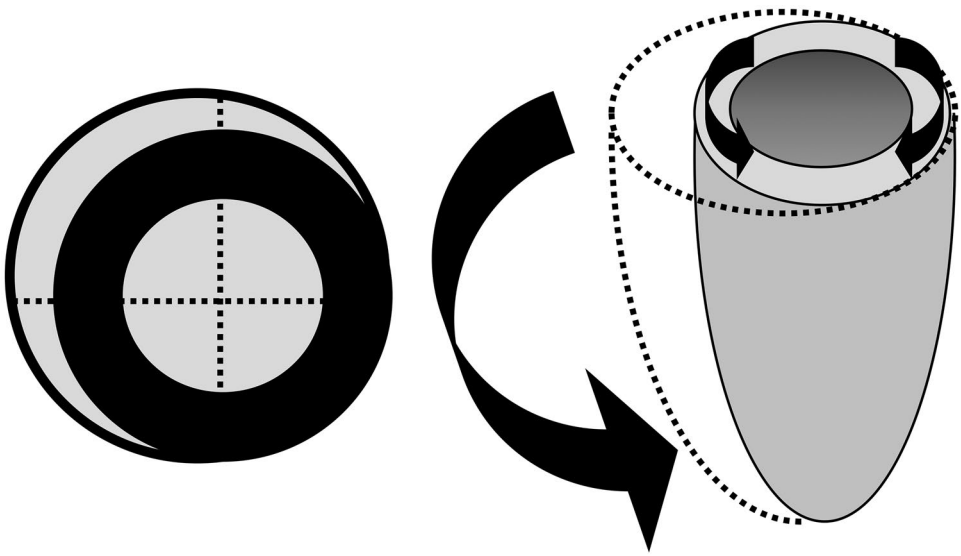

Fig. 1 Modalities of fibre shortening in the right ventricular wall

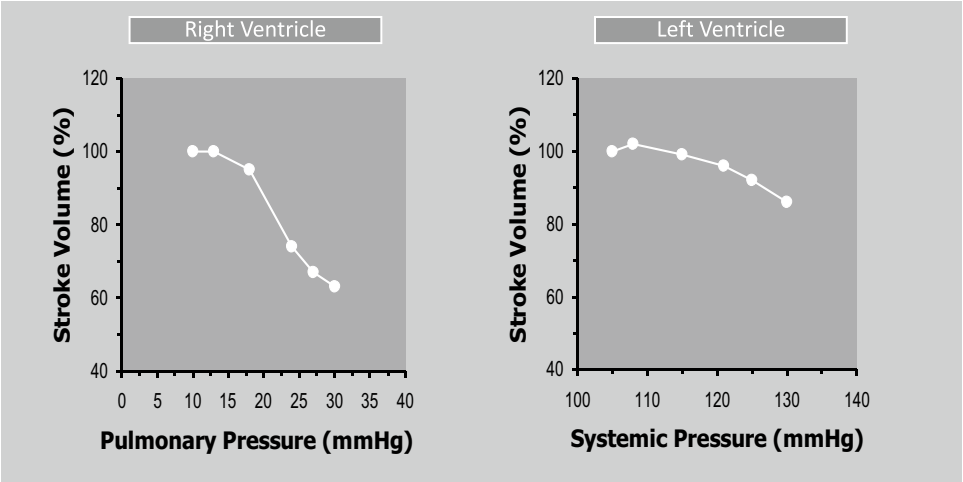

Fig. 2 Comparison of the right and left ventricle responses to increased afterload and volume overload

and explains why the occurrence of SVH is the prerequisite to the onset of right-sided HF and one of the leading clinical features of the syndrome.

Aetiology and epidemiology of right ventricular failure

RHF is caused by the inability of the RV to support blood flow in the circulation and to accommodate the venous return without increases in RA filling pressure. The mechanisms of the onset of RV failure may be either acute or chronic [11].

The most common causes of acute RHF are pulmonary embolism and acute myocardial infarction, mainly, but not exclusively, secondary to occlusion of the right coronary artery [12] (Table 1). Less frequently, acute RHF develops after cardiac surgery or LV assist device (LVAD) implantation [13].

Chronic RHF is most often associated with left-sided HF, as discussed in detail in a dedicated section of this article. The RV is directly affected at a much lower frequency by myocardial diseases, such as arrhythmogenic cardiomyopathy. Myocarditis may impair the RV in up to around 20% of patients, who usually also have LV inflammation [14]. It has been reported that a similar proportion of subjects has signs of RV involvement in Tako tsubo syndrome [15]. RHF may result from chronic cor pulmonale secondary to chronic obstructive pulmonary disease or other chronic lung disorders. RV overload and dysfunction have also been described in patients with COVID-19 as a consequence of multiple pulmonary embolisations and, possibly, direct myocardial injury [16]. Conversely, it remains unclear whether COVID-19 is also characterised by hypoxic pulmonary vasoconstriction increasing RV afterload [17]. Chronic volume overload due to atrial septal defects and primary tricuspid valve diseases, e.g. carcinoid syndrome or right-sided endocarditis, are other rare etiologies of adult-onset RHF. Finally, pulmonary arterial hypertension (PAH) is an essential cause of RHF since it exemplifies fundamental pathophysiological principles and can be treated with specific drugs [18].

Pathophysiology of right heart failure

RV mechanics and function are altered in the setting of either PAH or RV volume overload or primitive dysfunction. Both RV contractile impairment and afterload mismatch from

Table 1 Mechanisms and causes of right ventricular failure

Mechanism	Cause
Increased afterload	PAH associated with HFrEF, HFmrEF and HFpEF
	Mitral stenosis
	Heart transplant and LV assist device
	Acute pulmonary embolism and chronic pulmonary thromboembolism
	Acute respiratory distress syndrome
	COVID-19
	Idiopathic PAH
	Chronic pulmonary disease
	Sleep-related breathing disorders
Abnormal preload	Hypo- or hypervolemia
	Pericardial tamponade
	Mechanical ventilation
	Left-to-right shunt
Reduced contractility	RV ischemia/infarction
	Cardiomyopathies
	Myocarditis
	Arrhythmogenic RV cardiomyopathy

PAH pulmonary artery hypertension, *HFrEF* HF with reduced EF, *HFmrEF* HF with mildly reduced EF, *HFpEF* HF with preserved EF, *LV* left ventricular, *RV* right ventricular.

PAH may be responsible for RVD. PAH is defined as systolic pulmonary artery pressure (sPAP) and mean PAP (mPAP) exceeding 35 and 20 mmHg at rest, respectively, or mPAP exceeding 35 mmHg during exercise. Normal pulmonary circulation is a low resistance system with considerable reserve: therefore, substantial reductions in the size of the effective vascular bed must occur before PAH develops [19, 20].

RV hypertrophy is the initial adaptive response and allows for a reduction in wall stress and maintenance of SV. Chamber dilation ensues and is often accompanied by tricuspid regurgitation as a result of tricuspid annular dilation [21, 22]. However, since the RV cannot cope with pressure overload the same way as volume overload, RVD progresses, tricuspid regurgitation worsens, SVH is aggravated, and venous congestion increases [23, 24]. Increased afterload becomes the main mechanism for RVD and failure of both pulmonary and cardiac origin, either in the acute or chronic setting. Additional mechanisms, such as myocardial ischemia, neurohormonal activation, and unfavourable RV-LV interaction, may negatively impact the ability of the RV to respond to increased afterload [25]. However, the failing RV may still eject a normal or nearly normal SV despite considerable depression of function when its end-diastolic volume rises.

In severe forms, the right heart dilates, and the interventricular septum bulges to the left, increasing left heart filling pressure (LHFP), impairing LV filling, and causing left HF with a drop in CO. When abnormalities in pulmonary hemodynamics persist over time, pulmonary vascular resistance (PVR) rises, which may contribute to a decline in CO [26].

RVD may give rise to impaired RV filling and increased systemic venous pressure, but SVH may result from additional mechanisms other than the impairment of RV function, including inappropriate neurohormonal activation, with a subsequent considerable expansion of the extracellular fluid volume and abnormal RA filling due to thoracic and respiratory alterations [27]. Other mechanisms may contribute to the development of RHF, like severe breathing disturbances with hypoventilation secondary to chronic obstructive lung disease, interstitial lung disease, thoracic cage deformities or neuromuscular disorders. They can hamper blood drainage from the venous vessels into the pulmonary circulation, preventing the physiological decline of RA and systemic venous pressure. On the contrary, maintaining a normal venous return may be achieved by the aspiration of blood due to an efficient respiratory pump, even in cases of a severely dysfunctional RV [28, 29].

Elevated RA and systemic venous pressures are the main determinants of impaired renal function in acute and chronic RHF. SVH may be responsible for the rise in renal vein pressure, which may worsen renal function [30, 31]. Increasing creatinine levels may motivate clinicians to reduce loop diuretic therapy erroneously. However, this action may be harmful since it may prevent the reduction of SVH and further aggravate renal impairment. Activation of vasopressin, renin-angiotensin system and sympathetic nervous system may induce vasoconstriction with sodium and water retention, leading to decreased renal perfusion. A close relationship between RVD, impaired kidney function and persistent congestion has been demonstrated in patients with HF and reduced LV ejection fraction (LVEF) [32, 33]. Finally, fluid accumulation and venous congestion may be responsible for pro-inflammatory stimuli contributing to renal dysfunction and acute HF [33].

Right ventricular failure in left heart disease

All myocardial diseases involving the left heart may be responsible for RHF (Table 1). This may result from coronary artery disease, hypertension, valvular heart disease, cardiomyopathies and myocarditis [34]. The mechanisms responsible for RV failure secondary to LV dysfunction comprise (1) the same aetiology that affects both the LV and the RV and (2) the development of PAH due to increased LHFP [35].

In most patients, the onset of RV failure results from the development of pulmonary congestion and PAH that reflect the backward transmission of elevated LHFP [36, 37]. Chronic RHF due to left HF most commonly results from a gradual increase in RV afterload caused by post-capillary PAH [38]. Post-capillary PAH is characterised by a mean PAP ≥ 25 mmHg with elevated LHFP: pulmonary capillary wedge pressure (PCWP) ≥ 15 mmHg and LV end-diastolic pressure ≥ 18 mmHg. Most patients with HF have post-capillary PAH, characterised by low PVR [39].

Traditionally, HF has been divided into distinct entities based on the measurement of LVEF. The estimated prevalence of RVD varies according to the criteria used to identify RVD. RV impairment is frequently found in patients with HF with reduced LVEF [40, 41]. In a meta-analysis of studies of HF with preserved LVEF, RVD was present in 28%, 21% or 18% of patients depending on whether it was defined by tricuspid annular plane systolic excursion (TAPSE) < 16 mm, tricuspid annular systolic velocity (RV S') < 9.5 cm/s or fractional area change (FAC) < 35%, respectively [42]. In the Olmsted county cohort of subjects with HF and preserved LVEF, 35% of patients had a TAPSE value below the specified lower limit of normal (16 mm) and 21% had mild or moderate-severe RVD at semiquantitative assessment [43].

PAH in left heart disease can also depend on vascular changes within the pulmonary circulation, which comprise pulmonary vasculature remodeling, endothelial dysfunction and vasoconstriction related to hypoxia [44], which translates into elevated PVR i.e. combined pre- and post-capillary PAH [45]. These patients exhibit an out-of-proportion or mixed

PAH characterised by an increased transpulmonary gradient and a diastolic pulmonary gradient (diastolic pulmonary gradient = pulmonary artery diastolic pressure – PCWP).

Regardless of the pathogenesis, RVD and failure increase in prevalence with more advanced left heart disease. However, RV function may recover as a result of appropriate therapeutic interventions. A reversal of RVD at follow-up has been observed in patients with HF and LVEF < 50% that exhibited a compromised RV function at baseline [46].

Atrial fibrillation, commonly associated with left HF, may further contribute to RVD and pulmonary artery uncoupling due to either an increased left atrial pulsatile loading or a reduced CO due to the irregular cardiac cycle length [47].

In patients with HF due to left heart disease, symptoms and signs secondary to pulmonary congestion, as a consequence of disturbances of fluid transfer from capillaries into alveolar spaces, initially predominate and include pulmonary rales, orthopnea and paroxysmal nocturnal dyspnea [23]. With time, however, further increases of LHFP and exacerbation of PAH lead to RV overload and, eventually, RHF [48].

Finally, changes in LV configuration, loading and function can influence RV performance through systolic and diastolic ventricular interdependency, mediated by the shared interventricular septum, potentially contributing to RVD [49]. The presence of interventricular, intraventricular and atrioventricular dyssynchrony may further aggravate RVD, especially in the setting of pre-capillary PAH [50]. In PAH, there is prolonged contraction of the right ventricle, which ejects while the left ventricle is already relaxing, resulting in interventricular dyssynchrony. Furthermore, the timing of RV systolic contraction and relaxation of myocardial segments become heterogeneous, partially due to the non-uniform distribution of wall stress within the RV. The biomechanical overload of PAH that determines a rising RV wall stress is also associated with altered levels of circulating biomarkers that influence energy metabolism and stress response pathways. The latter may induce RV adaptive mechanisms to elevated mechanical stress [51].

Signs and symptoms

Despite advancements in diagnostic tools and biomarkers, the clinical examination (i.e. history and physical examination) remains central in managing patients with HF. Shortness of breath, fatigue, tachypnea and peripheral oedema are the most typical complaints, but they are little specific since they are often unrelated to RHF [52].

Manifestations of RHF due to excessive fluid accumulation has been known to physicians of the past ages. At that time, hydropsy, which consists of an extensive expansion of fluid in the body's tissues, was recognised as the most dramatic sign of heart disease.

Tricuspid regurgitation, which is often apparent from a systolic murmur on the right parasternal line, is a frequent finding but, in the absence of PAH, usually causes no clinical symptoms. The Rivero-Carvalho sign is a rare clinical sign in patients with tricuspid regurgitation consisting of a pansystolic murmur that becomes louder with inspiration. In the setting of PAH, tricuspid regurgitation may exacerbate the clinical expression of right HF.

RHF signs and symptoms are essentially due to SVH (Table 2), and tissue fluid accumulation as a result of the heart's inability to decongest the systemic venous system. Patients with RHF may present with several clinical signs, including swelling of the neck veins with an elevation of jugular vein pressure (JVP), positive hepatojugular reflux and ankle oedema. As the situation worsens, fluid accumulation becomes generalised with extensive oedema of the legs, congestive hepatomegaly and eventually ascites [53].

Jugular venous distension is a fundamental clinical manifestation of SVH. The patient's trunk should be positioned at a 45° angle to appreciate the jugular distension. Elevation of neck veins' meniscus higher than 4 cm suggests elevated

Table 2 Symptoms and signs of right-sided heart failure

More frequent	More specific
Shortness of breath and fatigue	Systemic venous hypertension
Palpitations	Neck vein distension with jugular turgor
Systemic venous hypertension	Congestive hepatomegaly
Neck vein distension with jugular turgor	Hepatojugular reflux
Peripheral oedema	Kussmaul sign
Congestive hepatomegaly	Holosystolic murmur with Rivero Carvalho sign
	Right ventricular gallop with third sound
	Ascites
	Hydrothorax
	Anorexia, nausea and abdominal pain
	Malnutrition and cachexia

JVP. The collapse of the inferior vena cava with forced inspiration is routinely evaluated during echocardiography to estimate RA pressure. This finding has been extrapolated to the jugular veins, wherein the absence of venous collapse during vigorous inspiration or sniffing indicates SVH [54].

SVH sometimes gives rise to other signs, such as the Kussmaul sign and hepatojugular reflux. The Kussmaul sign consists of the paradoxical increase in JVP with inspiration (instead of the expected decrease) and indicates impaired filling of the RV. The hepatojugular reflux results from a physical manoeuvre induced by applying manual compression over the liver.

Peripheral oedema is another important clinical feature of chronic RHF. It is usually bilateral, occurring gradually after the patient has been upright, and sometimes resolves with an elevation of the legs. Experience has taught us that a minimum of 5 l of extracellular volume is required before peripheral oedema can be detected. Several mechanisms are implicated in the development of peripheral oedema, including the elevation of the hydrostatic venous pressure, following the backward transmission of increased RA pressure and the neurohormonal activation with the increased absorption of salt and fluids from the renal tubule. Anasarca is the result of generalised oedema involving the upper as well as the lower extremities, genital regions and thoracic and abdominal walls. RHF patients frequently have indurated and highly pigmented lower extremities due to long-standing oedema.

Ascites, which consists of an increase in swelling of the abdomen, is not common today and usually follows extensive peripheral oedema. A possible concomitant of cirrhosis should be suspected when ascites seems out of proportion to peripheral oedema.

In patients with RHF secondary to LV dysfunction, fluid generally localises upstream to the right ventricle, in the legs, gut and liver, while symptoms resulting from pulmonary congestion become less common. Hepatomegaly is a prominent sign in patients with chronic right-sided HF. It may result from hepatic congestion and decreased hepatic perfusion [55]. Anorexia, nausea and abdominal pain are frequently related to congestive hepatomegaly and intestinal oedema.

Signs of fluid accumulation may also appear in patients with long-standing left HF without apparent RHF but are generally less pronounced and often limited to ankle oedema. Only when RHF occurs do patients with left-sided HF develop symptoms and signs of extensive fluid retention with the elevation of JVP, hepatomegaly and ascites. Oedema of the visceral organs contributes to alterations in hepatic, renal and intestinal functions. Malabsorption and reduced responsiveness to oral medications have been attributed to intestinal oedema. Severe liver injury can lead to reduced liver synthesis of clotting factors, prolonged prothrombin time and increased INR. Pleural effusion develops because of an impediment to pleural drainage by the lymphatic vessels. Advanced RHF is sometimes associated with extreme weight loss and cardiac cachexia due to impaired intestinal absorption of nutrients.

Diagnosis and prognosis

Early recognition of RHF and identifying underlying aetiology and triggering factors are crucial to treating patients and possibly reversing the clinical manifestations effectively. RHF is characterised by a compromised RV function or RV overload associated with elevated RA and venous pressures [56, 57].

The presence of signs of SVH, including dilation of neck veins, with at least one of the following criteria, are necessary for the diagnosis: (1) RVD as seen by cardiac instrumental techniques (see part 2); (2) pulmonary hypertension; (3) peripheral oedema and congestive hepatomegaly. Unlike generally believed, RVD is neither necessary nor sufficient to diagnose RHF.

The prognosis of HF depends essentially on the nature of the underlying heart disease and the presence or absence of triggering factors. There is increasing recognition of the crucial role of the RV in determining prognosis in multiple conditions [58, 59]. It is associated with poor clinical outcomes independently of the underlying mechanism: across the spectrum of LVEF, in patients with acute and chronic left HF, acute coronary syndromes, after cardiac surgery and congenital heart disease. Patients with HF with reduced LVEF and RVD had an increased risk of mortality, urgent transplantation or urgent assist device placement compared to those without RVD [60]. Similarly, increased morbidity and mortality have also been observed in patients with RHF and preserved LVEF [61]. Hemodynamic, radionuclide and echocardiographic parameters have been demonstrated to predict the outcome independently [62–66].

Principles of treatment

The goals of therapy include the reduction of RV afterload, the optimisation of RV preload and possibly the increase in RV contractility (Fig. 3). In both acute and chronic RHF, effective therapeutic management strategies involve identifying and effectively treating specific causes of RHF and triggering factors. Tailoring therapy to the specific cause of RHF, such as pulmonary hypertension, pulmonary embolism, infections, arrhythmias and others, is essential. An improvement in RV function and reduction in RV overload may be obtained by treating pulmonary congestion

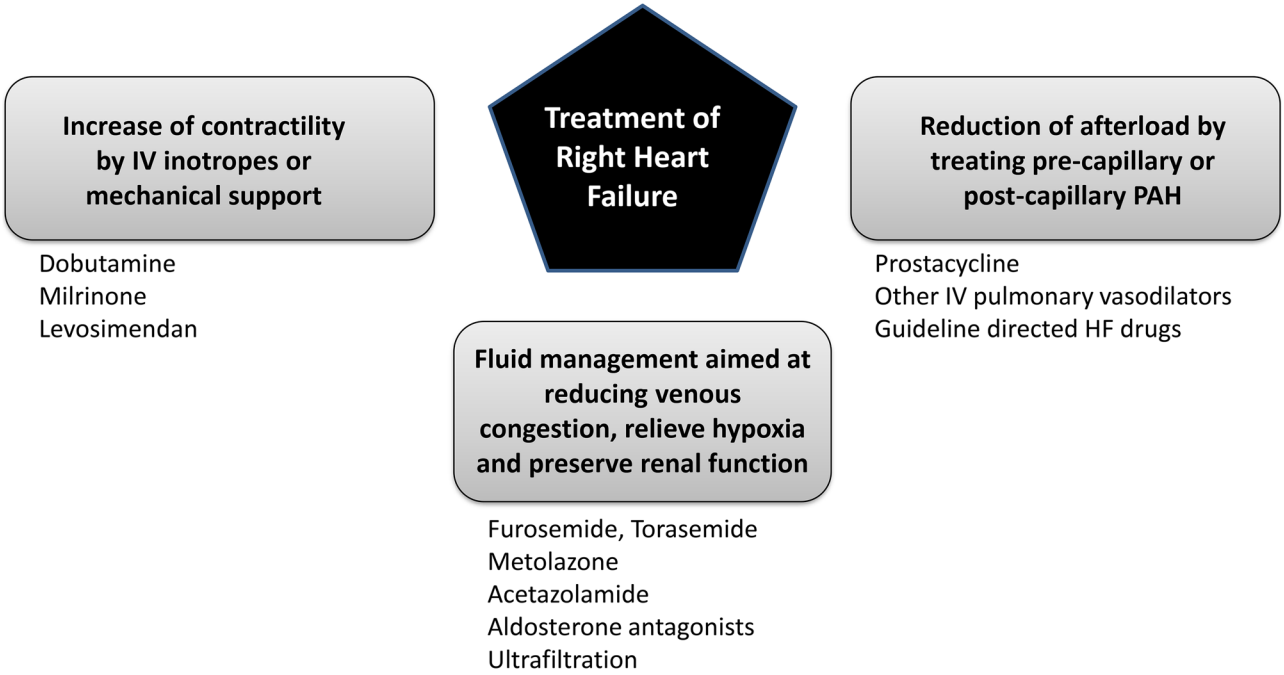

Fig. 3 Strategies to optimise right ventricular preload, afterload and contractility. IV: intravenous; PAH: pulmonary arterial hypertension

secondary to LV dysfunction and failure with drugs commonly used to treat left-sided HF [64].

Clinical experience has taught us that measures to increase RV contractility may be temporarily applied to patients with acute RHF and low output using inotropes, like dobutamine, milrinone and levosimendan, or mechanical support. The use of vasodilators, such as intravenous prostacyclin, to reduce RV afterload is restricted to a limited number of cases. As it is apparent, most of these approaches require the intravenous administration of drugs and, therefore, cannot be effective in the long term.

Fluid management is undoubtedly essential for treating patients with RV failure and signs of venous congestion [67]. A common misconception is that most patients with RHF are preload dependent and should be treated with volume supplementation to ensure an elevated RV filling pressure and consequently an optimal CO; conversely, the great majority of RHF is caused, associated with, or exacerbated by RV volume overload due to venous congestion. Volume overload is often responsible for increasing RV wall stress, augmenting tricuspid regurgitation severity, worsening RV-LV interaction and possibly decreasing CO. Systemic venous congestion plays a key role in the pathogenesis of the cardiorenal syndrome.

Diuretics are the mainstay therapy to treat congestion (Table 3). Diuresis in patients with RHF would lead to a decrease in venous congestion with resultant improvement in renal function, relief of hypoxia and acidosis of the cells of the splanchnic organs. Patients often require fluid and salt restriction and large doses of loop diuretics (i.e. furosemide), mainly because of concomitant neurohormonal activation, diuretic resistance and impaired oral drug absorption related to visceral oedema. In patients taking loop diuretics, greater diuretic effect and weight loss may be achieved in the supine rather than in the upright position. A diminished diuretic effect, sometimes referred to as the braking phenomenon, can occur with chronic loop diuretic therapy as a result of an increase in sodium reabsorption in the proximal and distal tubules. Removal of excess fluid is usually achieved by combination therapy of loop diuretics with thiazides and/or acetazolamide as a result of sequential nephron blockade of sodium reabsorption. Metolazone can be combined with furosemide to treat severe RHF and refractory oedema. Electrolyte imbalances are often induced by this association, and potassium supplementation and/or administration of a potassium-sparing agent may be beneficial. Metolazone produces a diuretic response despite a low glomerular filtration rate [68]. Torasemide is sometimes preferable to furosemide because of its better oral bioavailability. Aldosterone antagonists may help maintain potassium homeostasis from potassium losses. Finally, extracorporeal ultrafiltration is an alternative therapy for treating volume overload in acutely decompensated patients with RHF.

Table 3 Characteristics of diuretic agents

Type of drug	Site of action	Potency	Daily dose	Half lives	Adverse effects	Special considerations
Acetazolamide	PCT	4%	125–250 mg	2,4–5,4 h	Electrolytes imbalances	
Loop diuretics (furosemide, ethacrinic acid torasemide)	ALH	20–25%	Furosemide: 25 mg-500 mg Torasmide: 10–80 mg	Furosemide: 1.5–3.0 h Torasemide: 1.5–3.0 h	Electrolytes imbalances Hypokalemia Cardiac dysrhythmias	Steep dose–response curve (high ceiling)
Thiazides (HCTZ, chlortalidone)	DCT	5–8%	HCTZ 12.5–25 mg chlortalidone 50 mg	HCTZ 6.0–15.0 h, chlortalidone 45–60 h	Hyponatremia Hypokalemia Hyperuricemia Hyperglycemia	Low ceiling Ineffective in renal failure
Metolazone	DCT	> 10%	5–10 mg	6–20 h	Hyponatremia Hypokalemia	Effective in chronic renal failure. It is generally given 30–60 min before furosemide to ensure blocking of the DCT when sodium reaches the DCT
Aldosterone antagonists (spironolactone, canrenone, eplerenone)	CCT	2%	Spironolactone 25–200 mg, canrenone 25–200 g, eplerenone 25 mg	Spironolactone 1.5 h, canrenone 9–24 h, eplerenone 25 mg 3–6 h	Hyperkalemia, anti-androgenetic effects (gynecomastia)	Concomitant use of drugs that cause hyperkalemia require caution

ALH ascending limb of Henle's loop, *CCT* cortical collecting tubuli, *DCT* distal convoluted tubuli, *HCTZ* hydrochlorothiazide, *PCT* proximal convoluted tubuli.

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Data availability Not applicable.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no competing interests.

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