Chapter 4
Acute and Chronic Right Ventricular Failure

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Abbreviations

2D   Two-Dimensional
ARVC   Arrhythmogenic Right Ventricular Cardiomyopathy
CMRI   Cardiac Magnetic Resonance Imaging
CVP   Central Venous Pressure
ERA   Endothelin Receptor Antagonist
HF   Heart Failure
iNO   Inhaled Nitric Oxide
LV   Left Ventricle
LVAD   Left Ventricular Assist Device
PA   Pulmonary Artery
PAH   Pulmonary Arterial Hypertension
PCWP   Pulmonary Capillary Wedge Pressure
PDE-5I   Phosphodiesterase-5 Inhibitor
PE   Pulmonary Embolism
PH   Pulmonary Hypertension
PVR   Pulmonary Vascular Resistance
RAP   Right Atrial Pressure
RHC   Right Heart Catheterization
RIMP   Right Ventricular Index of Myocardial Performance

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RV   Right Ventricle
RVAD   Right Ventricular Assist Device
RVEF   Right Ventricular Ejection Fraction
RVFAC   Right Ventricular Fractional Area Change
RVI   Right Ventricular Infarction
TAPSE   Tricuspid Annular Plane Systolic Excursion
TPG   Transpulmonary Gradient

Introduction

Recent research has shed new light on the importance of the right ventricle (RV) in normal cardiac physiology and its prominent role in the pathophysiology of heart failure (HF). The RV was previously overshadowed by the left ventricle (LV), whose simpler anatomy conforms better to geometric models and is more accessible to non-invasive imaging. Furthermore, early experiments falsely suggested that the RV did not contribute significantly to the generation of cardiac output [1]. However, a series of investigations over the past 25 years have provided greater insight into the RV's distinct anatomy, its performance under normal physiological conditions, and its adaptations to specific disease states. Advanced imaging, including cardiac magnetic resonance imaging (CMRI), has provided critical assistance in the study of the RV, allowing for non-invasive characterization of the RV's response to stressors, as well as a tool for measuring the success of therapies. As a result, a detailed understanding now exists of the role of the RV in ischemic heart disease, congenital heart disease, pulmonary arterial hypertension (PAH) and chronic left-sided HF. Most importantly, studies have shown that RV failure is a crucial prognostic factor in all of these disease states. In particular, the importance of RV function in left-sided HF may outweigh the importance of LV function in terms of both morbidity and mortality.

Anatomy and Physiology of the Right Ventricle

The RV can be divided into three anatomical units: the inlet from the right atrium (including the tricuspid, the apex, and the outflow tract (infundibulum). The apex contains prominent trabeculations, in contrast to the smooth, muscular infundibulum. Viewed in cross-section, the RV resembles a crescent that lies over the anterior aspect of the LV. The free wall is thin and the overall mass of the RV is a fraction of the LV mass, despite a larger volume. The deep muscle fibers of the RV have a longitudinal orientation, resulting in a primarily vertical direction of contractile forces. The superficial muscle fibers of the RV are oriented in a more concentric direction and are intertwined with the superficial muscle fibers of the LV. This anatomical

interaction between the muscular fibers of the two chambers is also present in the interventricular septum, which is typically displaced into the RV throughout the cardiac cycle. Direct muscular continuity between the LV and RV plays a significant role in ventricular interdependence, which will be discussed in further detail below.

RV contraction proceeds sequentially, initiating in the inlet, continuing through the apex and concluding in the infundibulum. The longitudinal fibers draw the apex towards the tricuspid valve, while the free wall also moves inward toward the septum. Traction on the free wall is applied by LV contraction at attachment points in the superficial muscle layer. The RV is coupled with the high compliance of the pulmonary vasculature, leading to a pressure-volume relationship that is distinct from the relationship seen in the LV. Whereas the LV continues to generate pressure until the closure of the aortic valve, RV pressure falls prior to the closure of the pulmonic valve. Ejection continues however due to the low resistance within the pulmonary circuit (Fig. 4.1) [2]. The RV takes advantage of this physiology by producing an identical cardiac output to the LV with markedly reduced work and myocardial oxygen demand. However, one consequence of this interaction is the RV's heightened sensitivity to afterload, which can be deleterious in acute pressure overload states.

Ventricular interdependence occurs in both systole and diastole. Systolic interdependence is mediated by the shared musculature between the LV and the RV, which means that the contractile state of one ventricle can influence the performance of the
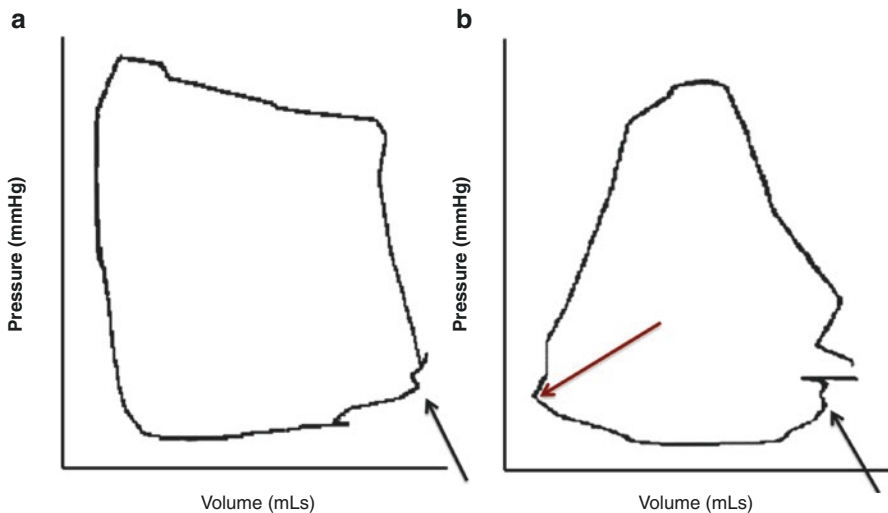

Fig. 4.1 A comparison of typical pressure-volume loops for a single cardiac cycle of the left ventricle (**a**) and right ventricle (**b**). In the left ventricle, pressure continues to increase slightly throughout the entire duration of ventricular ejection. In the right ventricle, intracardiac pressure falls prior to closure of the pulmonic valve (*red arrow*), resulting in less myocardial work. End-diastole is indicated by the black arrows (Adapted with permission from Redington [2], with permission from Elsevier)
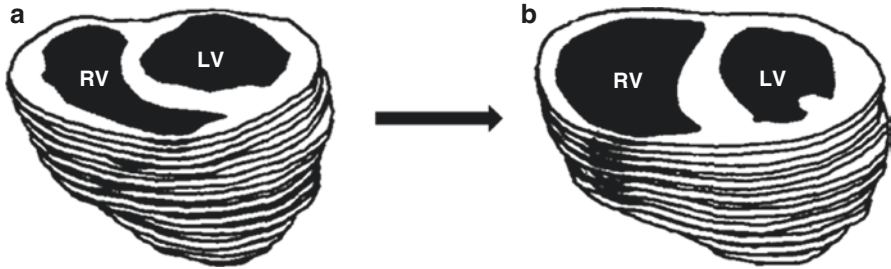
Fig. 4.2 Ventricular interdependence. During normal loading conditions (*left side of diagram*), the intraventricular septum bulges into the right ventricle (*RV*). In the context of right ventricular volume overload, the septum becomes flattened, with an increase in RV volume and a decrease in left ventricular (*LV*) volume (Reprinted with permission from Greyson [3], © 2008, with permission from Lippincott Williams & Wilkins/Wolters Kluwer/Society of Critical Care Medicine)

other ventricle. Diastolic interdependence is a result of the common pericardial sac. The pericardium is unable to stretch acutely in response to ventricular dilatation, and is limited in its ability to accommodate chronic ventricular dilatation. Therefore, a volume load in either chamber will cause displacement of the septum into the other chamber, resulting in a decreased diastolic volume and an impairment of ventricular output (Fig. 4.2) [3]. As the RV is the more compliant chamber, this diastolic interaction most commonly occurs in volume overload states of the RV, such as an atrial septal defect.

Right Ventricular Adaptations to Disease States

RV pathophysiology can be broadly categorized by the mechanism of the insult and its rapidity of onset. Acute events, such as a pulmonary embolism, lead to maladaptive compensatory responses, and quickly progress to RV failure. Chronic disease processes, such as congenital heart defects, often present a gradual stress on the RV, allowing it to develop adaptive mechanisms to preserve cardiac output for a prolonged period of time prior to decompensation. Conditions characterized by volume overload are generally well tolerated by the RV due to its compliant nature. On the other hand, the RV has difficulty adapting to pressure overload due to its afterload-sensitivity (Fig. 4.3) [4]. Interestingly, the timing of onset of pressure overload is a crucial determinant of the RV response. In Eisenmenger syndrome, the RV is able to remain compensated much longer than in adult patients with acquired pulmonary hypertension (PH). This finding has been attributed to the preservation of the fetal phenotype, which is accustomed to systemic levels of vascular resistance [5]. Intrinsic myocardial diseases, such as various forms of nonischemic cardiomyopathies, may impair RV contractility, but rarely affect the RV in isolation. However, RV involvement in a cardiomyopathy can play a significant role in morbidity and mortality, particularly in the setting of pulmonary hypertension (PH). A list of diseases that cause RV dysfunction and RV failure can be found in Table 4.1.

Fig. 4.3 Response of canine right ventricular and left ventricular stroke volume to acute changes in afterload. The steep slope in the right ventricle indicates enhanced sensitivity to afterload (Reprinted with permission from Abel and Waldhausen [4], © 1967, with permission from Elsevier)
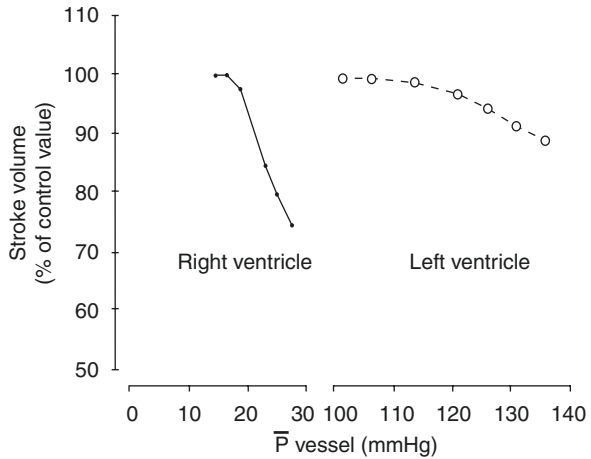

Table 4.1 Causes of right ventricular failure

Acute causes	Intrinsic myocardial disease
Pulmonary Embolism	Cardiomyopathy
Right Ventricular Infarction	Idiopathic
Sepsis	Viral
Acute lung injury	Familial
ARDS	Ischemic
TRALI	Infiltrative
Acute Chest Syndrome	Restrictive
Post-cardiotomy	Arrhythmogenic RV dysplasia
Pulmonary hypertensive crisis	
Cardiac tamponade	Pericardial disease
	Constrictive pericarditis
Chronic volume overload	Chronic pressure overload
Tricuspid valve regurgitation	Pulmonary arterial hypertension
Infective endocarditis	Pulmonary venous hypertension
Rheumatic disease	Left heart failure
Carcinoid	Pulmonary veno-occlusive disease
Traumatic	Hypoxia-associated PH
Pulmonic valve regurgitation	Chronic thromboembolic PH
Congenital heart disease	Congenital heart disease
Atrial septal defect	Tetralogy of Fallot
Ebstein's anomaly	Pulmonic stenosis
Coronary artery fistula	L-transposition of the great arteries
Anomalous pulmonary venous return	Pulmonary artery stenosis
	Eisenmenger's syndrome

ARDS acute respiratory distress syndrome, *PH* pulmonary hypertension, *RV* right ventricle, *TRALI* transfusion associated lung injury

Acute Pressure Overload

Following a submassive or massive pulmonary embolism (PE), there is a rapid rise in pulmonary vascular resistance (PVR) due to both obstructed blood flow and the release of vasoconstrictors [6]. Vasoconstriction may be further exacerbated by hypoxemia. The rapid rise in afterload increases RV wall tension, which quickly leads to RV dilatation and RV systolic dysfunction. As the RV pressure rises acutely, the interventricular septum shifts into the LV, reducing LV preload and further compromising cardiac output. Finally, coronary perfusion is impaired by both the compression of the right coronary artery by elevated RV wall stress and the reduction in cardiac output. In the setting of the increased myocardial oxygen demand in the failing RV, the reduction in coronary blood flow leads to a significant supply-demand imbalance. The final consequence of this sequence of events is worsening cardiac output, systemic hypotension and cardiac arrest.

Ischemia

Right ventricular infarction (RVI) occurs after occlusion of the right coronary artery in a sufficiently proximal portion to prevent perfusion of the RV branches. The immediate result of an RVI is RV free wall dyskinesis due to ischemia, although this alone may not be sufficient to produce clinical RV failure. Secondary effects include stiffening of the myocardium and dilation of the RV. Similar to the consequences of an acute PE, the acute pressure changes within the RV, in this case provoked by diastolic dysfunction, cause septal shifting and impaired LV-RV interaction. In addition septal ischemia further compromises LV performance, and diminishes the LV's ability to compensate for RV dysfunction [7].

Chronic Pressure Overload

PH is the end-product of many cardiovascular and pulmonary diseases and is the most common cause of a chronic pressure overload on the RV. As the pulmonary artery (PA) pressure gradually increases over time, the RV adapts to the increase in afterload through multiple compensatory mechanisms. Myocyte hypertrophy and the expansion of the extracellular matrix result in increased chamber thickness. At the same time, the RV remodels into a more spherical shape with a smaller radius [8]. Through the application of LaPlace's law, which states that wall stress is proportional to chamber radius and inversely proportional to chamber thickness, it is evident that the primary result of these initial adaptations is to reduce wall stress, countering the effect of the rise in afterload. In addition, central venous pressure (CVP) is allowed to rise, taking advantage of the Frank-Starling mechanism to maintain a normal stroke volume.
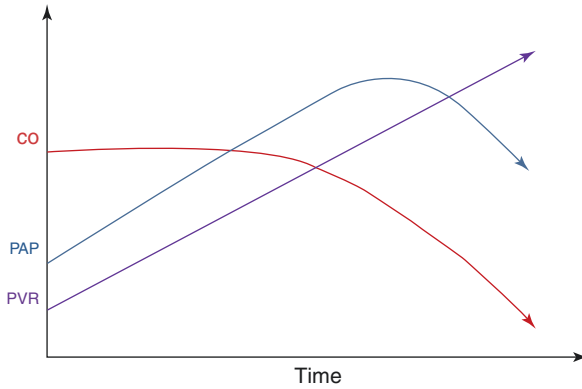
Fig. 4.4 The natural history of persistent pulmonary hypertension. As pulmonary artery pressure (*PAP*) and pulmonary vascular resistance (*PVR*) climb, cardiac output (*CO*) is initially maintained, but eventually begins to fall. When CO falls sufficiently to cause advanced RV failure, PAP fells as well due to insufficient pressure generation by the weak RV. PVR continues to rise despite falling PAP due to the concomitant fall in CO. *MPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure (Reprinted, with permission, from Haddad et al. [9], © 2008, with permission from Lippincott Williams & Wilkins/American Heart Association/Wolters Kluwer)

Several mechanisms have counterproductive effects, including reversion to a fetal gene pattern and upregulation of neurohormonal systems [8]. The result is a decrement in contractility, followed by progressive ventricular dilatation. As with acute RV pressure overload, dilatation increases myocardial oxygen demand while simultaneously reducing coronary perfusion and oxygen delivery. This supply-demand mismatch further compromises RV performance and ultimately leads to RV failure if the PH remains untreated. Both cardiac output and PA pressure fall when RV contractile reserve is no longer sufficient to maintain an adequate stroke volume (Fig. 4.4) [9].

Chronic Volume Overload

The thin, distensible wall of the RV permits it to accommodate large changes in preload without incurring significant changes in pressure. States of chronic volume overload, such as an atrial septal defect, can persist for decades prior to the development of RV dysfunction. Two consequences of persistent RV dilatation are distortion of the tricuspid annulus and septal shift. The dilated tricuspid annulus permits tricuspid regurgitation, which can further exacerbate the volume load on the RV. Septal shift occurs when the pericardium is unable to distend any further to accommodate the dilation of the RV. As noted above, septal shift can subsequently impair LV filling and adversely affect LV performance. Finally, prolonged volume overload may cause PA pressures to rise due to increased flow through the pulmonary circuit. The development of PH is often the trigger for

decompensation of the chronic volume overloaded state, as the dilated RV lacks the compensatory mechanisms to augment its contractility in the setting of increased afterload [10].

Intrinsic Myocardial Disease

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiomyopathy characterized by fibro-fatty replacement of myocardium, with a predilection for RV involvement. It may present with focal RV dysfunction at the sites of involvement, and may ultimately progress to RV dilatation and global RV dysfunction. The typical clinical presentation is ventricular arrhythmias, with symptoms of RV failure affecting less than 10 % of ARVC patients [11]. In most patients, RV dysfunction can be present for decades without significant symptomatology. A similar observation has been made in animal experiments, in which an isolated reduction in RV contractility does not impair cardiac output in the setting of a normal PVR. In these animals, central filling pressures rise to permit sufficient flow through the pulmonary circuit. However, when PVR is raised, there is rapid cardiac decompensation, suggesting that the progression of RV dysfunction to RV failure may require the presence of an additional stressor, such as PH [12]. The Fontan operation, in which a passive conduit is created between systemic venous return and the pulmonary arteries, takes advantage of this physiology to maintain adequate flow to the LV despite the absence of RV contractility.

Diagnosis and Assessment of Right Ventricular Dysfunction and Failure

A thorough history and physical examination can provide important clues to the presence of RV failure, including the presence of a right-sided third heart sound, elevated jugular venous pressure, ascites and peripheral edema. A prominent pulmonic component of the second heart sound (P2) indicates the presence of PH. Patients may report early satiety, abdominal fullness and fatigue. Hepatic function and renal function are often compromised, and should be followed regularly in a patient with RV failure. Imaging studies play a crucial role in the initial assessment and serial monitoring of RV function. Echocardiography is the most frequently used imaging modality for RV assessment due to its ease of use, low cost and accessibility. However, CMRI has become the gold standard for evaluation of the RV because of its ability to overcome some of the anatomic limitations of two-dimensional (2D) echocardiography. While both echocardiography and CMRI can provide some assessment of RV hemodynamics, invasive measurement of intracardiac pressures by right heart catheterization is often required to diagnose the etiology of RV failure and determine the appropriate therapeutic approach.

Non-invasive Imaging Studies

RV size and function can be assessed with radionuclide ventriculography, using either first-pass or gated equilibrium techniques. While accurate measurements of volume and RV ejection fraction (RVEF) can be derived, this modality does not provide additional anatomic information, and exposes patients to radioisotopes. With the widespread availability of echocardiography, radionuclide ventriculography is rarely indicated as the primary method for RV functional assessment in the current era.

2D echocardiography has excellent spatial and temporal resolution, enabling precise evaluation of RV anatomy and valvular function. RV dimensions can be obtained through multiple views, providing an estimate of RV size. However, due to the RV's anatomic configuration, the calculation of accurate RV volumes with 2D echocardiography is not possible. Qualitatively comparing RV size to LV size in the apical view can provide a reasonable assessment of RV dilatation. Additional anatomic information that can be easily obtained is the appearance of the tricuspid and pulmonary valves, and the presence of valvular stenosis or regurgitation. Doppler evaluation of the tricuspid regurgitant jet allows the estimation of the systolic pulmonary artery pressure through the use of the modified Bernoulli equation. Important information is also provided by the appearance of the interventricular septum in the short-axis views. Pressure overload states cause flattening of the septum, particularly during systole, which volume overload states cause flattening during diastole (Fig. 4.5). With increasing pressure or volume overload, the septum is further shifted into the LV, leading to the hemodynamic effects of ventricular interdependence discussed previously.

RV function is challenging to determine with 2D echocardiography due to the lack of accurate ventricular volumes and the sensitivity of the RVEF to loading conditions. Visual assessment is the most commonly used technique but may be limited due to the complex shape of the RV. Multiple techniques are available for quantitative measurement of RV function. RV fractional area change (RVFAC) measures the change in area of the RV between diastole and systole from the apical 4-chamber view. The tricuspid annular plane systolic excursion (TAPSE) measures the vertical motion of the tricuspid valve annulus, with a value of less than 1.6 cm indicating RV dysfunction. RVFAC and TAPSE are both load-independent, and may provide varying information under different hemodynamic conditions. The RV index of myocardial performance (RIMP), also known as the Tei index, is less influenced by loading conditions, and may be a more accurate measure of underlying RV contractility [13]. This index is measured with Doppler of flow through the RV outflow tract, and is calculated as the sum of RV isovolumic contraction time and RV isovolumic relaxation time divided by ventricular ejection time.

Recent advances in CMRI have established it as the best modality for obtaining accurate information about RV size and function. CMRI is not affected by the anatomic limitations that prevent 2D echocardiography from obtaining a complete picture of the RV. CMRI has excellent spatial and temporal resolution, permitting

Fig. 4.5 A 2-dimensional echocardiogram image showing dilation of the right ventricle (*RV*) and flattening of the intraventricular septum (*) due to right ventricular pressure and volume overload. *LV* left ventricle
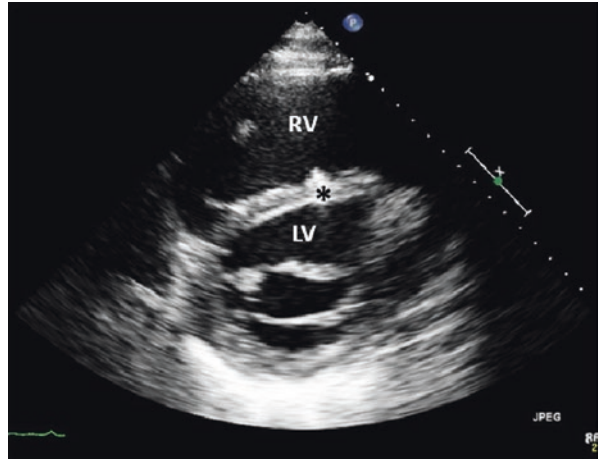
accurate assessment of RV volumes throughout the cardiac cycle. Additionally, CMRI provides information on ventricular hypertrophy, the presence of infiltrative diseases and the presence of fibrosis. For complex congenital heart disease, CMRI offers substantial advantages over 2D echocardiography for assessment of RV anatomy and function prior to and following surgical interventions. Barriers to more widespread application of CMRI in evaluation of the RV include the time required for testing, the cost of CMRI technology, and the need for technical expertise. Most importantly, CMRI is not compatible with most implantable cardiac devices, such as pacemakers, although the ongoing development of devices compatible with the magnetic field will allow for a broader application of CMRI in the assessment of RV failure [14].

Invasive Hemodynamic Assessment

Right heart catheterization (RHC) is a critical component of RV assessment, particularly in patients with PH. Measurement of the right atrial pressure (RAP), PA pressure and pulmonary capillary wedge pressure (PCWP) can distinguish the etiology of RV failure and help determine the therapeutic approach (Table 4.2). The most important information provided by RHC is about PH, which has been classified into groups by the World Health Organization:

- Group I incorporates PAH, which may be idiopathic, familial or associated with specific entities such as congenital heart disease, collagen vascular disease, HIV infection or toxins
- Group II includes PH that is found in conjunction with left heart disease and is the most common form of PH
- Group III includes PH associated with lung disease or hypoxemia

Table 4.2 Hemodynamic profiles of different mechanisms of right ventricular failure

Cause of RV failure	RAP	PAP	PCWP	TPG	PVR	Clinical examples
Volume overload without PH	↑	↓	↓	↓	↓	ASD Isolated TV disease
Precapillary PH	↑	↑	↓	↓	↓	Idiopathic PAH CTEPH Hypoxia-associated PH Congenital Heart Disease
Postcapillary PH						
Passive	↑	↑	↑	↓	↓	Left-sided Heart Failure MV Disease
Mixed	↑	↑	↑	↑	↑	
Reactive (after vasodilator challenge)	↑	↑	↓	↓	↓	
Nonreactive (after vasodilator challenge)	↑	↑	↓	↑	↑	

ASD atrial septal defect, *CTEPH* chronic thromboembolic pulmonary hypertension, *MV* mitral valve, *PAH* pulmonary arterial hypertension, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *TPG* transpulmonary gradient, *TV* tricuspid valve

- Group IV is PH due to chronic thromboembolic disease
- Group V is a miscellaneous category

A RHC can assist in the diagnosis of PAH, by identifying PH in the presence of normal left-sided filling pressures. While left heart disease is often manifested on imaging studies by a reduced LV ejection fraction or mitral valve disease, RHC can identify elevated PCWP in the absence of valvular disease or LV dysfunction (heart failure with preserved ejection fraction). Distinguishing the underlying etiology of PH will direct the choice of therapy, as therapies that have proven benefit in some forms of PH have been shown to be harmful in PH related to left heart disease [15]. Beyond anatomy, RHC provides information about the severity of RV failure. For example, the RAP is typically about 50 % of the PCWP [16]. As RV failure progresses, the RAP will approach or exceed the PCWP. Another sign of worsening RV failure is a decrease in the PA pressure despite a rising RAP due to insufficient power generation by the RV.

Another key variable obtained during right heart catheterization is the transpulmonary gradient (TPG), which is the difference between the PCWP and the mean PA pressure. This takes on importance in the assessment of PH due to left heart failure (i.e. patients with a PCWP >15 mmHg). When the PCWP is elevated, but the TPG is less than 10–12 mmHg, PH is termed "passive" or "post-capillary", indicating that the elevation in PA pressures can be solely attributed to the elevated left-sided filling pressures. When the TPG is greater than 15 mmHg, the PH is termed "mixed" indicating that there is both a pre-capillary and post-capillary component of the PH. This may be secondary to vasoconstriction and pulmonary arterial remodeling as a response to chronically increased pulmonary venous pres-

sures. Mixed PH can be further stratified into "reactive" and "nonreactive" forms through administration of a vasodilator, such as sodium nitroprusside or milrinone, to reduce the PCWP. In non-reactive PH, the TPG will remain elevated despite a lower PCWP, whereas patients with reactive PH will have concurrent decreases in the PCWP and TPG. The presence of reactive PH may indicate a more favorable prognosis, particularly when considering a patient for advanced therapies such as cardiac transplantation [17]. Whether patients with either reactive PH or nonreactive PH will benefit from selective pulmonary vasodilators is a subject of ongoing investigation.

When World Health Organization Group I PAH is present, the administration of selective pulmonary vasodilators, such as nitric oxide or epoprostenol, provides both prognostic and therapeutic information. Patients in whom the mean PA pressure drops by more than 10 mmHg to a value less than 40 mmHg without a reduction in cardiac output have an excellent prognosis, and typically respond well to calcium-channel blockers [18]. Non-responders have a worse prognosis, but still get a therapeutic benefit from selective pulmonary vasodilators.

Finally, RHC enables the calculation of the PVR, which provides a good estimate of RV afterload. PVR is both a prognostic factor, as well as a therapeutic target, that takes on considerable importance in the assessment of a patient's appropriateness for cardiac transplantation. A PVR >5 Woods Units is considered a relative contraindication to transplantation unless it can be lowered with medical therapy or mechanical circulatory support [19]. Frequency-domain analysis is an investigational method that accounts for the pressure wave reflected backwards into the main PA during late systole, and may provide a more accurate assessment of RV afterload [20].

Prognosis of Right Ventricular Failure

RV dysfunction plays a defining role in the pathogenesis of multiple diseases, ranging from left-sided HF to congenital heart disease to PH. In each of these entities, RV failure is the culmination of chronic pathophysiological disturbances, and often marks the transition to an advanced disease state. Numerous investigations have connected markers of RV dysfunction to adverse outcomes (Table 4.3). In chronic HF with LV dysfunction, RVEF, as measured by radionuclide ventriculography, invasive hemodynamics or CMRI, has been correlated with exercise capacity [21, 22], ventilatory efficiency [23], and survival [24–29]. This association has been demonstrated in both ischemic and nonischemic cardiomyopathies [24, 25, 29]. Importantly, there appears to be an additive effect of PH and RV dysfunction, leading to worse outcomes than the presence of either PH or RV dysfunction alone (Fig. 4.6) [30]. Other imaging parameters that have been associated with outcomes in chronic HF include CMRI-derived RV volumes [31], TAPSE [32–34] and RIMP [35]. Similar findings have been demonstrated in RV dysfunction due to PAH [36–40] and congenital heart disease [41, 42].

Table 4.3 Selected studies of the association of right ventricular dysfunction with adverse outcomes [21–23, 27, 29–32, 35, 36, 38–42]

	Population	Findings
Studies using radionuclide ventriculography		
Baker et al. [22]	25 pts. with symptomatic LV failure	RVEF associated with peak VO_2 LVEF not associated with peak VO_2
Lewis et al. [23]	30 pts. with symptomatic LV failure	Exercise RVEF and PVR associated with V_E/V_{CO_2} slope
Di Salvo et al. [21]	67 pts. referred for OHT evaluation	RVEF >35 % predictor of survival
Studies using RHC/thermodilution		
Gavazzi et al. [27]	142 pts. referred for OHT evaluation	RVEF lower in pts. who died or had OHT
Ghio et al. [30]	377 pts. with LVEF <35 % and NYHA Class III-IV	RVEF and PAP predictors of survival.
Studies using Echocardiography		
Damy et al. [32]	1547 pts. referred for HF	Low TAPSE predictor of mortality
Harjai et al. [35]	60 pts. with LVEF<30 %	RIMP >1.14 predictive of death
Forfia et al. [36]	63 pts. with idiopathic PAH	TAPSE <18 mm associated with mortality
Ghio et al. [38]	72 inpatients with idiopathic PAH	RV diameter >36.5 mm associated with mortality
Yeo et al. [39]	53 pts. with idiopathic PAH	RIMP independent predictor of death
Moceri et al. [41]	181 pts. with Eisenmenger syndrome	TAPSE, RIMP and elevated CVP strongest predictors of mortality
Studies using CMRI		
Larose et al. [29]	147 pts. post-MI	RVEF <40 % independent predictor of mortality
Bourantas et al. [31]	380 pts. with LVEF <45 %	RVESV predicts mortality; LVESV does not predict mortality
van Wolferen et al. [40]	64 pts. with idiopathic PAH	RV dilation, low RV stroke volume and decreased LV filling predict mortality
Knauth et al. [42]	88 pts. followed up at mean of 20.7 years after TOF repair	Severe RV dilation predictor of death, VT, advanced NYHA class

CMRI cardiac magnetic resonance imaging, *HF* heart failure, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end systolic volume, *MI* myocardial infarction, *NYHA* New York Heart Association, *OHT* orthotopic heart transplantation, *PAH* pulmonary arterial hypertension, *PAP* pulmonary artery pressure, *PVR* pulmonary vascular resistance, *RIMP* right ventricular index of myocardial performance, *RV* right ventricle, *RVEF* right ventricular ejection fraction, *RVESV* right ventricular end systolic volume, *TAPSE* tricuspid annular plane systolic excursion, *TOF* tetralogy of Fallot, V_E/V_{CO_2} ratio of minute ventilation to production of carbon dioxide, *VT* ventricular tachycardia

Management of Right Ventricular Failure

The initial approach to RV failure relies on identifying and correcting the underlying etiology. As opposed to the LV, in which dysfunction is often irreversible, the RV is highly pliable, and typically regains function after the causative factors
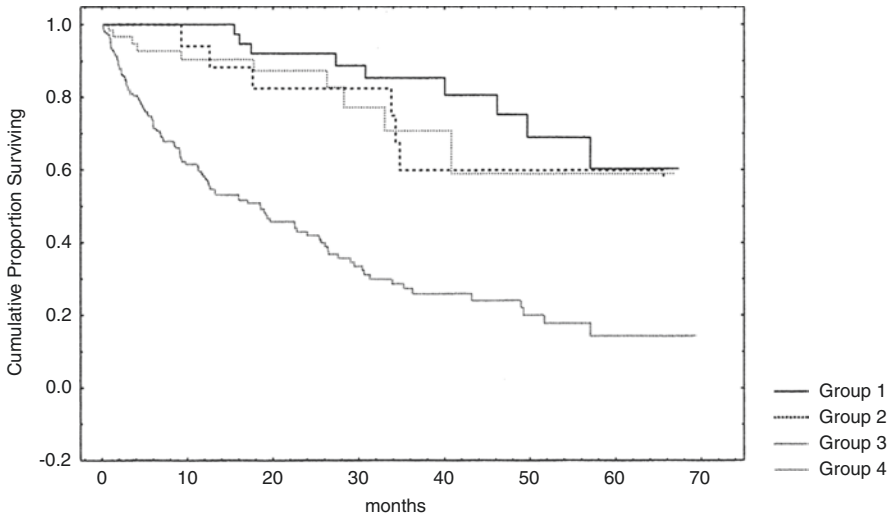
Fig. 4.6 Survival curves for heart failure patients grouped by presence or absence of pulmonary hypertension (PH) and presence or absence of an abnormal right ventricular ejection fraction (RVEF). Group 1 patients have normal RVEF and no PH. Group 2 patients have a low RVEF without PH. Group 3 patients have a normal RVEF with PH. Group 4 patients have both an abnormal RVEF and PH. The presence of both factors leads to significantly worse outcomes than any of the other three scenarios (Reprinted, with permission, from Ghio et al. [30], © 2001, with permission from Elsevier)

of RV dysfunction are addressed. This is especially important in acute RV failure, where reversing the underlying disease state may drastically alter a patient's outcome. For example, coronary revascularization for an RVI reduces RV dysfunction, hemodynamic compromise and increased mortality [43]. Likewise, for an acute PE, rapid relief of the thrombotic burden through medical or surgical intervention produces a substantial survival benefit [44]. Causes of chronic RV failure are not as easily corrected, although RV function improves over time with therapy that is appropriately targeted at the underlying pathophysiology. Ultimately, managing both acute and chronic RV failure requires an understanding of the roles played by preload, afterload and contractility. A management algorithm is shown in Fig. 4.7.

Preload

Optimizing RV performance requires adequate preload to generate a sufficient stroke volume without causing a degree of RV distention that impairs LV performance through ventricular interdependence. The ideal preload required may differ between patients and will rely on both the degree of RV contractility and the severity of RV afterload. In patients with acute RV failure, central venous
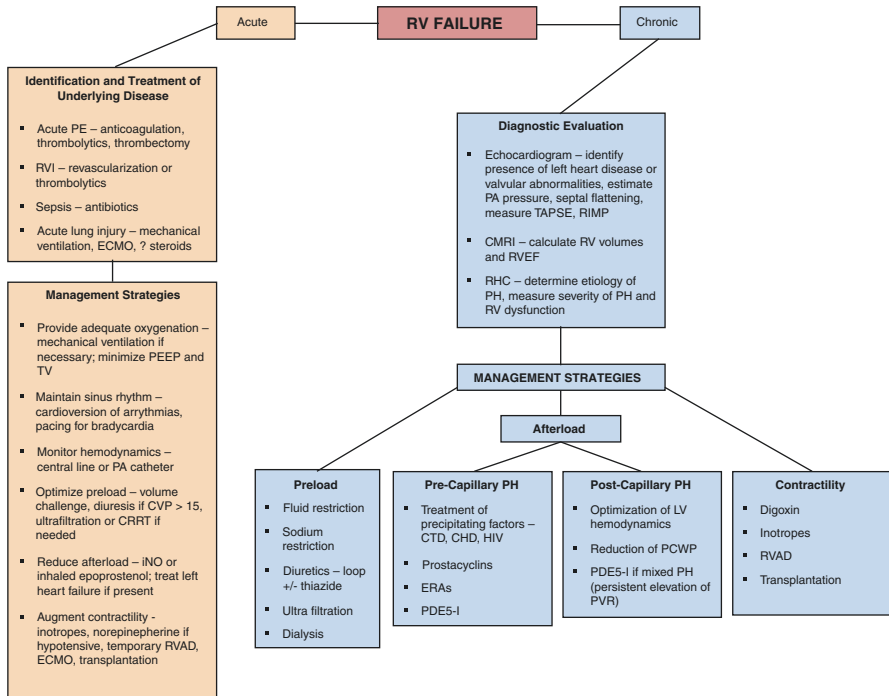
RV FAILURE

Acute — Chronic

Identification and Treatment of Underlying Disease

- Acute PE – anticoagulation, thrombolytics, thrombectomy
- RVI – revascularization or thrombolytics
- Sepsis – antibiotics
- Acute lung injury – mechanical ventilation, ECMO, ? steroids

Management Strategies

- Provide adequate oxygenation – mechanical ventilation if necessary; minimize PEEP and TV
- Maintain sinus rhythm – cardioversion of arrythmias, pacing for bradycardia
- Monitor hemodynamics – central line or PA catheter
- Optimize preload – volume challenge, diuresis if CVP > 15, ultrafiltration or CRRT if needed
- Reduce afterload – iNO or inhaled epoprostenol; treat left heart failure if present
- Augment contractility - inotropes, norepinepherine if hypotensive, temporary RVAD, ECMO, transplantation

Diagnostic Evaluation

- Echocardiogram – identify presence of left heart disease or valvular abnormalities, estimate PA pressure, septal flattening, measure TAPSE, RIMP
- CMRI – calculate RV volumes and RVEF
- RHC – determine etiology of PH, measure severity of PH and RV dysfunction

MANAGEMENT STRATEGIES

Afterload

Preload
- Fluid restriction
- Sodium restriction
- Diuretics – loop +/- thiazide
- Ultra filtration
- Dialysis

Pre-Capillary PH
- Treatment of precipitating factors – CTD, CHD, HIV
- Prostacyclins
- ERAs
- PDE5-I

Post-Capillary PH
- Optimization of LV hemodynamics
- Reduction of PCWP
- PDE5-I if mixed PH (persistent elevation of PVR)

Contractility
- Digoxin
- Inotropes
- RVAD
- Transplantation

Fig. 4.7 Management algorithm for acute and chronic RV failure. Abbreviations: *CHD* congenital heart disease, *CMRI* cardiac magnetic resonance imaging, *CRRT* continuous renal replacement therapy, *CTD* connective tissue disease, *CVP* central venous pressure, *ECMO* extracorporeal membrane oxygenation, *ERA* endothelin receptor antagonist, *HIV* human immunodeficiency virus, *iNO* inhaled nitric oxide, *PA* pulmonary artery, *PDE5-I* phosphodiesterase-5 inhibitor, *PE* pulmonary embolism, *PEEP* positive end-expiratory pressure, *PH* pulmonary hypertension, *RHC* right heart catheterization, *RIMP* right ventricular index of myocardial performance, *RV* right ventricular, *RVAD* right ventricular assist device, *RVI* right ventricular infarction, *TAPSE* tricuspid annular plane systolic excursion, *TV* tidal volume

monitoring can guide decision-making about the volume status. Patients with RVI are often described as "volume-sensitive", and may require higher preloads to maintain cardiac output. However, too much volume may have deleterious consequences because RV dilation will increase wall stretch, worsen ischemia and cause septal shifting. Although mechanical ventilation is sometimes necessary in the management of patients with acute RV failure, its use should be minimized due to the adverse effects of positive end-expiratory pressure on preload.

In chronic RV failure, the focus is typically on volume removal, which is primarily achieved with loop diuretics. Selecting an agent with better oral bioavailability, such as torsemide, may be preferred in the setting of RV failure due to the possibility of intestinal edema and poor absorption. Thiazide diuretics can be added as needed to enhance diuresis. As with LV dysfunction, sodium and fluid restriction

are essential to maintaining euvolemia. In extreme circumstances, ultrafiltration or hemodialysis may be required in diuretic-resistant patients, although these strategies have not been well studied in this population.

Afterload

Afterload reduction is a critical component of the management of most causes of RV failure. Addressing afterload is of particular urgency in acute RV failure due to the inability of the RV to compensate for acute changes in afterload. Persistently low oxygen saturations should be addressed with supplemental oxygen to alleviate hypoxia-induced vasoconstriction. If mechanical ventilation is required, tidal volumes should be minimized to prevent further augmentation of PA pressures.

Pulmonary vasodilators relax pulmonary vascular smooth muscle, lowering PA pressures and PVR. Inhaled nitric oxide (iNO) has the advantages of pulmonary selectivity, avoiding the hypotension associated with systemic vasodilators. It is also only active in ventilated areas of the lung, reducing the potential for V/Q mismatching. iNO is most commonly used in acute RV failure due to difficulty in administration to non-ventilated patients. Short-term hemodynamic improvements have been demonstrated with the use of iNO in the treatment of RVI [45] and in a study of intensive care patients with mixed causes of RV failure [46], but outcomes data are limited. Transitioning from iNO to oral vasodilators may prevent rapid rebound of PA pressures on discontinuation. Inhaled prostacyclins may be used as an alternative to iNO, although they have been less extensively studied.

In chronic RV failure, therapy depends on the underlying mechanism of the elevated PA pressures. In PAH, there are three classes of vasodilators that have shown clinical benefit: prostacyclins, endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE-5Is). As mentioned previously, a small subset of PAH patients will respond to calcium-channel blockers, and may not require any further treatment. Outside of this subset, most PAH patients will be started on oral therapy with an ERA or PDE-5I. As the disease progresses, these patients may need to be transitioned to intravenous prostacyclin therapy. Patients who present with severe symptoms, such as syncope, often require intravenous prostacyclin therapy from the outset.

When RV failure is due to post-capillary PH (i.e. LV dysfunction or valvular disease), the initial therapeutic target is the PCWP, which should be lowered into the normal range if possible. If the PH is reactive, lowering the PCWP should also reduce PA pressures and PVR. However, if PVR remains elevated, consideration should be given to pulmonary vasodilator therapy. Sildenafil citrate, a PDE-5I, has shown benefits on hemodynamics and functional status in patients with left-sided heart failure [47–49]. A large trial to assess outcomes of patients with PH related to LV dysfunction is underway. Neither ERAs nor prostacyclins should be used for post-capillary PH due to adverse outcomes in clinical trials [15, 50].

Contractility

In acute RV failure, inotropes are often required to support the RV until the etiology can be treated. Milrinone may be the preferred agent due to its vasodilatory properties in the pulmonary vasculature, but its use is limited in patients with significant hypotension. Dobutamine and dopamine are more likely to cause tachycardia, which may exacerbate ischemia in the setting of an RVI. In some cases of RVI, mechanical support with an intraaortic balloon pump or a temporary right ventricular assist device (RVAD) has been used, although neither of these approaches has been well studied. Temporary RVADs have also been used to treat RV failure that occurs following cardiovascular surgery or cardiac transplantation.

For chronic RV failure, choices for augmenting contractility are limited. Digoxin is often used as an inotrope in the management of RV failure, based on its short-term hemodynamic benefits in patients with PAH [51]. The use of intravenous inotropes for chronic left heart failure has been associated with worse outcomes. Intravenous inotropes may be used for management of exacerbations of chronic RV failure, but the chronic administration of these agents has been associated with worse outcomes. When biventricular heart failure is refractory, a RVAD may be placed in conjunction with a left ventricular assist device (LVAD) as a means of bridging a patient to transplantation. The devices that are approved for RV support are extracorporeal (i.e. non-implantable) and are not meant for long-term support, although the development of more durable RVADs is ongoing. In some cases, these devices can be explanted once stable LVAD support has been established. Cardiac transplantation is a definitive treatment for patients with advanced RV failure that is associated with LV failure, but this therapy is limited in use due to a shortage of donor organs. Cardiac transplantation should not be attempted in patients with high PVR (>6 Woods Units) due to high risk for RV failure and graft loss postoperatively.

Summary

The onset of RV failure carries a poor prognosis in multiple diseases and is often a marker of a progression to an advanced disease state. RV failure is the end result of a series of pathophysiological adaptations that are distinct from the pathogenesis of LV failure. A detailed understanding of the RV's response to specific disease states informs the clinical management of those diseases. Imaging plays a critical role in the assessment of RV dysfunction, and can provide information about the severity of RV failure. Hemodynamic assessment with cardiac catheterization complements the findings from imaging, directing the appropriate therapeutic approach. The treatment of RV failure due is highly dependent on the underlying etiology. Acute causes respond best to removal of the offending pathophysiology. Chronic RV failure requires a targeted approach, as has been applied in the setting of PAH. Research continues into the optimal treatment strategy for PH that is secondary to left heart failure.

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