

Hospital and intensive care unit management of decompensated pulmonary hypertension and right ventricular failure

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Published online: 20 October 2015
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Abstract Pulmonary hypertension and concomitant right ventricular failure present a diagnostic and therapeutic challenge in the intensive care unit and have been associated with a high mortality. Significant co-morbidities and hemodynamic instability are often present, and routine critical care unit resuscitation may worsen hemodynamics and limit the chances of survival in patients with an already underlying poor prognosis. Right ventricular failure results from structural or functional processes that limit the right ventricle's ability to maintain adequate cardiac output. It is commonly seen as the result of left heart failure, acute pulmonary embolism, progression or decompensation of pulmonary hypertension, sepsis, acute lung injury, or in the perioperative setting. Prompt recognition of the underlying cause and institution of treatment with a thorough understanding of the elements necessary to optimize preload, cardiac contractility, enhance systemic arterial perfusion, and reduce right ventricular afterload are of paramount importance. Moreover, the emergence of previously uncommon entities in patients with pulmonary hypertension (pregnancy, sepsis, liver disease, etc.) and the availability of modern devices to provide support pose additional challenges that must be addressed with an in-depth knowledge of this disease.

Keywords Right ventricular failure · Intensive care management · Pulmonary hypertension · Sepsis · Pregnancy

Introduction

The understanding of the function of the right ventricle (RV) in health and disease is an understudied field that has evolved considerably over the last century. The RV, once considered a passive conduit of blood and a bystander in disease, is now recognized to play an important role in determining the outcome of many patients admitted to the intensive care unit (ICU) [1–3]. Acute dysfunction of the RV, irrespective of baseline pulmonary vascular resistance (PVR), has been a well-recognized entity in ICU patients with septic shock and acute respiratory distress syndrome (ARDS) [4, 5]. The decompensation of the RV function is detrimental to survival, especially in patients with pulmonary hypertension (PH) who often have compromised RV function at baseline [6]. Despite the better understanding and available therapies for PH, the mortality of patients admitted to the ICU with decompensated PH and right ventricular failure (RVF) remains unacceptably high [7–10]. This review will describe the epidemiology, evaluation, and management of patients requiring hospitalization and ICU admission for decompensated PH and RVF.

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Epidemiology

The true prevalence of PH is unknown, likely due to the variable etiologies which have been classified into groups by the World Health Organization (WHO) (Table 1) [11]. Recent literature estimates the prevalence of group 1

Table 1 Classification of pulmonary hypertension

1. Pulmonary arterial hypertension
 - 1.1. Idiopathic PAH
 - 1.2. Heritable PAH
 - 1.2.1. BMPR2
 - 1.2.2. ALK-1, ENG, SMAD9, CAV1, KCNK3
 - 1.2.3. Unknown
 - 1.3. Drug and toxin induced
 - 1.4. Associated with
 - 1.4.1. Connective tissue disease
 - 1.4.2. HIV infection
 - 1.4.3. Portal hypertension
 - 1.4.5. Congenital heart diseases
 - 1.4.5. Schistosomiasis
 - 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
 - 1'' Persistent pulmonary hypertension of the newborn (PPHN)
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
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 (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
 - 5.1. Hematologic 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

BMPR bone morphogenic protein receptor type II, *CAV1* caveolin-1, *ENG* endoglin, *HIV* human immunodeficiency virus, *PAH* pulmonary arterial hypertension. Reproduced with permission from Simonneau et al. (2013)

(PAH) which is around 15 per million people [12, 13]. Left heart disease is the most common cause of PH and comprises group 2 with an estimated 25–100 % of patients with left heart disease having PH [14]. Chronic obstructive pulmonary disease (COPD) is the most common cause of group 3 PH, with prevalence varying with disease severity. Over 90 % of patients with severe COPD have a mean pulmonary artery pressure (mPAP) > 20 mmHg, and 3–5 % have mPAP > 35–40 mmHg [15, 16]. Chronic thromboembolic pulmonary hypertension (CTEPH), group 4, occurs in up to 3.8 % of patients suffering from an acute pulmonary embolism (PE) with an estimated prevalence of 3.2 cases per million adults [15–17]. Group 5 includes

patients with PH from multifactorial mechanisms with an unknown prevalence. As a whole, groups 2–5 are more common than group 1 and can progress to RVF conveying a higher mortality risk [18–21].

Right ventricular failure

RVF results from a structural or functional process that limits the right ventricle's ability to effectively pump blood through the pulmonary circulation to maintain adequate filling of the left ventricle (LV) and cardiac output (CO) [9, 22]. These processes cause derangements in RV preload,

contractility, or afterload (Table 2). The most frequent causes of decompensation are infection, anemia, trauma, surgery, unplanned modification or withdrawal of pulmonary vasodilator therapy, unplanned withdrawal of diuretics, cardiac arrhythmias, pregnancy, and PE. However, up to 48 % of cases have no apparent causative factor and mortality is very high, ranging from 32 to 61 % [10].

The RV is more effective at adapting to volume overload than it is to pressure overload, and the outcome of RVF depends on the underlying cause. A gradual increase in RV afterload leads to chronic adaptation of the RV enabling it to tolerate a significant elevation in pulmonary artery pressures (PAP), whereas the RV without pre-existing hypertrophy will be unable to generate a systolic PAP above 50–60 mmHg [7–10, 23]. RVF secondary to PE has a much better prognosis compared to decompensated PH in a patient with underlying connective tissue disease (CTD) [10]. The management of the patient with RVF is complex and should include the investigation of the underlying causes, appropriate routine ICU care, and hemodynamic optimization (Fig. 1).

Initial evaluation of RVF

The initial evaluation of any patient in the ICU should focus on promptly establishing the cause of decompensation and identifying reversible conditions. Owing to the increasing awareness of PH, most patients suspected of having RVF from PH have a pre-existing diagnosis [23]. However, physical examination findings may be helpful in the unknown patient, and, although no specific biomarkers for RVF exist, several serum chemistries, cardiac enzymes,

imaging, and diagnostic tests aid in the diagnosis and prognosis.

Physical examination

Physical examination, especially in the early stages, is neither sensitive nor specific. Patients can present with tachycardia, tachypnea, hypotension, hypoxia, anxiety, cyanosis, and facial plethora. Cardiac examination is characterized by an elevated jugular venous pulse with a large “v” wave, a prominent pulmonary component of the second heart sound (P2), a palpable RV heave, and a holosystolic tricuspid regurgitant murmur along the left lower sternal border that increases during inspiration. The height of the jugular venous distention and the quality of the venous wave pattern should be assessed (elevated *a* vs. *v* wave). The distance from the sternal angle to the top of the waveform is measured in centimeters, and by convention, the distance between the right atrium (RA) and the sternal angle is added (approximately 5 cm) [24]. Auscultation of the lungs is usually unremarkable unless an underlying condition exists (COPD, pulmonary fibrosis, ARDS). Patients often have tender, palpable hepatomegaly, ascites, and peripheral edema. Cyanosis and digital clubbing may be seen, especially in patients with chronic hypoxemia. Findings of underlying conditions such as CTD (e.g., telangiectasia, sclerodactyly, and malar rash) may also be apparent [25, 26].

Laboratory and ancillary examinations

Although no specific test exists to diagnose RVF, several routine and disease-specific biochemical parameters aid in the

Table 2 Common triggers for acute right ventricular failure in the ICU

Trigger	Mechanism
Left ventricular failure	Increased RV afterload and RV dysfunction due to ventricular interdependence effect
Right ventricular ischemia	Decreased RV contractility
Sepsis	Decreased contractility, decreased RV preload, and/or increased RV afterload
Acute lung injury	Increased RV afterload
Post-cardiothoracic surgery	Increased RV afterload
Acute chest syndrome	Increased RV afterload
Pregnancy/delivery	Increased RV preload and increased CO
Cardiac tamponade	Decreased RV preload
Hypoxemia/acidosis	Increased RV afterload
Pulmonary embolism	Increased RV afterload
Mechanical ventilation	Increased RV afterload Decreased RV preload
Arrhythmia	Decreased contractility

diagnosis, management, and prognostication of patients with decompensated PH and RVF (Table 3). Liver function tests may be abnormal as a result of underlying liver disease or due to hepatic congestion. Patients with $\text{Na} \leq 136$ mEq/L have more symptoms, markers for RV dysfunction, and higher hospitalization and mortality rates ($\text{HR} = 10.16$) than their counterparts with normal sodium levels [7, 27]. Elevated serum creatinine level is associated with a worse hemodynamic profile and increased mortality [7, 28]. Elevated C-reactive protein (CRP), common in infection and inflammation, is associated with an increased mortality [29, 30].

Cardiac enzymes, although not specific for RVF, can be elevated in settings overstretching and ischemia of the RV. B-type natriuretic peptide (BNP) is closely related to the functional impairment of PAH patients and parallels the extent of pulmonary hemodynamic changes and RVF [31]. It can provide prognostic information in patient with stable PH as well as in decompensated patients admitted to the ICU [32–37]. High-sensitivity troponin T levels have been associated with higher risk of death and hospitalization in patients with PH [38–40]. Moreover, patients presenting with acute PE and elevated troponin or BNP levels

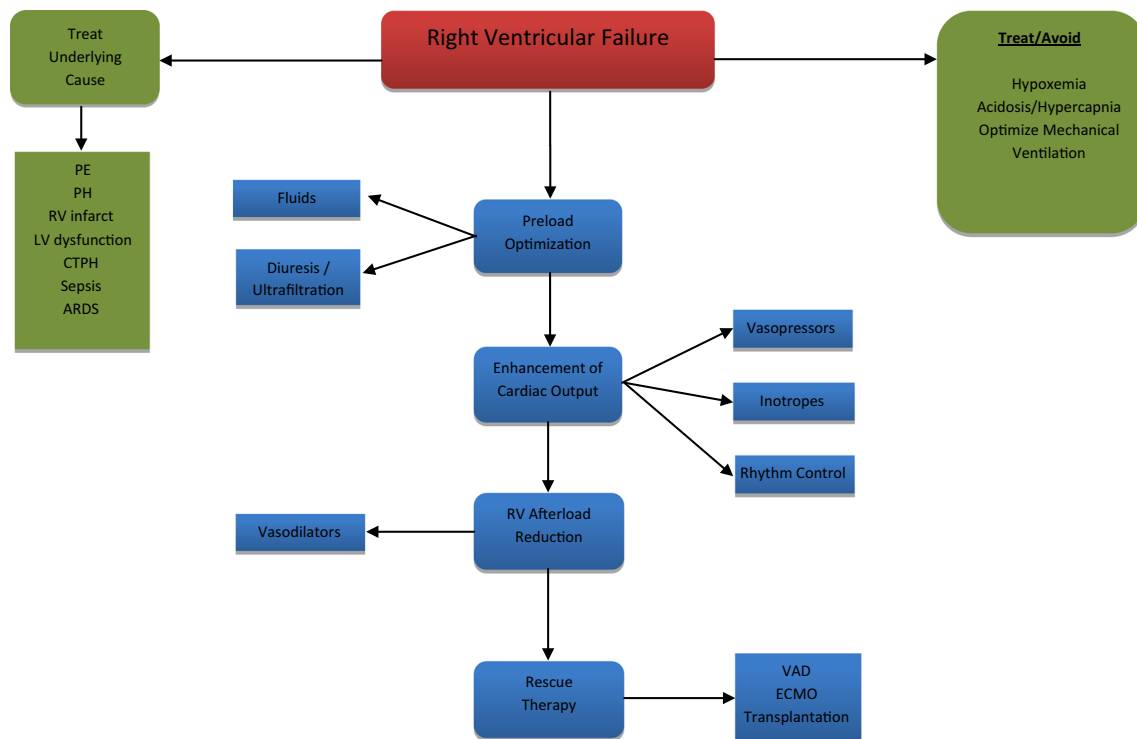


Fig. 1 Treatment of acute right ventricular (RV) failure in the intensive care unit (ICU). In addition to routine ICU care, treatment of RV failure consists of treating the underlying cause and optimizing hemodynamics in systematic approach. *PE* pulmonary embolism, *PH*

pulmonary hypertension, *LV* left ventricle, *CTPH* chronic thromboembolic pulmonary hypertension, *VAD* ventricular assist device, *ECMO* extracorporeal membrane oxygenation

Table 3 Biochemical markers associated with outcome of PH and RV failure in ICU

Serum sodium	Hyponatremia ($\text{Na} \leq 136$ mEq/L) is associated with increased symptoms, risk of frequent hospitalization, increased markers of RV dysfunction, and increased mortality
BNP, NT-pro BNP	Increased levels suggest worse RV dysfunction and increased mortality
Troponin	Higher levels are associated with increased mortality, especially in acute PE
Serum creatinine	Higher serum creatinine (≥ 1.5 mg/dL) is associated with increased mortality
C-reactive protein (CRP)	Predicts survival—higher levels (>4 mg/dL) are associated with increased mortality. Trend in CRP may be associated with response to therapy
Liver function (transaminases)	May be elevated due to congestive hepatopathy but do not have prognostic value

ASD indicates atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *MR* mitral regurgitation, *MS* mitral stenosis, *AS* Aortic stenosis, etc.

have a higher risk of adverse outcomes and mortality than those with normal levels [36, 37, 41].

Electrocardiography (ECG) is specific (83–95 %) but not sensitive (18–43 %) enough for the diagnosis of right ventricular hypertrophy (RVH) [42–44]. However, ECG parameters reflective of physiologic and anatomic abnormalities in the RV are significant predictors of mortality in patients with PAH. These include p-wave amplitude >0.25 mV in lead II, presence of qR in V1, and the WHO RVH criteria (Fig. 2) [45]. In addition, the ECG may reveal signs of RV ischemia or infarct.

Imaging

Radiographic examinations of the chest including chest X-ray and CT scan lack sensitivity or specificity in the diagnosis of early RV decompensation or failure, and their use is limited. Nonetheless, they can play an important role in defining an underlying pulmonary disease (pneumonia, pulmonary fibrosis, PE, etc.) [46]. Cardiac magnetic resonance imaging is a very effective noninvasive method to assess RV function, but is rarely used in the management of critically ill patients due to logistical issues [47].

Diagnostic strategies

Since electrocardiography and different biomarkers are not sensitive for the diagnoses of RVF in the ICU, the most reliable methods of diagnosis and monitoring of treatment

response in the ICU are echocardiography (transthoracic and/or transesophageal) and the pulmonary artery catheter (PAC).

Echocardiography

Bedside echocardiography has a pivotal role in the critically ill patient with decompensated PH and RVF, as it can provide information regarding the morphology and function of the RV, estimate RA and RV pressures, and identify cardiac causes of PH (Table 4) [48, 49].

Disease states that cause RV volume or pressure overload will lead to dilation and eventual hypertrophy of the RV. Findings of significant PH on echocardiography include: inferior vena cava dilatation, RA enlargement, RV enlargement and/or hypertrophy, decreased RV function, intraventricular septal flattening (D-shaped LV), and tricuspid regurgitation (TR) (Figs. 3, 4, 5). The TR jet or the pulmonary regurgitation jet velocities, in conjunction with an estimated RA pressure, are used to calculate the right ventricular systolic pressure (RVSP). RVSP correlates well with systolic PAP in the absence of pulmonary stenosis and can diagnose PH with a sensitivity of 83 % and specificity of 72 % (Fig. 5) [50, 51]. However, about 10–25 % of patients will have an insufficient spectral Doppler profile of the TR jet to measure the RV to RA pressure gradient; in these instances, the presence of right heart chamber enlargement or septal flattening suggests elevated right heart pressures [52, 53].

The severity of symptoms in patients with PH is strongly associated with RV function. This can be evaluated by

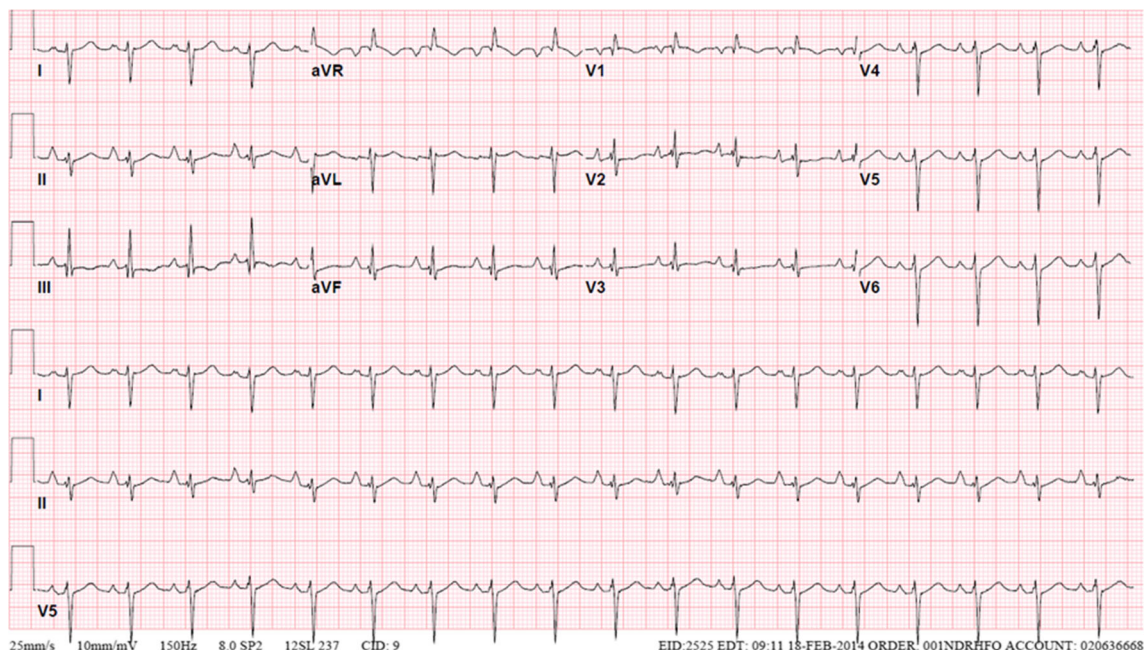


Fig. 2 Electrocardiogram of a patient with right ventricular hypertrophy due to pulmonary hypertension. Notice presence of qR pattern in V1, R amplitude $<$ S amplitude in V5, R amplitude $<$ S amplitude in I, p amplitude >0.25 mm in II, QRS complex right axis deviation $>110^\circ$

Table 4 Cardiac causes of PH/RVF that can be identified with echocardiography

1. Congenital disease with shunt: ASD, VSD, coronary fistula, PDA, anomalous pulmonary venous return
2. Congenital or acquired valvular disease: MR, MS, AS, prosthetic valve dysfunction
3. Other congenital diseases: coarctation, supraaortic AS, subaortic membrane, cor triatriatum
4. Severe left ventricular systolic or diastolic dysfunction
5. Pulmonary embolus, pulmonary vein thrombosis/stenosis

echocardiography using multiple parameters including the fractional area change (FAC), RV free-wall longitudinal systolic tissue velocity (s'), tricuspid annular plane systolic excursion (TAPSE) (Fig. 6), RV myocardial performance index (MPI or Tei index), isovolumic contraction velocity (IVCv), RV strain, and 3D RV ejection fraction [54–57].

Echocardiography provides prognostic information in patient with PH and RVF (Table 5). Several echocardiographic parameters of RV dysfunction predict worse outcomes including an increased RV diameter, a decreased

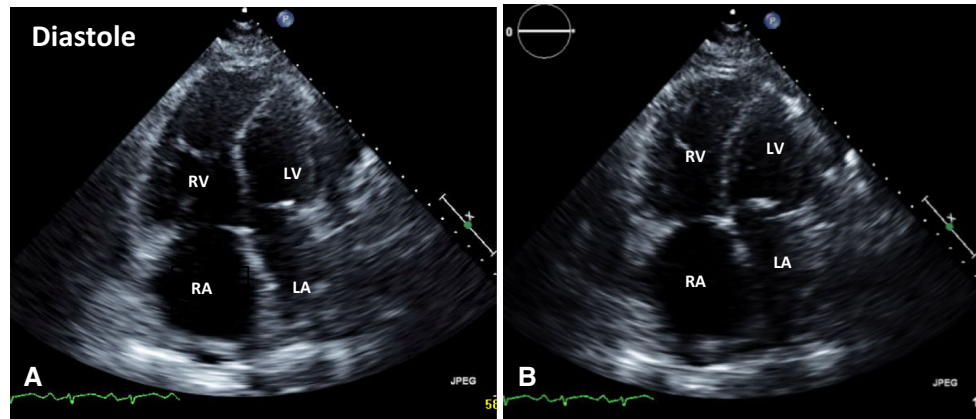


Fig. 3 Two-dimensional echocardiography apical four-chamber view during diastole (a) and systole (b) of a patient with pulmonary hypertension. Notice a dilated RV/RA and poor RV systolic function

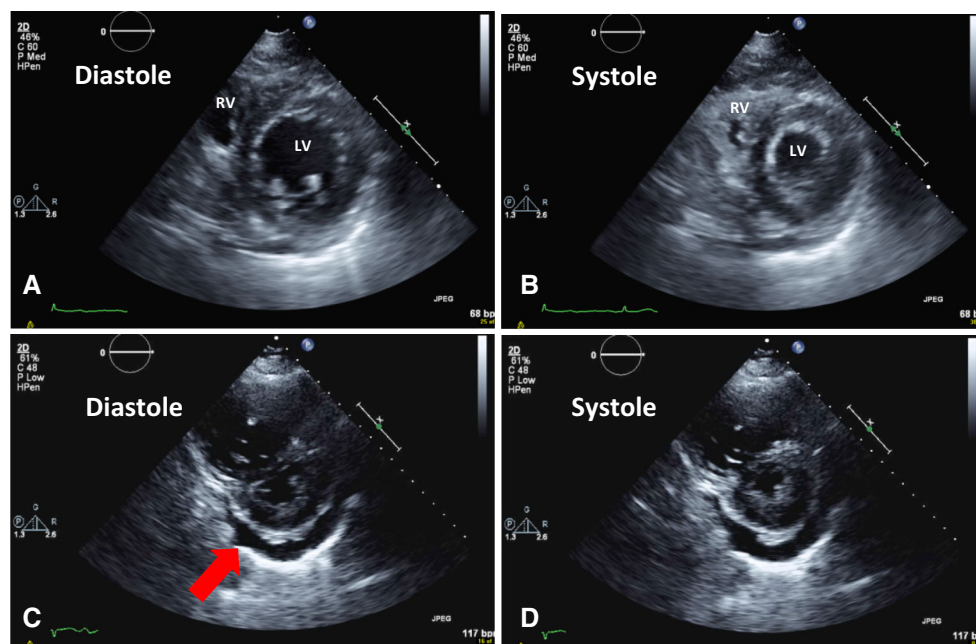


Fig. 4 Two-dimensional echocardiography (parasternal short-axis view) showing ventricular interdependence. Normally, LV end-diastolic pressure is greater than RV end-diastolic pressure, and the septum bows toward the RV during diastole (a, b). In patients with pulmonary hypertension and RV failure, RV end-diastolic pressure

exceeds that of the LV and the septum bows toward the LV during diastole forming a “D”-shaped pattern and impaired LV filling. Also, notice *red arrow* pointing to pericardial effusion (c). The combination of high RV systolic pressure and decreased LV filling may lead to near obliteration of the LV at end-systole (d)

TAPSE, an elevated Tei, an increased RA area, a decreased isovolumic contraction velocity (IVCv), and alterations in RV free-wall strain [58–65]. In addition, the presence and severity of a pericardial effusion, theoretically caused by elevated RA pressures due to RV dysfunction leading to impaired lymphatic drainage through the thoracic duct, are a strong predictor of mortality (Fig. 4) [63, 66, 67].

Pulmonary artery catheter

Accurate and complete invasive assessment of pulmonary hemodynamics is essential in the evaluation of patients with RVF, especially in those with RVF due to PH, as some hemodynamic values are predictors of survival [68–71]. In patients with newly diagnosed primary PH, the NIH registry showed that mortality was closely associated with an increased mean RA pressure, an increased mPAP, and a decreased cardiac index. An increase in mPAP from

<55 mmHg to ≥ 85 mmHg correlated with a decrease in median survival from 48 months to 12 months, an increase in RA pressure from <10 mm Hg to ≥ 20 mm Hg was associated with a decrease in median survival from 46 months to 1 month, and an increase in cardiac index from <2.0 L/min/m² to ≥ 4.0 L/min/m² correlated with an increase in survival time from 17 months to 43 months. Although these parameters have prognostic implications in chronic disease, their significance in acute decompensated PH or RVF has not been established [68].

In the critically ill patients, the hemodynamic values obtained when placing a PAC can help to assess the response to pharmacologic agents and aid in their titration to meet specific endpoints. When evaluating hemodynamic variables in a patient with RVF, the clinician must keep in mind that the mPAP may decrease as the RV function worsens. While patients who respond to the acute vasoreactivity test have excellent prognosis (95 % survival at

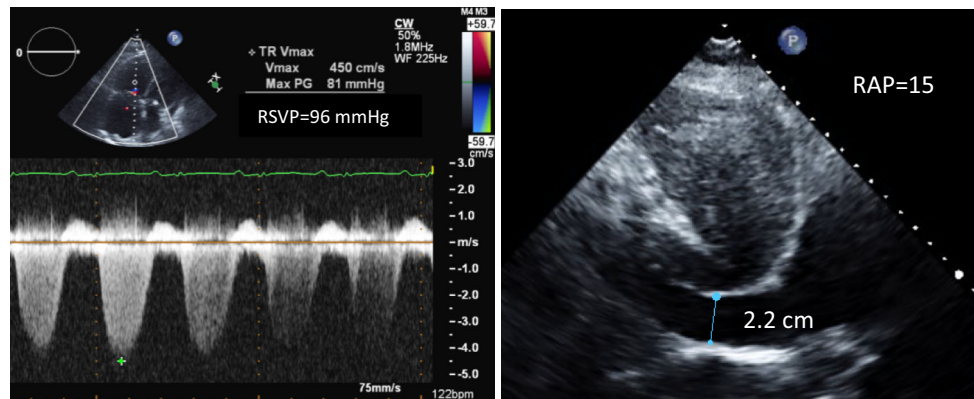


Fig. 5 Right ventricular systolic pressure (RVSP) estimation using the tricuspid regurgitation jet V_{\max} with CW Doppler. Bernoulli equation: pressure gradient = $4 \times V_{\max}^2$. RAP is estimated using

the size and collapsibility (during inspiration) of the IVC. V_{\max} maximum velocity, CW continuous wave, RAP right atrial pressure

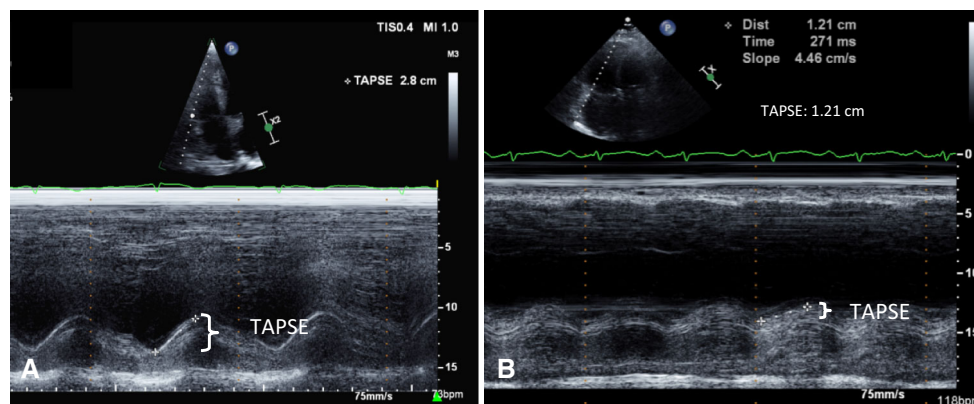


Fig. 6 Tricuspid annulus plane systolic excursion (TAPSE). M-cursor placed through the RV apex to the lateral tricuspid annulus (apical four-chamber view) to measure the distance traveled by the annulus in

centimeters from end-diastole to end-systole. **a** Normal TAPSE of 2.8 cm. **b** Abnormal TAPSE of 1.21 cm

Table 5 Echocardiographic parameters that provide prognostic information in patients with PH and RVF

Echocardiographic parameter	Characteristics, advantages, and limitations	Prognosis
RA and RV dimensions, ventricular interdependence, RVEF	Clinically validated, simple to perform, pre-load dependent [293]	Dilated RA and RV, as well as septal displacement predict adverse outcomes [58, 63]
Pericardial effusion	Clinically validated, simple to perform	The presence and severity have consistently shown to predict mortality [63, 66, 67]
Tricuspid annular plane systolic excursion (TAPSE)	Simple to perform, highly reproducible, not limited by endocardial border recognition, correlates well with RVEF, right heart remodeling and RV-LV disproportion [59, 294]	A TAPSE < 18 mm correlates with worse survival [59]
RV myocardial performance index (MPI or Tei index)	Index of combined RV systolic and diastolic function assessed by PW Doppler of the RVOT, TV inflow or regurgitation, or using DTI of the tricuspid annulus [61] Less affected by load and heart rate; may be underestimated in high RA pressure (as IVRT decreases)	A value ≥ 0.83 has shown to correlate with adverse outcomes [61, 62]
Isovolumic contraction velocity (IVCv)	Doppler tissue imaging, relatively preload and afterload independent and may reflect a more global ventricular contractility [295]	A value ≤ 9 cm/s correlates with worse survival [65]
RV strain	By speckle-tracking strain, requires additional processing, vendor specific deformation	Worsening of RV longitudinal strain has been associated with increased mortality [296, 297]

RA indicates right ventricle, RV right ventricle, RVEF right ventricular ejection fraction, PAH pulmonary arterial hypertension, LV left ventricle, PW pulse wave, RVOT right ventricular outflow tract, TV tricuspid valve, DTI Doppler tissue imaging, IVRT isovolumic relaxation time

5 years), while on calcium channel blockers, the utility of this test in the critical care setting is very limited [72, 73].

The placement of a PAC, albeit invasive, is a relatively safe procedure, especially when performed by experienced operators. A large cohort study reviewed, retrospectively and prospectively, the placement of 7218 PACs at 20 major pulmonary vascular centers over a 5-year period [74]. The overall number of serious adverse events was 76 (1.1, 95 CI 0.8–1.3 %). The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), arrhythmias, and hypotension related to vagal reactions or pulmonary vasoreactivity testing. Only four fatal events were recorded, resulting in an overall procedure-related mortality of 0.055 %. Similar results have been published in more recent but smaller cohorts [74, 75]. Although the evidence does not support the routine placement of PACs in the overall critical care population, this intervention has not been studied in patients with acute RVF and its use is advocated by most experts to monitor hemodynamic parameters and mixed venous oxygen saturation (SvO₂) [9, 23, 76, 77].

Hemodynamic management

The hemodynamic optimization of patients with RVF is complex and encompasses the precise manipulation of different variables to improve systemic perfusion including optimization of preload, enhancement of cardiac

contractility, RV afterload reduction, and maintenance of systemic perfusion pressure.

Preload Optimization

The optimization of right-sided filling pressures is crucial in the management of RVF as both hypovolemic and hypervolemic states have deleterious effects leading to decreased CO. In hypovolemic patients, fluid loading produces a 30 % mean increase in right ventricular end-diastolic volume index (RVEDVI) and a 17 % increase in LV end-diastolic volume index (LVEDVI) resulting in an enhanced stroke volume index (SVI) [78]. Similar response to fluid loading has been described in patients with RVF caused by massive PE [79]. The clinician must exert caution because excessive fluid administration in patients with increased PVR can have adverse effects that are explained by the phenomenon of *ventricular interdependence* (displacement of the interventricular septum toward the LV leading to decreased LV preload as seen in Fig. 4) and increased RV free-wall tension that result in increased myocardial oxygen consumption and decreased perfusion [80–83]. Therefore, liberal volume administration should be discouraged.

Most cases of RVF are associated with volume overload requiring the administration of diuretics or ultrafiltration to achieve a negative fluid balance. However, excessive volume removal can also be detrimental by reducing the already impaired CO. Although the optimal filling

pressures vary considerably between individual patients, preload should be kept at a goal between 8 and 12 mm Hg and subsequently adjusted to optimize cardiac output [22]. In summary, the clinician will need to closely monitor the effect of fluid administration or removal on filling pressures, CO, and perfusion parameters.

Enhancement of cardiac contractility

The enhancement of RV contractility with the addition of inotropic agents (Table 6) is important in the management of RVF.

Dobutamine, the most commonly used agent, has very dose-specific hemodynamic effects. At low doses (up to 5 µg/Kg/min), it produces increased cardiac contractility and decreased systemic vascular resistance (SVR) and PVR. At higher doses, it is associated with tachycardia and premature ventricular contractions without further reduction in the PVR [84]. In animal studies, doses > 10 µg/Kg/min were associated with increased PVR and hypotension [85]. The clinician must be aware of the latter complication that often necessitates vasopressors. Dobutamine is more effective than norepinephrine at improving CO, but it can increase the shunt fraction (venous admixture) affecting oxygenation (PaO₂). Simultaneous administration of dobutamine and inhaled nitric oxide can improve cardiac output without impairing oxygenation [86–88].

Milrinone produces a significant improvement in RV contractility, decrease in PVR, and improvement in LV filling [89, 90]. However, because of its vasodilator properties, it can cause or worsen preexisting hypotension [91]. Several studies report that inhaled delivery is well tolerated and produces similar effects in PAP and PVR with a higher SVR and less hypotension than the intravenous form [92–94]. In addition, the combination of milrinone and iNO has been associated with a more pronounced decrease in PAP than either agent alone [95].

Levosimendan has inotropic and vasodilator properties without increasing oxygen demand [96]. It increases right ventricular contractility and produces pulmonary

vasodilation in patients with ARDS and RVF caused by PE [97, 98]. In canine models, levosimendan had similar inotropic effects and stronger pulmonary vasodilatory effects than dobutamine [99]. In comparison with milrinone, levosimendan exerts a positive inotropic effect with a smaller increase in myocardial oxygen consumption [100]. In spite of these promising results, levosimendan has not been fully investigated in patients with RVF and its use can be complicated by arrhythmias and a low SVR leading to hypotension [98, 101–103]. Therefore, more evidence is needed before levosimendan can be widely used for this indication.

Vasopressor agents to restore systemic blood pressure

Maintaining adequate systemic arterial pressure has a dual importance in patients with RVF as it allows the organs to maintain autoregulation of perfusion and preserves blood flow to the right coronary artery (RCA) territory which is perfused throughout the cardiac cycle. The reduced RCA driving pressure due to lower aortic root pressure and/or higher RV pressure is detrimental to RV coronary perfusion. Therefore, increasing the aortic root pressure and SVR by using vasopressors in the setting of increased RV afterload will improve perfusion to the RCA territory [81, 104]. The ideal vasopressor agent should increase systemic arterial pressure (SVR) with minimal effect on the PVR (reduce the PVR/SVR ratio) and improve contractility of the RV. The clinician must exert caution because these drugs (Table 7) can increase PVR and cause unwanted effects.

Norepinephrine predominantly produces systemic vasopressor effects through the α₁ receptors. Doses of 0.5 µg/Kg/min do not cause a significant increase in PAP, whereas doses of 10 µg/Kg/min are sufficient to produce a 50 % increase in PVR. However, such high doses are not typical in the management of ICU patients [86, 105]. Norepinephrine reduces the PVR/SVR ratio in patients with chronic PH and can improve myocardial oxygen

Table 6 Inotropes

Agent	Effect	PVR	SVR	RV contractility	CO	Comments
Dobutamine	β ₁ agonist, minimal α ₁ and β ₂ agonist	↓	↓	↑	↑↑	Synergistic effect with iNO; higher doses cause ↑ PVR, hypotension, tachycardia
Milrinone	Phosphodiesterase-3 inhibitor	↓	↓	↑	↑↑	Synergistic effect with iNO; inhaled milrinone has minimal hypotension
Levosimendan	Cardiac troponin C calcium sensitizer	↓	↓	↑	↑↑	Not approved in the USA

delivery to the RV in septic patients with RVF [106, 107]. The stimulation of β_1 receptors improves the CO and the RV/PA coupling which is a measure of the efficiency of transmission of energy from RV to PA [86, 107, 108].

Dopamine increases CO and SVR. It exerts a pulmonary vasoconstrictor effect that can increase the PVR/SVR ratio leading to a decrease in the left to right shunt seen in infants with patent ductus arteriosus [109, 110]. Animal studies show that doses $\leq 10 \mu\text{g}/\text{Kg}/\text{min}$ increase CO leading to an increase in PAP without increasing the PVR [111, 112]. Nonetheless, dopamine has been associated with tachycardia in patients with PH, increased risk of arrhythmias in patients with septic shock, and increased mortality in patients with cardiogenic shock [113, 114].

Epinephrine has a potent vasoconstrictor effect due to its α_1 activity. In animal models, epinephrine at doses from 0.2 to 3.2 $\mu\text{g}/\text{Kg}/\text{min}$ was superior to dopamine in decreasing the PVR/SVR ratio [115]. After epinephrine administration, patients with RVF caused by septic shock experienced improved RV contractility, CO and mPAP without significantly affecting the PVR [116].

Phenylephrine has vasopressor but no inotropic activity. It has the ability to improve perfusion to the RCA because of the elevation of SVR [81, 117]. However, due to its effect of increasing the PVR, it can significantly impair RV function and decrease CO [106, 108].

Vasopressin produces systemic vasoconstriction while relatively sparing the pulmonary circulation; such combined effects produce a desirable decrease in the PVR/SVR ratio [118–123]. Vasopressin has been used in pediatric and adult settings as a rescue agent in the management of PH and RVF [120, 124–126]. However, at high doses ($>0.4 \text{ U}/\text{min}$), vasopressin can cause bradycardia and decrease in RV contractility and CO likely related to a decrease in coronary blood flow [127–130].

In summary, norepinephrine is the preferred agent given its effects on SVR, PVR, and improvement in RV/PA coupling. Vasopressin at low doses, dopamine, and norepinephrine are reasonable alternatives. Phenylephrine must be used with caution given the isolated α_1 effect that will increase systemic perfusion but will also increase PVR, potentially worsening RV function.

RV afterload reduction

Reduction in PVR is one of the most important components in the management of RVF because of the particular sensitivity of the RV to afterload changes. The pharmacologic agents (Table 8) to reduce PVR must be used with caution as they have the potential to cause hypotension.

Inhaled nitric oxide (iNO) is a very potent pulmonary vasodilator. Once inhaled, it diffuses across the alveolar capillary membrane into the smooth muscle of the pulmonary vessels and is rapidly inactivated by hemoglobin [131, 132]. iNO decreases PVR, has a neutral effect on SVR, and increases CO [133, 134]. In patients with RVF secondary to ARDS, iNO decreases PAP, increases PaO_2 by improving the ventilation perfusion relationship, and may decrease inflammatory cytokine production in the lungs [135–137]. iNO improves oxygenation with lower doses than those required to decrease mPAP, but it can have the opposite effect on oxygenation at higher doses [138]. Small studies have shown that iNO produces hemodynamic improvement in different settings of RVF including those caused by RV infarct, acute PE, post-surgical, post-left ventricular assist device (LVAD) implantation, and cardiac transplantation [139–155]. Complications encountered with the use of iNO include: accumulation of potentially toxic reactive metabolites, rebound PH, and rarely methemoglobinemia [156–161]. Despite reducing afterload and improving hypoxemia in RVF and ARDS, there is no demonstrated survival benefit [162–164]. Combination of iNO and prostacyclin derivatives has been reported with success in the perioperative management of portopulmonary hypertension (PoPH) and in RVF after high-risk cardiac surgery, LVAD insertion, and pulmonary endarterectomy [165–169].

The phosphodiesterase-5 (PDE5) inhibitors prevent the hydrolysis of cyclic guanosine monophosphate (cGMP), producing vasodilatory and antiproliferative effects in the pulmonary vasculature [170]. Sildenafil produces an acute decline in mPAP and PVR associated with an increase in CO. The vasodilatory effect of sildenafil is comparable to the effect of iNO with the added benefit of maintaining the pulmonary capillary wedge pressure (PCWP) and producing systemic vasodilatory effects [171–173]. Sildenafil has been used with success in patients with RVF at induction of

Table 7 Vasopressors

Agent	Effect	PVR	SVR	PVR/SVR	CO	Comments
Norepinephrine	α_1 and weak β_1 agonist	↑ at high doses	↑↑	↓	↑	Most favorable hemodynamic profile
Dopamine	Dopamine-1, α_1 , and β_1 agonist	↑	↑	↑	↑	Use limited by tachycardia and arrhythmias
Epinephrine	α_1 and β_1 agonist	↑	↑↑	↓	↑↑	
Phenylephrine	α_1 agonist	↑↑	↑	↑	–	May worsen RV function
Vasopressin	V1 receptor agonist	–	↑↑	↓	–	Low dose

Effects shown in table are at low doses. At high doses ($>0.4 \text{ U}/\text{min}$), vasopressin can cause bradycardia and affect RV contractility

Table 8 Pulmonary vasodilators

Mechanism	Agent	Effect	PVR	SVR	Comments
iNO	Inhaled nitric oxide	Cyclic GMP activator	↓	–	Short half-life with minimal systemic effects
PDE5 inhibitors	Sildenafil, vardenafil, tadalafil	Inhibit hydrolyzation of cGMP	↓	↓	Can reduce rebound PH when weaning iNO
Prostacyclin Analogs	Epoprostenol, iloprost, treprostinil	PGE2a and PGE2 → ↑cAMP	↓	↓	↑ CO; synergistic effect with iNO
ERAs	Bosentan, ambrisentan, macitentan	Block endothelin receptors in vascular smooth muscle	↓	↓	Long half-lives and associated with liver toxicity
sGC stimulator	Riociguat	Guanylate cyclase stimulator (NO receptor)	↓↓	↓↓	Not used in acute RVF

iNO inhaled nitric oxide, PDE5 phosphodiesterase-5 inhibitors, ERAs endothelin receptor antagonists, sGC soluble guanylate cyclase

anesthesia, during cardiac surgery, after LVAD placement, after cardiac transplant, and as an adjunct in the weaning of iNO to prevent rebound PH [174–181].

Prostacyclin derivatives are potent systemic and pulmonary vasodilators. These drugs act on the prostacyclin receptor (present in platelets and endothelial cells) that produces an increase in cyclic adenosine monophosphate (cAMP), resulting in inhibition of platelet aggregation, relaxation of smooth muscle, and vasodilation of the pulmonary arteries [182]. Prostacyclin derivatives decrease PVR and increase CO and exercise capacity in patients with PAH and have been used successfully in the perioperative setting in cardiac surgery and thoracic transplant [183–194]. In the setting of life-threatening PE, inhaled aerosolized prostacyclin was associated with a transient improvement in pulmonary hemodynamics and gas exchange [195]. In ARDS, inhaled prostacyclins have been associated with important physiologic benefits (improved hypoxemia, lower PAP, and improved RV function and CO) with no systemic hemodynamic effects given the aerosolized alveolar delivery. Unfortunately, there is no evidence supporting outcome benefits and, although controversial, its use should be reserved as a rescue therapy in refractory hypoxemia associated with ARDS [196–198].

Although the other available vasodilator agents including endothelin receptor antagonists (ERAs) and soluble guanylate cyclase stimulator (riociguat) are effective in PH, their use is not recommended in the setting of RVF. The ERAs have long half-lives and are associated with liver toxicity [199, 200]. Riociguat is a potent pulmonary vasodilator that produces significant systemic vasodilation and hypotension [201].

Intensive care unit supportive management

In addition to routine ICU care (nutrition, prophylaxis, etc.), the specific goals for care provided in the ICU are aimed at managing the factors that would further impair the

function of the failing RV. The management of hypoxemia, acidemia, increased intrathoracic pressures caused by mechanical ventilation, and the treatment of cardiac arrhythmias are extremely important.

Hypoxemia and acidemia

The management of the patient with RVF must address low oxygen saturation and acidemia as both increase mPAP and PVR with synergistic effects [202–205]. An oxygen saturation level $\geq 92\%$ has been proposed as an ideal target by experts [9, 22]. While acidemia increases the sensitivity of the pulmonary vasculature to hypoxemia, alkalemia decreases such sensitivity and produces pulmonary vasodilation [202]. Therefore, the clinician must strive for a PCO_2 and pH as close to normal as possible.

Mechanical ventilation

Mechanical ventilation, while often necessary in the management of patient with RVF, has the potential to produce unfavorable hemodynamic effects. The skillful adjustment of the ventilator to improve oxygenation and acidemia while minimizing the effects of increased intrathoracic pressures on the cardiovascular system becomes a priority.

Positive pressure ventilation causes decreased venous return, decreased RV stroke volume, distention of alveoli and compression of alveolar blood vessels, and increased PVR. Lung volumes near the functional residual capacity (FRC) minimally affect the PVR, whereas atelectasis and overdistention increase it (Fig. 7) [206–208]. While the patient with normal RV function may tolerate these changes relatively well, the consequences can be severe in patients with impending RVF. Therefore, the ventilatory strategy in the patient with RVF must strive to achieve normoxia using conservative tidal volumes and PEEP to avoid atelectasis, overdistention, increased PVR, and elevated intrathoracic pressures.

Although protective lung strategies are typically associated with respiratory acidosis, they confer a mortality benefit in ARDS that may be partially related to the lower incidence of RVF seen with lower tidal volumes and plateau pressures [209, 210]. Unfortunately, acute cor pulmonale is present in 20–25 % of patients with ARDS ventilated with protective lung strategies. Although this represents a decrease in the incidence of RVF from the pre-protective lung strategies era, it is still associated with poor clinical outcomes [210–215].

Prone positioning is associated with a significant decrease in airway pressures, PaCO₂, and improvement in echocardiographic parameters of RV pressure overload [216]. Moreover, it provides a mortality benefit in patients with severe ARDS [217].

High-frequency oscillatory ventilation (HFOV) is associated with unfavorable hemodynamic effects including an increase in central venous pressure, PCWP, and decrease in CO [218]. In patients with ARDS, HFOV can worsen RV function and does not provide a mortality benefit when compared with conventional protective lung strategies [219–221].

Rhythm control

Cardiac arrhythmias can be a cause or a complication of RVF in patients admitted to the ICU. Atrial flutter and fibrillation are the most common arrhythmias in this population,

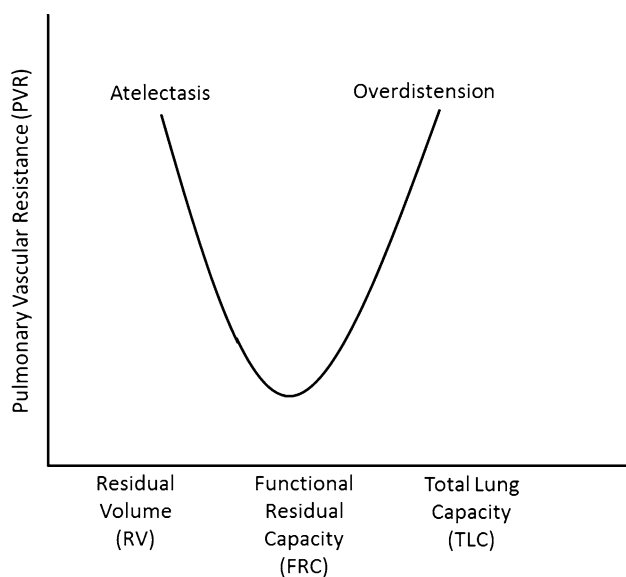


Fig. 7 Relationship of lung volumes and PVR. At volumes near FRC, the PVR is minimally affected. Atelectasis compresses extra-alveolar blood vessels leading to increased PVR. At high lung volumes, alveolar overdistension compresses intra-alveolar blood vessels resulting in increased PVR. *RV* residual volume, *FRC* functional residual capacity, *TLC* total lung capacity

whereas bradyarrhythmias and ventricular arrhythmias are rare except in the setting of cardiac arrest [222]. The RV is very sensitive to abnormalities in cardiac rhythm and synchrony. In RVF, augmented RA contraction and intact atrioventricular (AV) synchrony are important determinants of CO. The augmented RA contractility constitutes a compensatory response to RV dysfunction [223]. Restoration of AV synchrony produced positive hemodynamic results in patients with RV infarct and congenital heart disease [224–229]. AV pacing in patients with right bundle-branch block and RV dysfunction augments RV and systemic performance [230]. Although there are no large-scale studies to support resynchronization therapy in RVF, this intervention could be considered as part of the management.

Mechanical circulatory support

Mechanical circulatory support is typically reserved for patients with persistent RVF in spite of medical interventions and used as a bridge to heart, lung, or dual heart–lung transplantation. The currently available mechanical circulatory support modalities include the different ventricular assist devices and extracorporeal membrane oxygenation (ECMO).

The mechanical assist devices are available as left, right, or biventricular (LVAD, RVAD, or BiVAD, respectively). LVADs have been used with success in patients with PH and RVF caused by left heart dysfunction with the goal to reduce the mPAP and PVR, effects that are typically achieved in 3–6 months. A higher number of patients can be considered for heart transplantation after LVAD therapy with a possible benefit in post-transplant survival [231–236]. Although beneficial for the RV in the long term, LVADs can exacerbate or cause new-onset RVF because the decrease in LV end-diastolic volume will shift the interventricular septum to the left, increasing the RV end-diastolic volume, compromising its contractility [237]. Approximately 6–10 % of patients with a LVAD will require the implantation of a RVAD [238].

RVADs have been successfully used for the management of RVF in patients with RV infarct, after cardiac surgery, after LVAD implantation, and following heart transplantation [239–244]. RVADs will increase pressure but not sufficiently to overcome the increased RV afterload potentially injuring the lung [245]. BiVADs may be used in cases of bilateral ventricular failure as a bridge to transplantation [246].

Veno-arterial (V-A) ECMO has the ability to provide both cardiovascular and respiratory support as it drains deoxygenated blood from the venous circulation and returns oxygenated blood to the arterial circulation. V-A ECMO can be considered in patients with RVF secondary to increased afterload as a bridge to transplantation when medical interventions do not suffice. Although small studies suggest

favorable outcomes with the use of ECMO, further research is needed before general recommendations can be made and its use should be reserved for centers with expertise [247].

Miscellaneous ICU situations

Given the improvement in survival in patients with PH produced by modern available therapies, an increase in other conditions that were not as common in this group of patients has occurred. The clinician must be familiar with the pathophysiologic differences of the PH patient to provide the best possible care.

Pregnant patient with PH

During pregnancy, significant physiologic changes occur including increased blood volume, increased CO, decreased SVR, and increased pulmonary blood flow [248]. During delivery, pain, anxiety, raised levels of catecholamine and uterine contractions produce an increase in CO. After delivery, the venous return increases significantly as a result of the involution of the uterus producing a sizeable increase in CO. Patients with normal PVR can readily tolerate these changes through vasodilation and recruitment of pulmonary vessels, whereas patients with PH cannot adapt making them prone to develop acute RVF [249]. Consequently, the mortality rate, albeit lower than in previous times, remains very high ranging from 17 to 28 %, with most complications occurring in the peripartum period [250, 251].

Vaginal delivery may be better tolerated by PH patients given the smaller shifts in blood volume and greater stability in hemodynamics, but cesarean section (CS) may become urgently necessary in cases of fetal distress or maternal deterioration. Recent literature reports a more frequent use of CS and a higher proportion of premature deliveries; this change in practice may be explained by closer surveillance and a lower threshold for intervention in cases of maternal deterioration or fetal distress [251]. A multidisciplinary team including the cardiac anesthesiologist, obstetrician, and neonatologist should be involved if a CS is the chosen route of delivery. The PH patient should undergo close monitoring during the peripartum period with particular attention to arterial oxygenation, cardiac rhythm, and hemodynamics. The use of invasive monitoring devices seems reasonable and should be considered on a case-by-case basis [252, 253]. Successful outcomes have been reported with the use of various pulmonary vasodilators during the peripartum period including epoprostenol, iNO, and combination of sildenafil and epoprostenol [254–259].

Liver disease and PH

PoPH is a complication of portal hypertension that occurs more commonly in patients with chronic liver disease. It is often asymptomatic and discovered during the perioperative period for liver transplantation when it poses the highest risk [260, 261]. The acute increase in CO at the time of reperfusion cannot be handled by the RV of the patient with PoPH leading to acute RVF [262]. The evaluation of risk, indications for advanced therapy, and contraindications to liver transplant are based on hemodynamic variables including mPAP and PVR. A mPAP > 50 is considered a contraindication for liver transplant, whereas a mPAP < 35 is considered safe [263, 264]. Pulmonary vasodilators are used in the management of PoPH to improve hemodynamics. Several small studies report the use of prostacyclin analogs [265–267], ERAs [266, 268–270], and PDE5 inhibitors [268, 271, 272] in the management of patients with PoPH. In the perioperative period, combined use of iNO and epoprostenol has been reported with good outcomes [165, 166].

PH in biventricular failure

Left ventricular failure is among the most common causes of RVF [9]. The backflow caused by left heart disease increases LV end-diastolic pressure and RV afterload. Therefore, the treatment of patients with biventricular failure should focus on optimizing LV function through improvement in preload, contractility, and afterload. However, even after optimization of the left heart function, the transpulmonary gradient (mPAP–PCWP) may remain elevated, a phenomena known as “out of proportion” PH that is thought to be caused by an intrinsic abnormality in the pulmonary vasculature [273, 274]. The persistent elevation in PVR is especially important in patients being considered for cardiac transplant or LVAD placement because of an increased perioperative risk and decreased long-term survival after transplantation and the potential need for additional mechanical RV support [238, 275]. Sildenafil has been linked to improved exercise capacity and pulmonary hemodynamics in secondary PH patients with systolic heart failure, but not in patients with diastolic heart failure [276–278]. Prostacyclin analogs have also been used with positive hemodynamic changes [279, 280]. ERAs have not been associated with improved clinical outcomes and may increase the risk of decompensation [281–284]. Nevertheless, more evidence is needed before general recommendations can be made regarding the use of pulmonary vasodilators in this setting.

Sepsis

Sepsis poses a myriad of physiologic derangements including increased vascular permeability, vasodilation, hypovolemia, and decreased SVR that must be overcome by an increment in CO [4–6, 10]. Low SVR leads to decreased RV coronary perfusion, myocardial ischemia, and failure. In addition, there is often an increase in PVR causing decreased RV output. An increase in RV afterload or intrinsic myocardial depression may be the dominant cause of RV dysfunction in sepsis [4–6, 10]. Given the increased PVR, increasing cardiac output may prove very difficult in patients with PH and sepsis can trigger acute RVF. The management of the septic patient with PH must include early administration of antibiotics and hemodynamic optimization that should encompass the optimization of preload, enhancement of SVR, improvement of CO, and prevention of increase in PVR (as discussed above) [285]. Fluid resuscitation should not be liberal in this population and ideally must be guided by invasive hemodynamic monitoring devices. The use of pulmonary vasodilators in sepsis should be reserved to cases where further decrease in PVR is needed to improve cardiac output and systemic perfusion, keeping in mind that these agents produce systemic effects that could worsen the hemodynamic status.

Advance directives and resuscitation outcomes

The etiology of acute RVF largely influences the prognosis; patients with severe left heart disease or progressive PH in the setting of CTD have a worse prognosis compared to patients with acute PE [10, 286]. Despite the recent advancements in therapy that have improved the quality of life and survival in PH, it still remains a progressive disease that will ultimately have fatal outcomes. Therefore, it is important that the patient's wishes pertaining to end-of-life care be discussed in a serene environment during the course of the disease. Grinnan et al. reported that the majority of patients with PAH died in the hospital and most of those deaths happened in the ICU [287]. Unfortunately, the ICU may not be the best setting to have this conversation for the first time when decompensation typically occurs rapidly and decisions may need to be made very quickly. Cardiopulmonary resuscitation (CPR) is attempted in 25 % of patients that ultimately die of progression of the disease. The survival of PH patients who arrested and had CPR is quite low (0–6 %) compared to the survival from other causes of cardiac arrest, a fact that is not surprising given that chronic disease is associated with poor outcomes after CPR [288, 289]. Moreover, almost every patient that survived had a correctable cause [290]. Recent evidence shows that palliative care services were infrequently utilized in the care of patients with PH [287, 291, 292].

The care of patients with progressive disease should include a discussion of goals of care, potentially limiting aggressive therapy, and referral to palliative care when appropriate for the management of symptoms and potentially improve quality of life.

Conclusions

PH and concomitant RVF present a diagnostic and therapeutic challenge in the ICU and have been associated with increased mortality. Prompt recognition is essential for the appropriate management in these patients. The use of biochemical markers and echocardiography may help in the diagnosis and have prognostic value, and invasive monitoring with PAC is likely necessary to monitor hemodynamics and therapeutic changes. Careful manipulation of RV preload is required as under- or overfilling of the RV will worsen its contractility. Pulmonary vasodilators have a profound effect on PVR and can be used to increase CO but co-administration of systemic vasopressors and restoration of cardiac output with the use of inotropes are usually required. Mechanical circulatory support is predominately being utilized as a bridge to transplant. Despite the advances in therapy that have improved the survival in patients with PH, realistic expectations should be discussed in the outpatient setting as patients who suffer cardiac arrest have very poor outcomes. Overall, more studies of RVF are required to improve overall outcomes of this disease.

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