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REVIEW

Diagnostic workup, etiologies and management of acute right ventricle failure

A state-of-the-art paper

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Abstract

Introduction: This is a state-of-the-art article of the diagnostic process, etiologies and management of acute right ventricular (RV) failure in critically ill patients. It is based on a large review of previously published articles in the field, as well as the expertise of the authors.

Results: The authors propose the ten key points and directions for future research in the field. RV failure (RVF) is frequent in the ICU, magnified by the frequent need for positive pressure ventilation. While no universal definition of RVF is accepted, we propose that RVF may be defined as a state in which the right ventricle is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism (i.e. increase in stroke volume associated with increased preload). Both echocardiography and hemodynamic monitoring play a central role in the evaluation of RVF in the ICU. Management of RVF includes treatment of the causes, respiratory optimization and hemodynamic support. The administration of fluids is potentially deleterious and unlikely to lead to improvement in cardiac output in the majority of cases. Vasopressors are needed in the setting of shock to restore the systemic pressure and avoid RV ischemia; inotropic drug or inodilator therapies may also be needed. In the most severe cases, recent mechanical circulatory support devices are proposed to unload the RV and improve organ perfusion

Conclusion: RV function evaluation is key in the critically-ill patients for hemodynamic management, as fluid optimization, vasopressor strategy and respiratory support. RV failure may be diagnosed by the association of different devices and parameters, while echocardiography is crucial.

Keywords: Right ventricle failure, Pulmonary hypertension, Critically ill patients, Echocardiography, Shock

Introduction

For years, the left ventricle (LV) has been considered by cardiologists and intensivists as the essential ventricle for maintenance of effective circulation. The LV, after all, holds the central role in defining arterial pressure, one of the main determinants of organ perfusion with blood flow. However, as better bedside hemodynamic monitoring and advanced imaging techniques have evolved, the linkage between Guytonian physiology and cardiovascular assessment demonstrated the essential role of right ventricular (RV) function in cardiovascular homeostasis. This realization is supported by several parallel lines of evidence. First, many critical care patients receive positive-pressure ventilation. The increasing airway pressure artificially increases right atrial pressure (RAP), the back pressure to venous return [1], limiting cardiac output, while simultaneously increasing RV afterload [2]. The phasic changes in RV output due to positive-pressure breathing define most of the dynamic changes in LV output, quantified as either arterial pulse pressure

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or LV stroke volume variations [3]. Second, the RV is the main limiting factor of fluid-responsiveness, as shown in pulmonary embolism (PE) [4] and in septic shock [5]. Indeed, its primary function is to optimize systemic venous return by decreasing or keeping RAP as low as possible while simultaneously ejecting its highly varying end-diastolic volume into a highly compliant and low resistance pulmonary circulation. When the RV fails, it cannot achieve these goals and the patient becomes fluid-unresponsive. Third, many situations in the critical care setting may promote RV failure (RVF) by causing increases in pulmonary vascular resistance, as described below.

Thus, it is not surprising that the occurrence of RVF reflects loss of cardiovascular reserve and is strongly associated with a poor prognosis. Worsening RV function is both a marker of adverse outcome and a direct contributor to mortality in a variety of disease states experienced in the critical care settings, as discussed later in acute respiratory distress syndrome (ARDS), RV myocardial infarction (MI) or decompensated pulmonary artery hypertension (PAH). The interplay between the RV and the pulmonary vasculature is a critical component of cardiac performance and patient outcomes while a number of diseases can directly or indirectly alter this interaction.

This state-of-the-art paper is an invited paper for the cardiovascular issue of Intensive Care Medicine. It reports the current definition, epidemiology and etiologies of RVF in the critical care setting, as well as the current recommendations for diagnostic workup and management. This paper is written by recognized experts in the field who also propose 10 key points regarding RVF based on the current knowledge, as well as main uncertainties/controversies in the field (Table 1

Pathophysiology and definition of acute RV failure

Acute RVF in critically ill patients is sometimes called the "acute right heart syndrome" (ARHS). A commonly used definition for RVF does not exist, while a recent statement defined ARHS as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output [6]. We propose here a universal definition of RVF based on pathophysiology. In critically ill patients, ARHS is usually clinically diagnosed by a combination of systemic hypoperfusion (cool extremities, confusion, chest pain, arrhythmia, ileus, oliguria, lactic acidosis) and systemic congestion (turgescent jugular veins, hepatomegaly, oedema, ascites). Oedema and ascites are only present in patients with pre-existing chronic RVF or dysfunction. If a pulmonary artery catheter (PAC) is present in patients with predominant RVF, it displays a RAP higher than the pulmonary artery occlusion pressure, at which point the patient is usually hemodynamically unstable. In patients with severe biventricular failure, RAP may be elevated without an elevated ratio. Bedside echocardiography shows dilated or remodelled right heart chambers and depressed indices of systolic function most often in the presence of increased pulmonary artery pressures (PAP), as measured directly by the PAC or estimated by echo on the basis of increased velocity of tricuspid regurgitation and shortened acceleration time of RV ejection flow-velocity. A notch on the pulmonary flow signal is often indicative of pulmonary vascular obstruction (proximal or more distal). When a paradoxical intraventricular septal motion is also observed, some authors have also named this pattern *cor pulmonale* [7].

In situations where pulmonary hypertension (PH) is prominent, the ARHS is basically caused by a failure of RV systolic function adaptation to increased loading conditions (homeometric adaptation, or Anrep mechanism). According to the Anrep mechanism, rapid increase in PAP (within minutes) augments RV contractility (measured by end-systolic elastance, E_{es}) in order to match the afterload (measured by pulmonary arterial elastance, E_a). However, homeometric adaptation is often limited in critically-ill patients where pulmonary hypertension is associated with systemic hypotension and systemic inflammation, two factors contributing to RV injury. Optimal RV-arterial coupling relies on an E_{es}/E_a ratio of 1.5–2 to ensure flow output at minimal energy expenditure. When the E_{es}/E_a decreases to 1 and below, the RV enlarges to preserve flow output (heterometric adaptation, or Starling mechanism), at the price of increased filling pressures and systemic congestion [8]. The tricuspid valve is an essential part of RV structure and function. Unlike the mitral valve, the tricuspid value can dilate in its lateral dimension over a short time period resulting in acute regurgitation. This is a useful short-term adaptation, as it serves to decompress the acutely overloaded RV chamber preventing further dilatation. This adaptive regurgitation however results in increased venous and hepatic congestion and reduced forward flow.

Accordingly, RVF is defined by a state in which the RV is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism (i.e. increase in stroke volume associated with increased preload). This definition was initially proposed by Sagawa and colleagues after having shown that the "laws of the heart" (i.e. Anrep and Starling mechanisms) equally apply to both the RV and the LV [9] in spite of their obvious embryological and structural differences [10]. The evolution of RV functional adaptation to increased loading conditions is non-linear. RV dimensions may markedly increase with moderate increases in preload or afterload

Table 1 Key points, uncertainties and clinical research recommendations in acute RV failure in critically ill patients

Key points
1. RV function is essential to cardiovascular homeostasis, especially in critically ill patients undergoing mechanical ventilation
2. Phasic changes in RV output define most of the dynamic changes in LV output. This explains that "left" parameters for predicting fluid-responsiveness are less accurate in case of RV failure
3. The RV can maintain an optimal ventriculo-arterial coupling in case of PH (homeometric adaptation or Anrep mechanism), especially when its loading conditions increase occurs progressively and is not severe in nature (unless it occurs early in the post-natal period). This adaptation is limited in ICU because of the frequently associated systemic hypotension and inflammation
4. When the homeometric mechanism is overtaken (acute increase in PH, end-stage chronic PH), the RV enlarges to preserve stroke volume (heterometric adaptation or Frank–Starling mechanism)
5. RV failure may be defined by a state in which the RV is unable to meet the demands for flow without excessive use of the Frank–Starling mechanism
6. RV failure in the ICU usually associates with systemic hypoperfusion and systemic congestion
7. Causes of RV failure (medical or perioperative) are numerous and related to pressure overload, volume overload or decreased contractility, as well as tachyarrhythmias
8. Positive pressure ventilation has a major impact on RV function, either directly (via changes in airway pressures) or indirectly (via changes in PaO_2, $PaCO_2$, pH)
9. Echocardiography is crucial for diagnosis, but may be combined with invasive monitoring (increased filling pressure)
10. Management includes optimization of respiratory support and hemodynamic support. The failing RV does not tolerate fluid expansion and significant diuresis may be needed. Vasopressors such as norepinephrine are the primary salvage treatment
Current uncertainties and knowledge gaps
1. A commonly used and proven definition of RV failure does not exist. Which thresholds for CVP and effective stroke volume index should be used?
2. The relation between RV end-diastolic volume and distending pressure can be highly variable over short intervals of time
3. Should a significantly dilated RV that is still meeting the demand for flow qualify as RV failure? Should it be called RV dysfunction (early stage RV failure)?
4. The "true" incidence of RV failure is unknown in the ICU (recognizing that the incidence based on different criteria may vary)
5. Since RV failure is a key mediator of poor prognosis in critically ill patients, should RV be systematically protected?
6. Are new imaging techniques, such as CT-scan, MRI and 3D-Echo useful for diagnostic process in the critically ill?
7. Is fluid removal an appropriate approach to improve RV function? If so, what is the best method and how can therapy be guided?
8. Which parameters are sufficiently accurate and practical to optimize fluid status in RV failure?
9. What is the role of inodilators (e.g., levosimendan) to improve ventriculo-arterial coupling? Are there specific situations in which this should be used (or not be used)?
10. What is the role of dobutamine or milrinone in RV failure? Is one drug superior? Should these drugs be generally used or limited to specific scenarios?
Clinical research priorities
1. To investigate in a large observational multicenter and prospective study, including unselected consecutively admitted patients in the ICU, the incidence of RV failure and its impact on the fluid responsiveness, hemodynamic support, organ failure, and prognosis
2. To investigate the use of non-invasive monitoring of pulmonary vascular compliance, ventricular interdependence and ventriculo-arterial coupling to guide treatment decisions
3. To investigate the role of advanced echo techniques (e.g., strain) or RV end-systolic dimension measurement to early identify RV injury before the onset of failure
4. To investigate the role of portal vein flow and renal flow monitoring as read-outs for RV function in the intensive care setting
5. To investigate in an RCT the impact of applying a systematic RV protective strategy on mortality. A first application could be pursued in ARDS
6. To develop clinical trials in acute HFpEF based on RV phenotypes
7. To investigate the role of PDE5 inhibition in patients with acutely HFrEF or HFpEF and evidence of RV dysfunction and PH
8. To investigate the role of perioperative inhaled prostanoids in patients with RV failure undergoing high-risk surgery
9. To evaluate the value of prolonged mechanical support systems of the acutely failing RV
10. To develop enriched clinical trials based on molecular imaging, or pathway specific phenotyping of the RV

ARDS acute respiratory distress syndrome, *CT* computed tomography, *CVP* central venous pressure, *HFpEF* heart failure with preserved ejection faction, *HFrEF* heart failure with reduced ejection faction, *ICU* intensive care unit, *LV* left ventricle, *MRI* magnetic resonance imaging, *PDE5* phosphodiesterase 5, *PH* pulmonary hypertension, *RCT* randomized controlled trial, *RV* right ventricle

even though homeometric adaptation remains [8]. Thus, RV dimensions can be increased above normal limits (defined on healthy control populations), yet flow output remains sufficient without onset of systemic congestion. This intermediate zone may be called RV maladaptation or RV dysfunction, as it may be associated with eventual biological alterations and "pending" RVF.

Once RV systolic function becomes uncoupled from the pulmonary circulation and the RV dilates, there is a negative diastolic interaction due to ventricular

competition for space within indistensible pericardium. Associated with RV dilation both LV filling and cardiac output decrease [11]. This decreasing cardiac output eventually manifests as a decreased systemic arterial pressure, decreasing coronary blood flow and its associated negative systolic interaction. The vicious circle is further aggravated by RV ischemia due to decreased coronary perfusion pressure (gradient between diastolic blood pressure and right atrial pressure) [12] and contraction asynchrony [10, 13]. Right heart distension reflexly activates the sympathetic nervous system and the renin–angiotensin–aldosterone sequence which both result in renal salt and water retention aggravating systemic congestion and worsening ventricular interactions by further dilatation of the RV [14, 15].

Understanding these mechanisms, summarized in Fig. 1, helps to identify targets of therapeutic interventions.

Etiologies and epidemiology of RVF in the critical care settings

RVF in medical situations

RVF is a heterogeneous syndrome rather than a single disease. Treatment approaches, therefore, must be individualized based on the underlying etiology and mechanism of dysfunction. Because of differences in methodology and definition of RVF, as well as a paucity of prospective studies, the prevalence of acute RVF in the critical care setting has not been defined precisely. Moreover, the prevalence or incidence of RVF may vary depending on the criteria used.

Acute RVF occurs in many different situations (Fig. 2), which induce the described RV-arterial uncoupling. The most common cause of RVF is PH. Uncoupling of RV systolic function is generally observed with rapid increase of PAP or end-stage PAH, but also occurs with only mild PH in patients with lung inflammatory states (e.g. ARDS), sepsis and LV failure, all conditions also associated with negative inotropic effects. RVF may also develop in patients with PAH, because chronic RV remodelling has already occurred and the clinical presentation and treatments can be different from acute PH, for example, PAH with connective tissue diseases causing marked RV hypertrophy. In many of these acute and chronic situations, high airway pressure and high tidal volume mechanical ventilation intensify or even may cause acute RVF by increasing pulmonary vascular resistance [16]. In ARDS, one of the most common causes of acute RVF in the critical care setting, pulmonary vascular dysfunction is common [17]. Acute cor pulmonale (ACP) occurs in 14–50% of ventilated ARDS, with most studies reporting a prevalence of

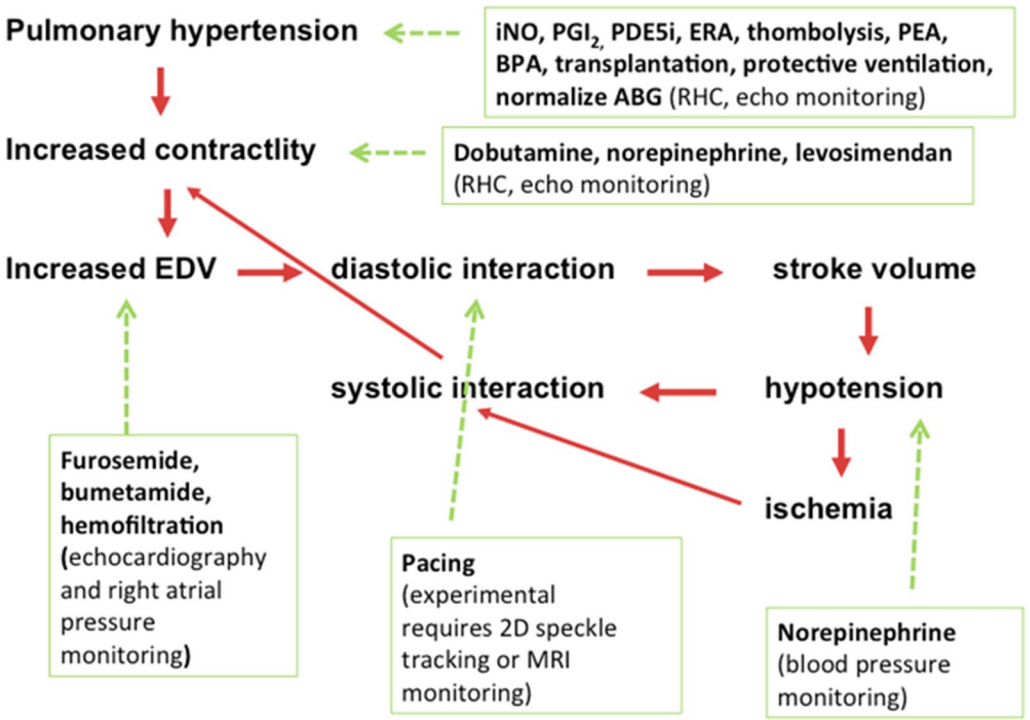

Fig. 1 Pathophysiology of RV failure process (bold arrows) with the main target for therapeutic interventions (striped arrows). *EDV* end-diastolic volume, *RHC* right heart catheterization, *PEA* pulmonary endarterectomy, *iNO* inhaled nitric oxide, *PGI_2* prostaglandin I_2, *PDE5i* phosphodiesterase type 5 inhibitor, *ERA* endothelin receptor antagonists, *BPA* balloon pulmonary angioplasty, *ABG* arterial blood gases

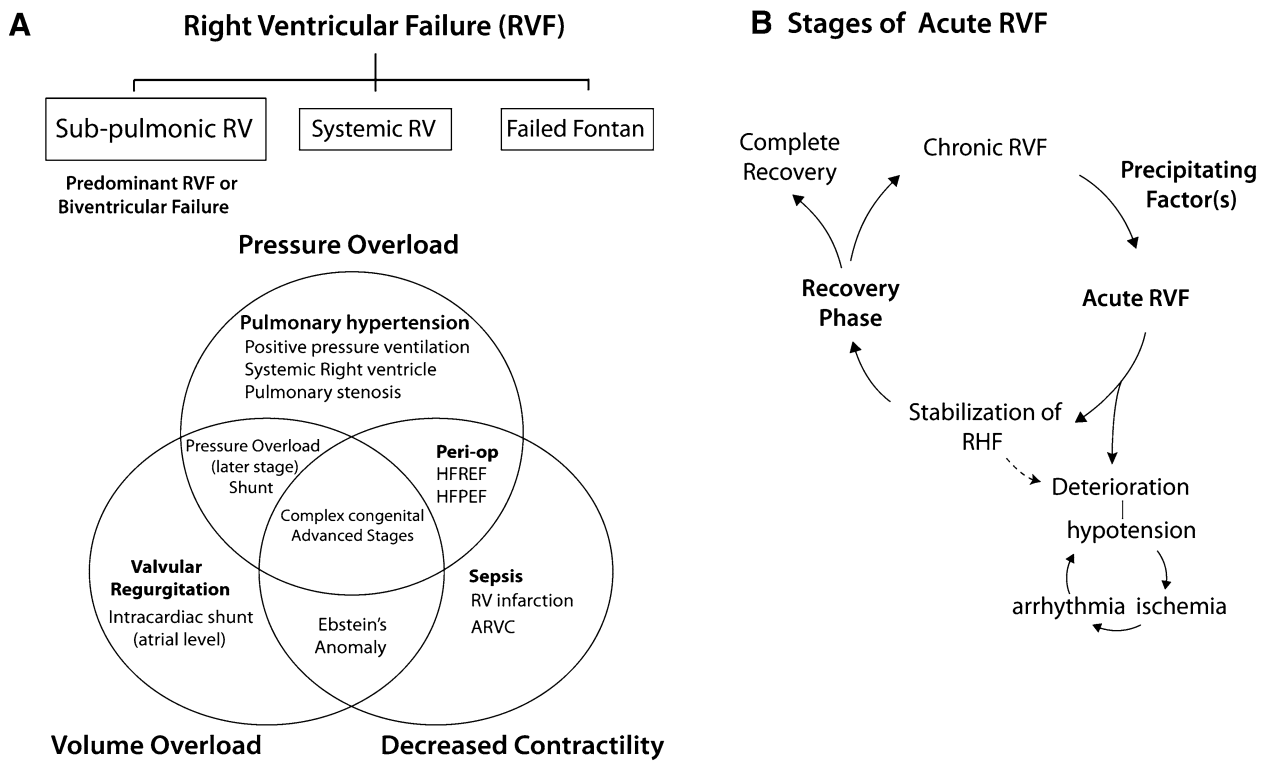

Fig. 2 Classification and stages of acute right ventricular failure (RVF). **a** RVF may affect a sub-pulmonic (by far the most common) or the systemic ventricle in transposition of the great arteries. Failed Fontan circulation is rare, but observed more frequently in referral centres. Although ventricular failure often affects both ventricles because of ventricular interactions, for clinical purposes it is useful to classify RVF as predominantly affecting the right ventricular or part of a biventricular failure profile. Pulmonary hypertension is the most common cause of RVF in the ICU. In many cases in the ICU, pressure overload, volume overload and decreased contractility often coincide. **b** Stage of acute RVF. Patients with acute RVF may present as there first presentation or as an acute on chronic RVF. In acute RVF the vicious cycle of hypotension, ischemia and arrhythmia has to be avoided as it leads to clinical deterioration. Recovery of acute RVF may be variable and the early recovery-post-discharge phase is known to be also vulnerable. *RV* right ventricle, *HFREF* heart failure with reduced ejection fraction, *HFPEF* heart failure with preserved ejection fraction, *ARVC* arrhythmogenic RV cardiomyopathy

around 25% [18]. Causes are multiple and usually combined lung inflammation, pulmonary artery injury and the effects of positive pressure ventilation [19]. In a large cohort of more than 700 patients with moderate to severe ARDS and ventilated in a "protective" manner (e.g. with a tidal volume around 6 mL/kg and a strict limitation of plateau pressure below 30 cmH_2O), ACP was found in 22% of cases. Four risk factors were identified, i.e. pneumonia, $PaO_2/FiO_2 < 150$ mmHg, $PaCO_2 \geq 48$ mmHg and driving pressure ≥ 18 mmHg [20]. Those patients with ACP are usually more tachycardic, have a lower systolic and mean arterial pressure and are more frequently in shock (86 versus 67%) [21]. In acute PE, cardiogenic shock occurs in ~ 4.5% of patients [22], and some evidence of RV strain occurs in about one-third of acute PE patients [23]. Pulmonary artery thrombosis has also been reported in sickle cell disease during acute chest syndrome in 17% of cases [24]. This is associated with an overall 24% incidence of RVF, especially when ARDS is also present [25]. RV MI is seen in about one third of cases of inferior wall acute MI [26]. Like other causes of acute RVF, RV MI causes uncoupling of RV systolic function and the pulmonary circulation, producing systemic congestion and reduced flow [6]. However, unlike most conditions associated with critical illness, in RV MI the lesion resides within the right ventricle, rather than in the pulmonary circulation.

The prevalence of acute RVF in other conditions (e.g. COPD exacerbations, left heart failure, sleep-disordered breathing) is not exactly known. However, many of these conditions are common, and some form of RV dysfunction (acute or chronic) may occur in as many as 80% of these patients [27, 28]. RVF is also common in various forms of PAH and may occur as acute-on-chronic RVF or as new-onset RVF. Precipitating factors include infection, volume overload, myocardial ischemia, PE, anaemia, trauma, surgery, arrhythmias, medical non-adherence, and progression of previously undiagnosed PAH [29, 30].

A common theme in all these conditions is that the occurrence of RVF is associated with a significantly worse survival. For example, the 90-day mortality rate

for patients with massive PE is 52% [22]; RV MI raises the risk of death more than twofold [31]; severe ACP is associated with increased mortality in ARDS [20]; and ICU mortality for patients admitted with decompensated PAH and RVF is 41% [30].

Lastly, there has been a recent focus on the management of patients who are resuscitated from cardiopulmonary arrest and transferred to a critical care unit. Up to 50% of these patients will need vasopressor support for hemodynamic instability [32]. A study investigating RV function in the first few hours after cardiac arrest showed that around 90% of this group of patients demonstrated both RV structural and functional abnormalities and that increase in the chamber dimensions was associated with increased mortality [33].

Perioperative RVF

RVF is much more likely to complicate cardiac surgery with numerous causes [34], while patients with existing severe PH and undergoing non-cardiac surgery may also have perioperative RVF. Patients with pre-existing PH, impaired RV function and tricuspid valve insufficiency are at increased risk of acute decompensation [35, 36]. RVF may occur following cardiac surgery secondary to acute left sided pathology, including LV failure, ventricular septal defects following MI and acute severe mitral valve regurgitation. Isolated acute right-sided failure may occur because of inadequate intraoperative right-sided cardioplegia administration or complications related to coronary artery graft flow or tricuspid valvuloplasty surgery. Intracoronary air and long cardiopulmonary bypass times may be contributory factors. Surgery involving the pulmonary arteries such as lung transplant and pulmonary endarterectomy can precipitate RVF [37]. An identifiable group of patients at higher risk of acute RVF are those undergoing cardiac transplantation, where RVF has been identified as an important cause of early deaths, and those receiving a LV assist device (LVAD) [38]. Transplant patients can develop acute RV pressure overload as a consequence of myocardial ischemia–reperfusion injury associated with organ preservation combined with either acute or chronically raised pulmonary vascular resistance. In a recent large study of 2988 patients from the European Registry of patients with Mechanical Circulatory Support (EUROMACS), RVF following LVAD implantation occurred in 22% of patients within 30 days of surgery with 7% requiring Mechanical Circulatory Support (MCS). Consistent with other risk stratification models, patients with evidence of RV function impairment were at higher risk [39]. Congenital heart disease and corrective surgeries such as those for Tetralogy of Fallot may result in RVF for a number of reasons and may limit the feasibility of the procedure. Acute cardiogenic shock mimicking RVF may also occur in the presence of pericardial thrombus causing a localized compression and obstruction to RV filling with significantly raised central venous pressure.

Diagnostic workup

Clinical presentation, examination, ECG, biochemical assessment and imaging are involved in the diagnosis of acute RVF and monitoring response to treatment. Signs, symptoms and laboratory tests can elucidate acute RVF etiologies. However, these findings lack sensitivity and specificity [40] and abnormal signs, symptoms and lab results can be from a variety of other pathology causing organ hypoperfusion (Table 2). There is no specific biochemical marker that identifies acute RVF [6, 41]. Diagnostic workup is, therefore, highly dependent on the clinical diagnosis aided by imaging. In particular, echocardiography plays a major diagnostic role [42]. We suggest a possible diagnostic pathway in the Fig. 3.

Best standard of care (for diagnosis and investigation)

A high level of suspicion ensures timely identification of acute RVF, which is essential for appropriate management. Delayed diagnosis and treatment of the underlying cause, as well as failure to prevent further injury to the RV (e.g. through fluid overload or worsening RV afterload) are all associated with worse outcomes. Early signs which should raise concern include hypoxemia, acidosis, hyperlactatemia, troponin rise, minor coagulopathy, and acute renal and liver dysfunction due to increased venous pressure. These are all non-specific findings and should prompt further investigation, particularly a thorough echocardiographic examination.

Initial assessment

Clinical presentation and examination vary with etiology and presence of co-morbidities, especially chronic RV changes. Recognition of pre-existing PAH (e.g. from parenchymal lung disease) is important as it dramatically impacts the patient's ability to cope with increases in PAP [43] and predisposes to death from acute on chronic RVF [44]. ECG and CXR findings may be normal, however, ECG may identify arrhythmias or RV strain pattern and CXR examination may suggest new parenchymal lung disease or volume overload potentially caused by left-sided heart disease [45].

Echocardiography (Fig. 4, Table 3)

Echocardiography plays an important role in the diagnosis of acute RVF in the ICU, initially by identifying presence of left-sided heart disease. In addition, echocardiography can non-invasively assess RV preload, contractility and afterload. Focused cardiac studies provide a

Table 2 History, investigation, laboratory tests and CXR abnormalities associated with acute RVF, all lack sensitivity and specificity and can be caused by other etiologies causing organ hypoperfusion

History	Chest pain (pleuritic or non-pleuritic) Shortness of breath Syncope or dizziness Confusion Right upper quadrant pain History of pulmonary hypertension
Signs	Hypoxia, tachycardia, tachypnoea Cyanosis Raised JVP or CVP Lower limb swelling (chronic) Hepatojugular reflux Ascites (chronic) Pericardial effusion Hepato/splenomegaly (chronic) Tricuspid regurgitation murmur Third heart sound Parasternal heave Shock (reduced capillary refill, hypotension, tachycardia etc.) Low pulse pressure
Laboratory investigations	Acidosis Hypoxaemia Hyperlactatemia Raised Troponin Acute renal failure Transaminitis Mild coagulopathy Mild hypoglycaemia Hyperbilirubinemia Raised BNP
ECG	V1–V4, II, III, aVF ST changes and/or T wave inversion Complete or incomplete right bundle branch block Low limb lead voltage QRS axis > 90°/right axis deviation Dominant R wave V1 RV hypertrophy Deep S wave I, Q wave and T wave inversion lead III
CXR	Enlarged heart size Right atrial dilation (increased curvature) Right heart border prominence Pleural effusions Proximal pulmonary artery dilation

method to identify RV dysfunction and dilation and its use has been suggested to decrease mortality in the ICU setting [46]. Comprehensive studies using Doppler enable hemodynamic and valvular assessment. The ability to rapidly assess response to treatment in terms of cardiac output, filling pressures, RV size and function and PAP makes echocardiography highly versatile. The complex RV geometry and position can make accurate analysis challenging. All views should be used to assess RV size and function, particularly the apical four-chamber view (the RV is normally less than 60% the size of the LV) where there is reduced inter-observer variability [45]. Care should be taken if there is LV enlargement as RV size may be underestimated (dimensions and area should be measured). Moreover, the concept that RV dilation must be present to diagnose RVF is contentious and it would be more accurate to describe a dynamic situation of increasing RV volumes by fluid expansion without changes in cardiac output as a signature of acute RVF. LV and left atrial enlargement point towards postcapillary PH involvement (although other etiologies need to be considered), whereas RVF associated with precapillary PH can be associated with a shift of the interventricular septum towards the left and a relatively under-filled LV. RV function can be assessed with multiple parameters and qualitative, as well as quantitative parameters are important [47]. The majority of echocardiography parameters for assessment of pulmonary hemodynamics in the critically ill have been shown to be accurate. Particular care should be taken with integration of findings into the clinical presentation. Importantly, dynamic measures of RV systolic function, such as speckle tracking, have proven highly sensitive in defining both early RV strain prior to overt RVF and improvements in RV function in response to specific therapies, such as pulmonary vasodilator therapy [48, 49].

In RV MI, a key distinguishing characteristic is that RV systolic pressure, along with related echocardiographic indices such as the tricuspid regurgitation jet velocity, is not significantly elevated. Thus echocardiographic assessment is essential for distinguishing RV MI from other causes of acute RVF. However, some of these patients may also require positive pressure ventilation in case of associated cardiogenic pulmonary edema due to large inferior MI or mitral regurgitation, and the pattern of RVF is closer to that is usually observed in situations with injury of the pulmonary circulation.

Transoesophageal echocardiography (TOE) is the essential diagnostic tool for all RVF following cardiac surgery, transthoracic windows are generally poor in patients following sternotomy. A more recently developed disposable TOE probe has been described that can be used for up to 72 h, and can track RV functional recovery and inform changes in hemodynamic therapy [50, 51].

Computed tomography (CT) (Fig. 4)

CT pulmonary angiography is the imaging method of choice in acute PE and echocardiography should not be used to exclude venous thromboembolism [52]. RV size is assessed, with or without ECG-gating [53], by analysing RV/LV diameter ratio (greater than 1 predicts risk for adverse outcomes in PE); however, there are reports of significant inter-observer variability and volumetric analysis may be better [54]. Increased RV/LV ratio can

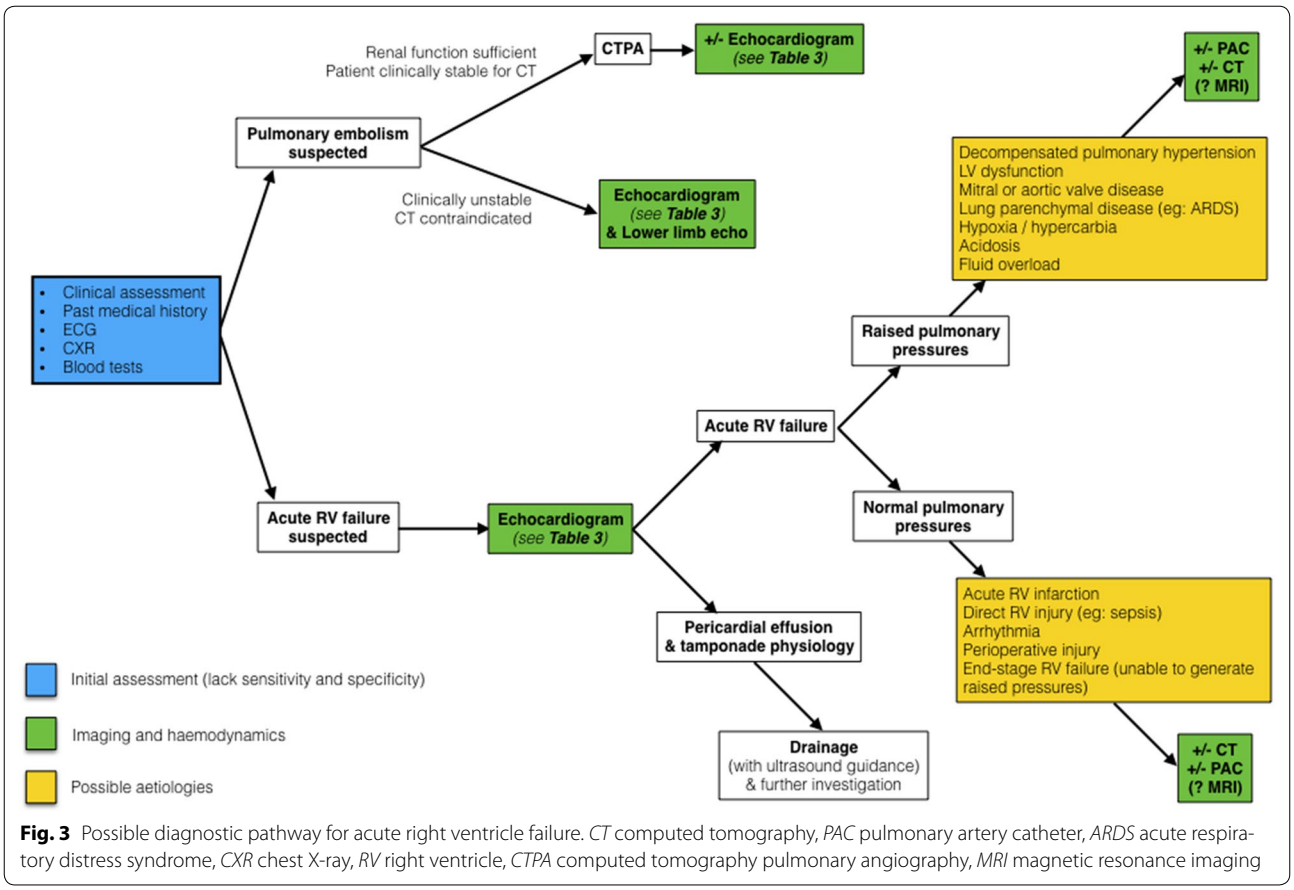

Fig. 3 Possible diagnostic pathway for acute right ventricle failure. *CT* computed tomography, *PAC* pulmonary artery catheter, *ARDS* acute respiratory distress syndrome, *CXR* chest X-ray, *RV* right ventricle, *CTPA* computed tomography pulmonary angiography, *MRI* magnetic resonance imaging

also point towards PH that is not related to acute PE, in particular when it is accompanied by pulmonary artery diameters exceeding that of the aorta [55]. RV function can be further assessed by the determination of ejection fraction (assessment requires ECG gating) and the presence of interventricular septal bowing and inferior vena cava contrast reflux [56]. Additionally, CT angiographic determination of the left to right atrial ratio can help to distinguish between pre- and post-capillary forms of PH [57].

Invasive monitoring

Pulmonary artery catheter (PAC) use provides continuous monitoring of PAP and may identify those patients with acute RV dysfunction with poor compliance through monitoring of RV pressures (using proximal port in RV) vs PAP (steeper RV diastolic pressure slope) [58]. Since PAC use is still common in cardiac surgical critical care [59] clinicians need to be cognizant of these hemodynamic signatures when following these patients post bypass. Although less used nowadays due to the risks of placement, use of the PAC may help in those at risk of acute RVF (e.g. history of significant PAH) or those not responding to conventional treatment. Still, when available, the estimate of pulmonary vascular compliance (pulmonary arterial pulse pressure to stroke volume ratio) offers more insight into defining RV performance in ARDS patients than doing measures of pulmonary vascular resistance [60, 61]. Combining echocardiography with invasive PAC monitoring seems the ideal method for monitoring this challenging group of patients. Temporal trends in PAP and RAP likely hold more benefit than static measures (e.g. increasing PAP and decreasing RAP may indicate improved RV output into a pulmonary system with high resistance). Thermodilution-based cardiac output estimations should be used with caution in acute RVF as significant acute tricuspid regurgitation may lead to underestimation [62], especially when the severity of the regurgitation is not fixed for beat to beat, as it may occur in mechanically ventilated patients. However, when used very rigorously, it has been suggested to have a good accuracy in a small population of spontaneous ventilated patients with PAH [63]. Transpulmonary thermodilution (PICCO® device), another popular invasive monitoring device, has been reported not to be appropriate in detecting isolated RVF [64].

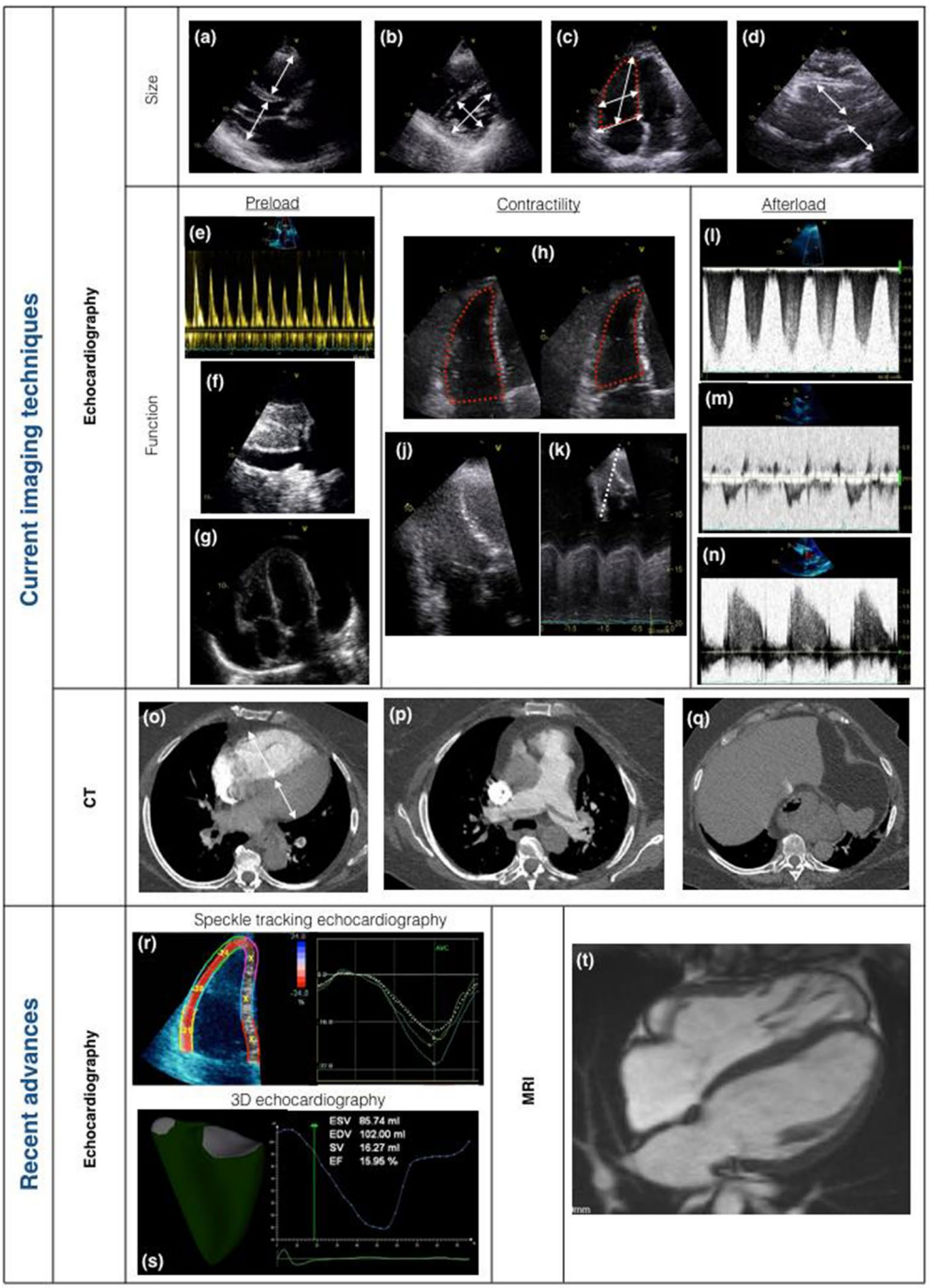

Fig. 4 Current imaging techniques in acute right ventricle (RV) failure diagnosis and recent advances. Echocardiography: panels **a**–**n**. All view needs to be used to assess RV size and RV function, **a** parasternal long axis view, **b** parasternal short axis view (including eccentricity index in assessment of ventricular interdependence), **c** apical four chamber view (dimensions and area may be useful particularly if the LV is dilated), **d** subcostal view. Preload analysis: **e** assessment for fluid responsiveness by stroke volume variation with respiration ± passive leg raise, **f** IVC size variation with respiration (less accurate in presence of RVF and significant tricuspid regurgitation), **g** presence of pericardial effusion. Contractility assessment: **h** fractional area change, **j** subjective analysis, **k** TAPSE (tricuspid annular plane systolic excursion). Afterload assessment: **l** tricuspid regurgitation jet used for estimation of peak systolic pulmonary artery pressures (4[TRV_{max}]2 + right atrial pressure), where TRV_{max} is the maximal velocity of the tricuspid regurgitation, **m** RV outflow tract flow analysis (e.g.: "flying W sign" in raised pulmonary vascular resistance), **n** pulmonary regurgitation flow for estimation of diastolic pulmonary artery pressures (4[PRVend-diastolic]2 + RAP), where PRV is the velocity of the pulmonary regurgitation. Computed tomography (CT): panels **o**–**q**. **o** LV/RV diameter ratio, **p** pulmonary artery size and presence of thrombus, **q** IVC contrast regurgitation in acute RV failure. Recent advances: panels **r**–**t**. **r** Speckle tracking echocardiography, **s** 3D echo volumetric analysis, **t** apical dyskinesia by magnetic resonance imaging (MRI) due to pulmonary embolism Image courtesy of Dr. Faraz Panthan

Table 3 Role of echocardiography in the diagnosis and management of right ventricular failure

Echocardiographic variables	Acute RV failure phenotype
General	Features may help differentiate: Acute, acute on chronic Predominantly RV failure vs. biventricular failure SPECIFIC etiology Predictive parameters of response to therapy
Diagnostic considerations	
Severe RV enlargement	Suggest either severe acute pressure overload or acute on chronic RV failure
RV hypertrophy	Best assessed in the sub-costal view; suggests chronic pressure overload state
Aneurysms	This suggest arrhythmogenic RV cardiomyopathy
Segmental wall motion abnormalities	Presence of "hyperdynamic apex" or McConnell sign suggests acute PH Preserved apical contraction can also be seen in RV MI. Patients with RV MI may also have preserved infundibular contraction in the presence of separate branch
Septal curvature	Very useful to assess ventricular interactions depends on relative dimensions of ventricles, relative pressure and ventricular synergy. Septal flattening suggests pressure overload when occurring at end-systole
Pulmonary flow	The presence of a pulmonary notch is indicative of pulmonary vascular disease with significant obstruction (proximal or distal)
Pressure estimates	Evaluation of RVSP or early diastolic pressure flow gradient is useful in estimating pulmonary pressure (c.f. Fig. 4)
Thrombus near right atrium	Careful assessment of local tamponade is essential as may be an important cause of hemodynamic compromise
LV phenotypes	Presence of LV enlargement suggests chronic LV pathology. LV systolic function may be decreased in the presence of severe RV involvement and indicates low effective stroke volume of the entire system
Other	Displaced septal position of the tricuspid valve may suggest Epstein's anomaly; also screen for the presence of shunts
Pitfalls in the assessment of acute RV failure	
Post-operative pitfalls	Annular indices such as TAPSE and RV longitudinal strain are usually not reliable post-pericardectomy and may remain altered in the long term
Pressure assessment	Avoid reporting pressure with sub-optimal signals; ensure consistency with the other markers such as septal curvature
Estimation of RAP	The IVC diameter may not be reliable to estimate RAP in intubated patients
Different definitions CT/echo	RV strain on CT and echo refer to different concepts: by CT mainly refers to RV enlargement, and echo refers to functional indices
Management consideration	
Preload assessment	Estimating dynamic change in stroke volume or its surrogates using PLR or limited volume load challenge may be useful to assessing potential response to fluid resuscitation. Assessment of septal curvature may also be useful to assess response to preload optimization. Interest in assessing portal vein and renal vein flow is gaining interest to assessing pressure overload
Response to inotropic therapy	Assessment of contractile reserve to dobutamine or other agents may help tailor therapy and avoid dangerous escalation of inotropic support
Ramp echocardiographic protocol	Assessment of recovery of the right ventricle during weaning of ECMO support and continuous flow LVAD

CT computed tomography, *ECMO* extracorporeal membrane oxygenation, *IVC* inferior vena cava, *LV* left ventricle, *LVAD* left ventricular assist device, *MI* myocardial infarction, *PH* pulmonary hypertension, *PLR* passive leg raising, *RAP* right atrial pressure, *RV* right ventricle, *RVSP* right ventricular systolic pressure, *TAPSE* tricuspid annular plane systolic excursion

Recent advances

Several novel PH biomarkers are described that relate to heart failure, inflammation, cardiovascular remodelling and endothelial cell-smooth muscle cell interaction [65]. They have predominantly been studied in animals or in small patient numbers, in single centres for risk stratification of PE and chronic PAH cohorts, and never in acutely ill patients [66–68]. Many studies also suffer from publication bias, multiple testing and retrospective analysis which limits their validity [65].

Speckle tracking echocardiography appears to be a promising monitoring approach. Recently developed software can track the movement of the grey-scale pixels relative to each other providing a quantitative measure of

deformation (known as "strain"), a negative dimensionless value, which describes a relative change in distance between pixels. Strain is used as a surrogate for systolic performance but not contractility; the greater the negative value, the greater the degree of deformation. RV function is classically assessed by tracking the movement of the RV free wall only. Known as RV free wall strain (normal values are more negative than −20 to −25%), it has been shown to describe cardiac dysfunction not elucidated by conventional echocardiographic techniques [69] and is highly prognostic in PAH cohorts [70], as well as in septic patients [71]. Speckle tracking echocardiography requires a reasonably high level of experience and training to perform as erroneous results are easy to acquire if the tracking is inappropriately performed. Measuring RV free wall longitudinal strain using manual tracing of RV end-diastolic and end-systolic length may be more simple and has been shown to be prognostic in patients with PAH [72]. As RVF induces congestion, the role of portal vein flow and renal flow monitoring by simple Doppler method should also be investigated to evaluate RV function.

Three-dimensional echocardiography is emerging with the potential to overcome the limitations of single-plane imaging seen in conventional echocardiography. For the RV this has particularly interest due to the abnormal concentric shape. Widespread use has been limited by imaging difficulties and availability, however its accuracy has been validated against cardiac magnetic resonance imaging (CMR) [73]. Further advances include the development of 3D speckle tracking of the RV in PAH [74]. To date, the use of 3D imaging of the RV has not been well investigated in the critically ill.

CMR is often used as the reference standard in studies investigating accuracy of RV imaging [75, 76]. CMR allows comprehensive evaluation of RV anatomy, volume, function and tissue characterization, with features such as RV dilation, abnormal septal and free wall motion, and tricuspid regurgitation easily recognized [77]. RV functional changes over time are much more accurately assessed by CMR than by echocardiography [78]. Native T1 mapping [79], T2-weighted and late gadolinium enhancement [80] potentially enable characterization of oedema, infarction or inflammation, although the RV free wall is not always easily detected and RV analysis is not well-validated or imprecise. However, CMR studies in the critically ill are currently lacking due to the restricted access, limitations of compatible equipment, patient and staff safety and time needed for imaging. Newer methods, as open-MRI with limited magnetic field [81], or methods aimed to reduce speed of MRI from 45–60 min to potentially 15 min [82] should make CMR increasingly available for critically ill patients.

Management

Treatment of the cause

It is obvious that, when reversible, the priority must be to specifically treat the cause of RVF. For instance, fibrinolysis or even surgical embolectomy may be considered in RVF-related PE [52]. RV MI also presents some unique options for treatment, including percutaneous coronary intervention. Precipitating factors of decompensated chronic RVF have to be controlled (see previous sections for the precipitating factors).

Hemodynamic support (Fig. 5)

The management of acute RVF focuses on stabilizing hemodynamics, optimizing loading conditions and treating potential reversible cause. Prompt treatment of arrhythmias (tachy or brady) is also essential to avoid the vicious circle of hypotension, ischemia and further arrhythmias.

One of the most important misconceptions in managing RVF is assuming that the majority of patients are on the preload dependent zone of the Frank–Starling relationship and would, therefore, benefit from volume loading. However, acute RVF leads to diastolic LV failure [83, 84], wherein both hypovolemia and hypervolemia are poorly tolerated and the optimal RV filling volume is often difficult to define. Even small fluid boluses can be poorly tolerated in acute RVF and ACP. In 13 patients with hemodynamic and radionuclide ventriculographic evidence of RV MI, progressive volume loading has been demonstrated to significantly increase RAP and PAOP but without significant change in cardiac index [85]. In canine model of PE or in the positive pressure ventilated setting, the lack of hemodynamic improvement following fluid challenge has been reported [86, 87]. In a landmark study in the setting of experimental RV MI (pig model), the importance of pericardial constraint was demonstrated, highlighting the importance of ventricular interactions [11]. Experimental studies in RV MI, PE and PAH have all shown that volume loading can increase right cavity size, increase pericardial constraint and further limit LV filling through the mechanisms of ventricular interdependence [88–90]. In a model of acute-on-chronic pulmonary thromboembolic disease, Boulate et al. also recently demonstrated that fluid challenge is not associated with an increase in stroke volume or cardiac output [91]. Taken together, these experimental and clinical studies would argue against routine volume loading in acute RVF unless clear evidence of hypovolemia or stroke volume responsiveness to physiological variation is noted. Patients with RV MI could benefit from volume repletion in the presence of clear evidence of hypovolemia; the usually lower afterload and lower ventricular wall stress compared to patients with chronic pressure

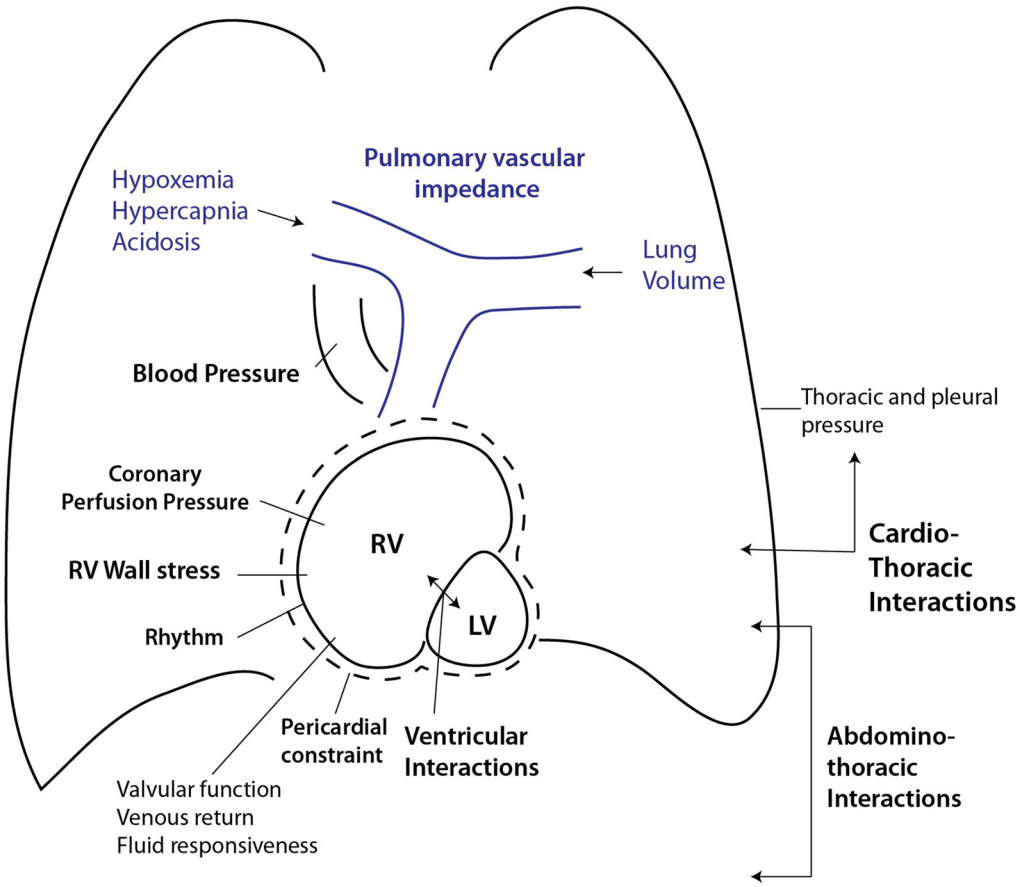

Fig. 5 Physiological consideration during the management of acute RVF. The cardiopulmonary unit is central in tailoring management of RVF. Pulmonary vascular resistance or impedance is influences by hypoxemia, hypercapnia and acidosis, lung volumes and positive pressure ventilation. Maintenance of blood pressure and coronary pressure is essential in managing RVF. In addition, management of RVF including fluid management has to take into account zone ventricular interactions, pericardial constraint, fluid responsiveness (zone of the Starling curve). Abdomino-thoracic and cardio-thoracic are essential to consider in acute RVF in the ICU setting as these can be overlooked caused of hemodynamic instability

overload can placed them at a more favourable portion of the Frank–Starling relationship. If fluid is given, starting with low volume repletion of 100–250 mL is often preferred while monitoring stroke volume or blood pressure response (unless active source of rapid volume loss is known to co-exist). Several studies including an excellent comprehensive review by Marik et al. have shown than RAP alone should not be considered a reliable marker of volume status or volume responsiveness [92], while other parameters for fluid responsiveness have been proposed [93], some of them unfortunately limited in RVF. Briefly, echocardiography is key in optimizing fluid loading, while IVC diameter has been recently reported to poorly predict the response to fluids in mechanically ventilated patients [94] and in fact there is no magic parameter to guide the need for fluids [95]. Measuring changes in cardiac output in response to a passive leg raise manoeuvre define volume responsiveness and can be used to attempt judicious fluid loading (with assessment of response to the intervention) [96]. In fact, the majority of patients with acute RVF associated with chronic PAH, congenital heart disease or biventricular failure would respond more to volume removal than infusion.

Since most RV coronary flow occurs in systole, if PAP increases above systemic arterial pressure, RV ischemia can develop. The primary salvage treatment to sustain cardiovascular function is the infusion of vasopressors (e.g. norepinephrine, vasopressin or terlipressin) to keep systemic arterial pressure greater than pulmonary arterial pressure. In a canine model of acute obstruction of the pulmonary circulation, fluid loading worsened RVF, while in contrast norepinephrine infusion restored mean arterial pressure to baseline, decreased biventricular filling pressure and increased cardiac index [97]. Inotropic drugs have also been proposed, while no reasonable study may clearly recommend their use in acute RVF-related

PH. There is probably no place for isoproterenol in the management of ARF, as in a model of experimental PE, all dogs randomized to receive isoproterenol died [98]. In PE, dobutamine has been reported to improve hemodynamics and reduced pulmonary vascular resistance [99]. In RVF related to ARDS, it makes sense to use inodilator to improve RV-pulmonary circulation coupling, as reported in a pilot study in which levosimendan was infused in 35 patients [100]. In 25 patients with cardiogenic shock related to myocardial infarction not sufficiently improved after percutaneous revascularization and infusion of dobutamine or norepinephrine, RV performance, as well as hemodynamics, was improved by levosimendan infusion [101]. However, at this time, no clear recommendation can be made due to the absence of sufficient data.

An exciting novel direction in the management of RVF is the use of MCS devices. In situations where medical therapy is inadequate, the employment of MCS devices to augment cardiac output, decrease RA and RV preload and improve oxygenation and acidosis can provide a life-saving bridge to either recovery or transplant. Surgically implanted RV assist devices (RVADs) have been used for more than two decades for this purpose. However, their placement via sternotomy or thoracotomy is often not feasible in critically ill patients. More recently, interest has turned to percutaneously placed support devices, which have the potential to revolutionize our approach to this patient population, providing the advantage of rapid deployment without the surgical risk. The Impella RP (Abiomed Inc) can be placed via one venous access site (usually the femoral vein) with delivery of blood from the RA to PA via a 22F impeller mounted on an 11F catheter. In a prospective cohort study including 30 patients with refractory RVF, 18 post LVAD and 12 following cardiotomy or RV infarct, hemodynamics improved in all patients immediately following device placement [102]. The overall mortality at 30 days was 73.3%, which compares favourably to previous case series of surgically placed RVADs. Two other percutaneously placed MCS devices also exist, one requiring two venous catheters and the other a dual-lumen cannula for RA inflow and PA outflow [103–105]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can offer both right and left sided circulatory support and is currently the most widely utilized percutaneously deployed MCS for acute or acute on chronic RVF. The creation of mobile "ECMO teams" allows the utilization of this treatment modality throughout the hospital in a rapid response manner, including code situations. The successful use of "awake" ECMO, with placement of the venous and arterial catheters using only conscious sedation, avoiding mechanical ventilation, has garnered recent attention in the management of PH as a bridge to transplant.

Respiratory strategy

RVF in the ICU is clearly promoted and worsened by positive-pressure ventilation, either related to respiratory settings or to their consequences, which are blood gasses (PaO_2, $PaCO_2$). Though especially true in ARDS, it can potentially be seen in any mechanically ventilated patient. In general, plateau pressure and driving pressure have to be limited [20, 106]. As hypercapnia by increasing the hypoxic pulmonary vasoconstriction is deleterious for the right ventricle, especially when inducing acidosis [107], $PaCO_2$ has to be controlled. This may be achieved by different ways: limiting intrinsic PEEP ($PEEP_i$) by decreasing respiratory rate (RR) in acute exacerbation of COPD or acute asthma, increasing RR without inducing $PEEP_i$ in ARDS, and removing CO_2 by extracorporeal circulation [108]. Hypoxia also contributes slightly to PH [109], thus oxygenation has to be optimized. However, recruitment manoeuvres followed by application of a high PEEP, to "optimize lung aeration and oxygenation", increase mortality and hemodynamic compromise in ARDS patients [110]. At the opposite, ventilation in prone position has been reported to increase oxygenation, decrease $PaCO_2$, plateau pressure and driving pressure in ARDS, and finally to correct RVF [111]. Nitric oxide inhalation (iNO) could also be tried in refractory PH with acute RVF, not to improve oxygenation, as it failed to improve prognosis in ARDS [112], but with a goal to decrease PAP and RV afterload and then to improve hemodynamic status. iNO has been suggested to be associated with a lower mortality in patients with PAH at risk of RVF after orthotopic heart or lung transplantation which is not the case after cardiac surgery or in medical patients with hypoxemia [113].

Conclusion

We propose in this manuscript a universal definition of RVF, which is defined by a state in which the RV is unable to meet the demands for blood flow without excessive use of the Frank–Starling mechanism. RVF is frequent in the critically ill ICU patient, while studies are lacking to precisely know its incidence in unselected population. It may occur de novo ("acute") or by decompensation of a pre-existing condition ("acute-on-chronic"). It is associated with worse prognosis. Hemodynamic and respiratory management is mainly based on pathophysiological rationale, as the absence of sufficient clinical studies to compare one direction or the other does not allow doing any formal recommendation. Future research should be based on large database study of admitted unselected patients to evaluate incidence, impact and management.

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Compliance with ethical standards

Conflicts of interest
AVB has received Grant from GSK for conducting clinical research and is membership of the scientific advisory board. RN has relationship with drug companies including AOPOrphan Pharmaceuticals, Actelion, Reata, Lung Biotechnology Corporation and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research Grants, and membership of scientific advisory board. FH declares no conflict of interest with regards to the content of this manuscript. HJB declares research Grants from Actelion, GSK, Therabell and speaker fees from Actelion, GSK. TMB declares investigator initiated Grant from Bayer Pharmaceuticals NF declares no conflict of interest. TL declares conflict of interest with Bayer (speaker bureau), Actelion (consulting), Gilled (scientific review committee) and Eli Lilly (research reagents). SM declares no conflict of interest with regards to the content of this manuscript. SO declares no conflict of interest. GS declares no conflict of interest with regards to the content of this manuscript. MRP declares no conflict of interest with regards to the content of this manuscript.

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