Management of Right Heart Failure in the Critically Ill

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KEYWORDS

• Right ventricular failure • Right ventricular dysfunction • Pulmonary hypertension • Acute respiratory distress syndrome

KEY POINTS

- Right ventricular failure complicates a number of commonly encountered conditions in the critically ill and is generally associated with worsened outcomes.
- An understanding of the pathophysiologic changes seen in the failing right ventricle is essential for developing an appropriate treatment strategy.
- Echocardiography is the screening test of choice for right ventricular failure. Focused critical care echocardiography can facilitate timely diagnosis by the bedside clinician.
- Timely diagnosis and treatment of the cause of right ventricular failure is essential.
- Reduction of right ventricular afterload and optimization of right ventricular preload and contractility form the principles of management. Oftentimes this requires combined use of vasopressors, inotropes, and pulmonary vasodilators.

INTRODUCTION

The critical importance of the right ventricle (RV) has long been underestimated, as classic teaching of cardiac physiology has emphasized left ventricular (LV) structure and function. Once thought a relatively unimportant conduit facilitating the flow of blood to the pulmonary vasculature, the RV is now recognized as a dynamic structure intricately linked to LV systolic and diastolic function. Likewise, research and clinical experience continue to demonstrate the importance of RV function in a variety of clinical conditions, including heart failure, myocardial infarction, congenital heart

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disease, pulmonary embolism, and pulmonary hypertension. Critically ill patients in the intensive care unit (ICU) with RV failure have increased morbidity and mortality compared with those patients with preserved RV function, and clinical management of these patients remains a formidable challenge.[1] Despite advances in technology, support of the failing RV, whether acute or chronic, has lagged behind that of the failing LV.

In this review, we describe the anatomy and physiology of the healthy RV and contrast it with the maladaptive responses of the failing one. We provide a conceptual framework for the etiology of RV failure, discuss basic techniques for diagnosing RV dysfunction, and provide general management strategies for the critically ill patient with RV failure. Finally, the article focuses on the treatment of conditions frequently seen in the critically ill patients in the ICU, including decompensated severe pulmonary arterial hypertension (PAH), massive pulmonary embolism (PE), and RV infarction.

ANATOMY AND PHYSIOLOGY ON THE HEALTHY RV

The healthy RV serves 2 roles: to pump venous blood to the lungs and to fill the systemic LV. In the normal heart, the RV fills with blood from the inferior and superior vena cava and pumps it into the pulmonary arteries. During LV diastole, oxygenated blood returns from the lungs by the pulmonary veins. The RV and LV are pumps in series, with roughly equivalent cardiac outputs, although each is characterized by the vasculature they are connected to. The pulmonary vasculature is composed of thin-walled and large-diameter vessels, contrasting sharply with the high-resistance, muscular arteries of the systemic vasculature. Under normal conditions, the pulmonary vasculature is a low-impedance, high-capacitance system, with lower vascular resistance and greater distensibility than the systemic vasculature.[2] Accordingly, the myocardium of the RV is thin, approximately one-third the thickness of the LV, and is more compliant, allowing the RV to accommodate large variations in venous return without significantly altering end-diastolic pressures.[3] Compared with the LV, the RV has increased sensitivity to changes in afterload. Under normal conditions, the systolic pressure of the RV is approximately 25 mm Hg, less than one-fifth the systolic pressure generated by the LV.[2]

The RV appears triangular on longitudinal section and crescent-shaped in cross section.[4] The RV relies primarily on longitudinal shortening during systole whereas the LV uses circumferential constrictor fibers for contraction.[5] This results in a “peristaltic” contraction that moves in a wave from the RV apex to the outflow tract.[3,5] Under normal circumstances, the RV follows the Frank-Starling mechanism by which increases in preload improve myocardial contractility. Factors that influence RV filling include intravascular volume, RV compliance, heart rate and rhythm, LV filling, and abnormalities of the pericardium. Excessive RV volume loading can result in constraint by the pericardium, compression of the LV, and an increase in ventricular interdependence.

The RV has increased resistance to ischemic injury compared with the LV. Besides a lower rate of oxygen consumption, the RV has a more extensive system of collateral vessels. In most individuals, the right coronary artery (RCA) perfuses the RV free wall and the posterior third of the interventricular septum, whereas the anterior two-thirds of the interventricular septum and apex of the RV are supplied by the left anterior descending artery (LAD).[3] Because the RV tissue pressure is lower than aortic root pressure under normal conditions, the RV receives continuous perfusion throughout both systole and diastole.[5] Although patients with acute RV ischemic injury tend to be hemodynamically challenging to manage, those who recover typically do well because of the absence of permanent RV ischemic injury.

Ventricular interdependence acknowledges the relationship between the 2 ventricles. The size, shape, and compliance of one ventricle affects the size, shape, and compliance of the other ventricle through the direct mechanical interactions of sharing the ventricular septum and pericardial space. Systolic ventricular interdependence is characterized by the contribution of LV septal contraction on RV emptying; up to 40% of RV systolic function may be attributable to this mechanism.[6] Diastolic ventricular interdependence is characterized by acute RV pressure or volume overload states, where a shift of the interventricular septum toward the left results in decreased distensibility, potentially resulting in decreased preload and cardiac output.

PATHOPHYSIOLOGY OF THE FAILING RV

Right ventricular failure (RVF) is defined as low cardiac output and systemic hypoperfusion due to the inability of the RV to provide adequate circulation through the pulmonary vasculature despite normal central venous pressures.[7] RVF may occur secondary to increases in RV afterload, decreases in RV contractility, or alterations in RV preload.[8] (**Fig. 1**) understanding the underlying pathophysiological alterations is essential for the treatment of RVF. Of the 3 scenarios, the most common is that of increased afterload. Given the RV is a compliant structure well suited to changes in end diastolic volume, these same features leave the RV with little contractile reserve and vulnerable to increases in afterload. When a patient with previously normal pulmonary artery pressures is presented with an acute increase in pulmonary vascular resistance (PVR), the ability of the RV to compensate is quickly exceeded. A previously healthy RV can acutely increase peak systolic pressures to approximately 60 mm Hg before contractile failure and systemic hypotension ensue, resulting in decreased cardiac output and potential cardiovascular collapse.[9]

When faced with less abrupt increases in PVR, the RV undergoes changes in an effort to maintain adequate cardiac output. To maintain sufficient stroke volume, the

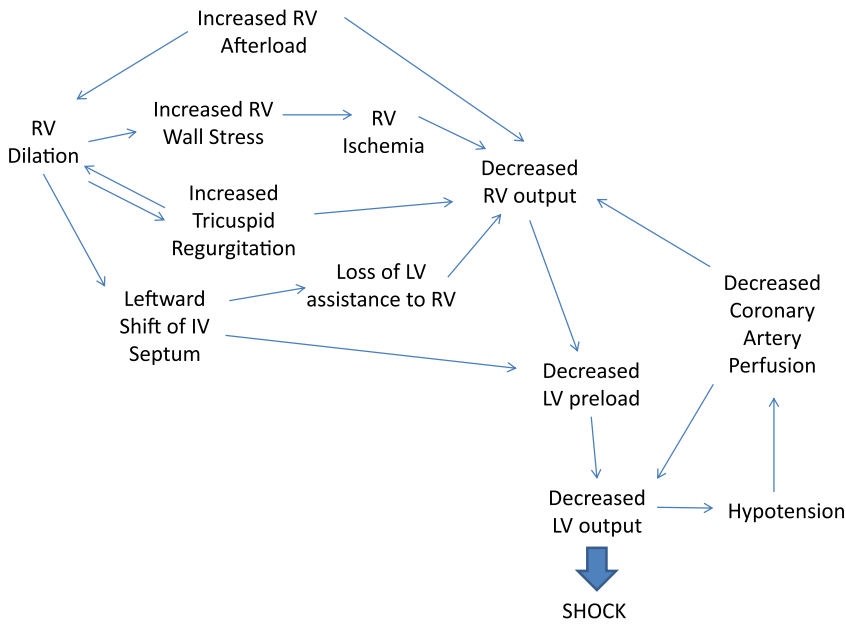

Fig. 1. Pathophysiologic changes in RVF.

RV initially dilates, thereby increasing preload.[1] However, if RV dilation progresses, a number of deleterious effects may occur. Alterations in the RV geometry will cause dilation of the tricuspid annulus and inadequate coaptation of the valve leaflets, resulting in regurgitation.[1] Further RV dilation and volume overload cause a leftward shift of the interventricular septum, reducing LV diastolic filling. LV systolic function decreases and the normal contribution of LV systolic function to RV emptying is impaired due to this geometric distortion.[3,5] Eventually, volume overload surpasses the compliance of the RV and pressure overload develops. RV pressure overload increases wall stress, leading to increased myocardial oxygen consumption.[5] If RV pressures are sufficiently elevated, myocardial blood supply from the RCA may occur only during diastole, leading to myocardial ischemia and further decreases in RV contractility.[5] Collectively, these maladaptive, inter-related physiologic derangements reduce cardiac output and result in significant hemodynamic compromise.

CAUSES OF RVF IN THE CRITICALLY ILL

Physicians caring for patients in the ICU must be well-versed in the management of RVF, as it complicates a number of commonly encountered disorders in the critically ill. RVF may develop de novo, as a direct result of critical illness (eg, massive PE, acute respiratory distress syndrome [ARDS]), or it may complicate the care of a patient with preexisting RV dysfunction (eg, sepsis in a patient with PAH). A simple method of categorizing causes of RVF is by the primary pathophysiologic disturbance responsible for the particular cause. Causes can be organized into 1 of 4 categories: increased RV afterload, decreased RV contractility, increased RV preload, or decreased RV preload. It should be emphasized that such categorization oversimplifies the underlying pathophysiology of RVF, as most causes of RVF are characterized by some degree of overlap of these pathophysiologic conditions. The most common causes of RVF encountered in the ICU are LV failure, acute PE, decompensated PAH, sepsis, ARDS, RV ischemia, cardiac tamponade, and post–cardiothoracic surgery, although several less common causes exist.[8] **Table 1** summarizes the causes of RVF.

EPIDEMIOLOGY AND IMPACT OF RVF

The prevalence of RVF and its impact on outcomes in the critically ill remain poorly defined. Multiple reasons exist for the gaps in our understanding of this process, including the relatively recent recognition of its importance, variable definitions of RVF, heterogeneity among ICU populations, and the myriad of etiologies leading to RVF. Examining the available data on individual diagnoses provides some insight.

RV dysfunction is a powerful predictor of mortality in patients with left heart failure.[10–13] Ghio and colleagues[10] examined right heart catheterization (RHC) data in 377 patients with chronic systolic heart failure and found that 75% of patients had a depressed RV ejection fraction, an independent predictor of death even after controlling for pulmonary hypertension. Isolated RVF or RVF in association with concurrent LVF is associated with mortality rates of approximately 40%.[14–16] Postoperative RVF also is well-described as a complication of cardiac surgery, including cardiac transplantation and left ventricular assist device (LVAD) implantation, and carries a similar mortality rate of nearly 40%.[17–20]

Of patients presenting with PE, 30% to 50% have “RV strain” either by elevated levels of biomarkers or echocardiographic evidence of RV dysfunction,[21] and 4.5% of patients with PE meet criteria for “massive PE,” defined as systemic hypotension, cardiac arrest, syncope, or a decrease in systolic blood pressure by greater than 40 mm Hg for at least 15 minutes. Massive PE is associated with 90-day mortality rates

Table 1
Causes of RV failure

Primary Physiologic Disturbance	Etiology
Increased RV afterload	• Pulmonary arterial hypertension • Secondary causes of pulmonary hypertension • Pulmonary venous hypertension (owing to left heart failure) • Pulmonary embolism • Hypoxic pulmonary vasoconstriction • Mechanical ventilation • Post–cardiothoracic surgery • Acute chest syndrome in sickle cell disease • Pulmonary stenosis • Tumor emboli
Impaired RV contractility	• RV infarction • Cardiomyopathy • Sepsis (cytokine-mediated myocardial depression) • Arrhythmogenic RV dysplasia
Increased RV preload	• Tricuspid regurgitation • Pulmonary regurgitation • Post–left ventricular assist device • Atrial/ventricular septal defects
Decreased RV preload	• Superior vena cava syndrome • Tricuspid stenosis • Cardiac tamponade • Hypovolemia/Capillary leak

Abbreviation: RV, right ventricular.

of up to 50%.[21] The reported prevalence of RV dysfunction in sepsis ranges from 30% to 100% and is associated with decreased survival in some studies, although a recent meta-analysis failed to demonstrate a difference in RV ejection fraction or RV dimension between survivors and nonsurvivors.[22–28]

RV dysfunction in ARDS has been reported in multiple studies, with prevalence ranging from 14% to 73%.[29–38] This wide range is likely due to variability in the diagnostic techniques and patient populations examined. Early studies demonstrated poor outcomes in ARDS complicated by RV dysfunction.[38,39] Studies using a lung protective ventilatory strategy generally report a lower incidence of RV dysfunction and have failed to demonstrate an association between RV dysfunction in ARDS and mortality.[29,32] This suggests that mortality benefit associated with lung protective ventilation may be in part because of minimization of the impact of mechanical ventilation on the RV.[40,41]

Based on the available data, it appears that RVF commonly complicates the course of patients in the ICU, and when it occurs, is associated with poor outcomes. It comes as no surprise then that patients with chronic RV dysfunction fare poorly when acutely ill. Mortality rates of 32% to 41% have been reported in patients with PAH or inoperable chronic thromboembolic pulmonary hypertension when admitted to the ICU.[5]

DIAGNOSIS OF RV DYSFUNCTION IN THE CRITICALLY ILL

RVF in the critically ill patient may be difficult to detect, and requires a high degree of clinical suspicion. Physical examination findings of chronic right heart failure, such as peripheral edema, hepatomegaly, ascites, elevated jugular venous pressure with

prominent *v* waves, and the blowing holosystolic murmur of tricuspid regurgitation may be absent in patients with acute RVF.[42] Hypotension and evidence of end-organ hypoperfusion due to low cardiac output may be the only clinically evident findings of RVF and should lead to further diagnostic investigation. Likewise, many of the diagnostic tests readily available in the ICU may lack sensitivity and specificity for RVF.

Clinically available biomarkers include brain natriuretic peptide (BNP), troponins, and creatininie phosphokinase-MB (CPK/MB), although each have limited utility in the diagnosis of RV dysfunction because of a lack of specificity. Released by the walls of the atria in response to increases in wall tension, plasma levels of BNP have been demonstrated to increase proportionally with increasing degrees of RV dysfunction. However, elevated levels of BNP alone do not constitute RVF. A number of commonly found conditions in patients in the ICU confound interpretation of BNP, including renal failure, which decreases clearance of BNP, and acute lung injury and chronic obstructive lung disease, both of which chronically elevate right atrial pressure.[43,44] Although BNP is nonspecific, the test has high negative predictive value, making RVF unlikely if BNP levels are normal.[45]

Standard 12-lead surface electrocardiography (ECG) lacks sensitivity for the diagnosis of RVF, although it may provide information in specific instances. The combination of right axis deviation, P pulmonale, and R/S wave >1 mm in V_1 with R wave >0.5 mV have greater than 90% specificity for RV hypertrophy.[46] Normotensive patients with PE and evidence of "RV strain," defined as complete or incomplete right bundle branch block, "S1Q3T3" pattern, and inverted T-waves in V_1 through V_4, were 8 times more likely to die or decompensate than those without these findings.[47]

Chest radiography or computed tomography (CT) cannot diagnosis RV dysfunction, but may reveal evidence of parenchymal disease causing RV dysfunction or signs of chronic pulmonary hypertension, including RV hypertrophy, right atrial enlargement, or pulmonary artery enlargement.[8,46]

Transthoracic echocardiography remains the diagnostic test of choice for diagnosing structural and functional abnormalities of the RV. It is noninvasive, inexpensive, well-validated, and is easily obtained at the bedside. A complete study includes 2-dimensional imaging of the 4 cardiac chambers and valves in multiple planes, color flow and Doppler interrogation of the cardiac valves, interatrial and interventricular septums, and assessment of the great vessels and pericardium. Besides assessing RV and LV size and function, echocardiography allows assessment of valvular pathology, presence of a pericardial effusion, determination of tamponade physiology, detection of shunts, visualization of congenital abnormalities, and estimation of pulmonary arterial pressures.[42]

Echocardiographic signs of acute RVF include RV dilation and paradoxic septal motion.[48] Assessment of RV dilation is performed by comparing the size of the RV to that of the LV in an apical 4-chamber view. RV dilation is present when the RV is greater than two-thirds the size of the LV. If the RV is equal to or larger than the LV, then severe dilation exists (**Fig. 2**).[49] The absence of RV dilation on echocardiography in a patient with shock makes RVF unlikely to be the cause of shock.[50] RV dilation is also suggested by the appearance of a "D-shaped" septum on the parasternal short-axis view (**Fig. 3**). Paradoxic septal motion during systole is a specific sign of RV pressure overload.[40] More advanced techniques, such as the tricuspid annular plane systolic excursion (TAPSE) and Tei index, can provide assessments of RV systolic function.[51] In mechanically ventilated patients with poor acoustic windows precluding adequate transthoracic echocardiographic (TTE) assessment, transesophageal echocardiography can be used.[52]

Typically performed by dedicated echocardiography technicians and later interpreted by cardiologists once the study has been downloaded to a dedicated work

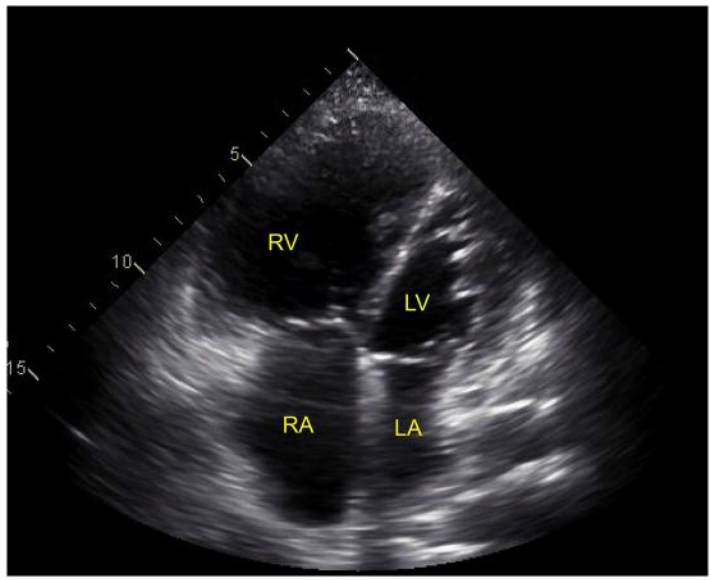

Fig. 2. Apical 4-chamber view from a TTE demonstrating severe RV dilation in a patient with severe PAH and RVF. LA, left atrium; RA, left atrium.

station, transthoracic studies are limited by the availability of resources, which can lead to substantial delays. More recently, focused critical care echocardiography (CCE) has allowed clinicians to rapidly diagnose a variety of cardiac conditions, including RVF, in a timely manner by using nondedicated, portable ultrasound machines.[53] In addition, serial CCE examinations allow assessment of response to interventions. With appropriate training, competence in basic CCE can be readily achieved

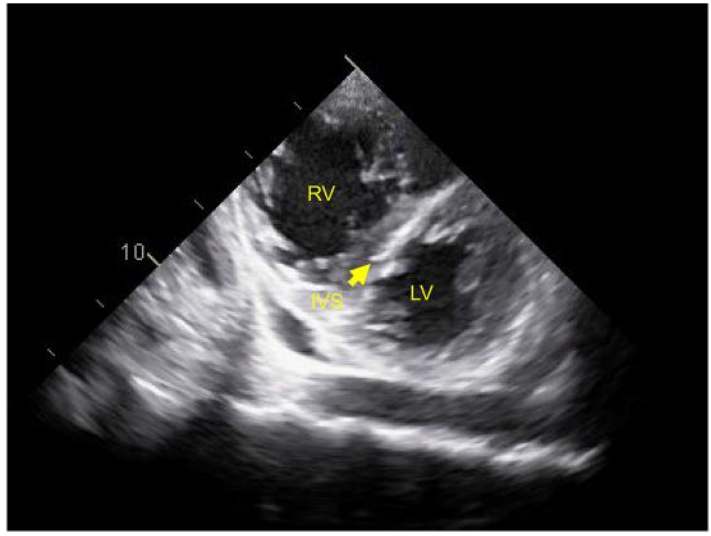

Fig. 3. Parasternal short-axis view from a TTE demonstrating a "D-shaped" septum in a patient with severe PAH and RVF. IVS, intraventricular septum.

by the noncardiologist clinician.[48] Although a substantial amount of information can be derived from a focused CCE study, CCE is not a substitute for a complete transthoracic echocardiography study.

RHC provides a wealth of hemodynamic data by allowing direct measurement of central venous pressure, right atrial pressure (RAP), RV pressure, pulmonary arterial pressure, and pulmonary artery occlusion pressure (PAOP). In patients without pulmonary arterial hypertension, PWP is a surrogate for left atrial pressure, and in the absence of mitral stenosis, reflects LV diastolic pressure. Both PVR and systemic vascular resistance (SVR) may be calculated. Cardiac output may be calculated by 2 different methods, although each have inherent flaws that require results to be carefully scrutinized. The assumed Fick method, which uses direct measurement of mixed venous oxygen saturation, assumes oxygen consumption of the patient, which is difficult in the critically ill patient. The thermodilution technique, in which a fixed quantity of a substance (typically room temperature saline) is injected and measured by a thermistor sensor, is unreliable in patients with moderate to severe tricuspid regurgitation and is vulnerable to operator error. The role of RHC in the management of patients in the ICU remains controversial.[54–57] The PAC-MAN trial randomized more than 1000 critically ill patients to management with versus without RHC. No difference in outcomes was detected.[54] The Fluid and Catheter Treatment Trial (FACTT) randomized 1000 patients with acute lung injury to treatment directed by pulmonary artery catheter versus care without one. No difference in mortality or end organ dysfunction was detected, but pulmonary artery catheters were associated with increased risk of complications.[56] Based on the negative outcomes of these trials, routine use of RHC in the ICU has declined in recent years. It should be noted that utility of RHC has never been studied specifically in the setting of RVF.

Understanding a critically ill patient's hemodynamics is important in a variety of settings, and RHC should be considered when a patient with RVF continues to decline despite attempted optimization of surrogate end points (central venous pressure [CVP], lactate, cardiac output) or when RVF is of unclear etiology. In patients with suspected decompensated PAH, RHC remains the gold standard for the diagnosis and classification of PAH, as well as the titration of therapies. The RHC may be left in place for a period of time, allowing for continuous hemodynamic monitoring and tailoring of therapies. As with any in-dwelling catheter, there are risks of complications, including infection, which limits its utility. The rate of serious complications from RHC is reported to be 1.1% when performed by experienced operators, although many of the procedures in this trial were not done in an ICU setting.[58]

A number of "minimally invasive" cardiac output monitors have been developed in recent years. These devices rely on pulse pressure analysis, pulse-Doppler technology, the applied Fick principles, or bioimpendance.[59] These devices have not been specifically validated in the setting of RVF but in the future may provide a less invasive means of continuously monitoring cardiac output in this population. Cardiac magnetic resonance (CMR) is the gold standard for assessment of RV size and function.[51] Cine images of the cardiac cycle can be obtained and allowing assessment of septal and regional wall motion. Dobutamine-stress CMR can be used to investigate contractile reserve.[51] The logistics of obtaining CMR limit its utility in the critically ill.

MANAGEMENT STRATEGIES IN ACUTE RVF

Despite increased recognition of acute RVF in critically ill patients and substantial progress in understanding the pathophysiologic changes of the failing RV, few

experimental or clinical data exist to guide treatment. The goal of therapy is to maintain adequate end-organ perfusion until targeted therapies address the underlying etiology or until the initial insult responsible for decompensation resolves.[1] This is achieved through optimization of RV preload with volume management and rhythm control, afterload reduction by minimizing the harms of mechanical ventilation and the use of pulmonary vasodilator therapy, and augmentation of RV perfusion and contractility with pressors and inotropes. Although this article provides a general framework for treatment of RVF, optimal therapeutic strategies must be individualized to the patient's hemodynamics and underlying cause of RVF.

GENERAL MEASURES

Early diagnosis of RVF is essential, and an exhaustive search for possible precipitating factors should be undertaken immediately, with prompt institution of appropriate therapies so as to optimize outcomes. Supplemental oxygen should be administered to maintain oxygen saturations greater than 92% to avoid hypoxemic pulmonary vasoconstriction and increases in RV afterload.[8,60,61] Likewise, metabolic and respiratory acidosis should be corrected, as both can increase pulmonary vascular resistance.[62] Recent guidelines regarding the treatment of anemia and transfusion practice in the critically ill favor a conservative strategy. Although the optimal hemoglobin level in RVF is not known, correction of anemia causing inadequate end-organ perfusion should be corrected.[63]

OPTIMIZATION OF RV PRELOAD: VOLUME STATUS

Optimization of RV preload is crucial for maintenance of adequate cardiac output, and inadequate RV preload requires correction; however, clinicians should be cognizant of the deleterious effects of volume overload in these patients. Although some patients with acute RVF may be volume responsive, such as those with RV infarction or massive PE, the most patients in the ICU will be volume overloaded.[64–66] Inappropriate fluid administration in patients with RVF and volume overload can further hemodynamic deterioration by furthering RV dilation, increasing tricuspid regurgitation, causing RV ischemia, and impair LV filling by shifting the interventricular septum leftward.[1] If fluid administration is deemed appropriate, it should be done cautiously. Patients should receive small boluses of 250 to 500 mL with assessment of response after administration. The total volume administered should generally not exceed 2 L.[1] Fluid administration in patients with an elevated CVP should be done with caution.

Determining the volume status of a critically ill patient may be difficult. Tracking CVP in patients may be helpful, although filling pressures are poorly predictive of fluid responsiveness and low filling pressures do not predict which patients will benefit from volume administration.[67] Echocardiography may be helpful in assessing RV preload. Severe RV dilation, leftward shift of the interventricular septum in systole and diastole, or a decreased TAPSE all indicate elevation of RV preload, and further volume administration should be avoided.[50] Passive leg raising, by transiently increasing RV preload, simulates volume administration. This is an easy bedside test to assess whether a patient will respond to intravenous fluids without the harms of fluid administration in those who demonstrate no improvement in cardiac output.[68] Patients who are volume overloaded should be treated with intravenous (IV) diuretics, either by bolus administration or continuous infusion to achieve a negative fluid balance. Patients who are refractory to diuretic therapy may require hemofiltration, although this technique has not been shown to offer any mortality benefit.[5]

OPTIMIZATION OF RV PRELOAD: RHYTHM CONTROL

Atrial dysrhythmias are commonly encountered in critically ill patients. In RVF, augmentation of atrial contractility is an important compensatory mechanism.[69] Given the dependence of the failing RV on atrial contraction, atrial arrhythmias can lead to severe hemodynamic compromise.[4] Rate control alone is generally inadequate to restore hemodynamic stability, as these patients have increased reliance on atrial-ventricular synchrony.[65] Treatment with beta-blockers and calcium channel blockers may be harmful due to negative inotropic effects and can further impairment of RV function.[65] Prompt electrical cardioversion should be performed in the hemodynamically unstable patient. Antiarrhythmic therapy may be necessary to maintain sinus rhythm; IV amiodarone is typically well tolerated in patients with RVF, although it has a high volume of distribution. Sotalol should be avoided in patients with structural heart disease and digoxin should be used with caution in patients with impaired renal function.[4,65] Sequential atrioventricular pacing, either by the patient's indwelling device (if present) or by placement of a transcutaneous pacing wire, is another therapeutic consideration.[4] Ventricular dysrhythmias are typically poorly tolerated and require urgent cardioversion.

REDUCTION OF RV AFTERLOAD: MINIMIZING HARMS OF MECHANICAL VENTILATION

Intubation and mechanical ventilatory support of patients with RVF should be avoided if possible. Application of positive-pressure ventilation in combination with induction agents can result in systemic hypotension leading to RV ischemia and ultimate cardiovascular collapse.[65] If intubation is required, etomidate or ketamine are thought to be the induction agents of choice, as they provide adequate anesthesia while minimizing postinduction hypotension.[3] Vasopressors should be readily available or initiated preemptively to combat postintubation hypotension.[5] The optimal sedation regimen in mechanically ventilated patients with RVF is not known. A reasonable strategy in keeping with current sedation and analgesia guidelines is to first optimize analgesia with a fentanyl infusion, which has less propensity for hypotension than benzodiazepines or propofol. In addition, opiates do not adversely affect RV function.[70,71] If additional sedation is required, this can be achieved with incremental increases of propofol or a benzodiazepine.[65]

Mechanical ventilation exposes the RV to a number of detrimental physiologic effects. Positive intrathoracic pressure decreases RV preload and stroke volume and increases RV afterload. The optimal ventilatory strategy in RVF aims to minimize the impact of these effects by avoiding high lung volumes and pressures by using a combination of increased respiratory rate and small tidal volumes.[52] The minute ventilation must remain adequate to prevent hypercapnia, which can increase PVR.[46] Clinicians must also monitor for development of "auto-PEEP (positive end-expiratory pressure)," as it will adversely affect the RV. Plateau pressures should be maintained at less than 27 cm H_20.[52] PEEP should be titrated to optimize lung recruitment, thus minimizing the adverse effects of atelectasis, while avoiding the harms of overdistention. Patients with severe ARDS may be difficult to oxygenate with this ventilatory strategy and may derive benefit in both gas exchange and hemodynamics with prone positioning.[31,52,72]

REDUCTION OF RV AFTERLOAD: PULMONARY VASODILATORS

Because of its thin-walled, highly compliant design, the RV is exquisitely sensitive to increased afterload and may fail with even minimal increases in PVR.[1] The primary

pathophysiologic disturbance in many of the most commonly encountered causes of RVF in the ICU is increased RV afterload, including ARDS, massive PE, and decompensated PAH. Additionally, many of the physiologic derangements found in the critically ill (hypoxemia, hypercarbia, and acidosis) acutely raise PVR. Consequently, reducing RV afterload by pharmacologic means is a cornerstone of therapy in RVF. Pulmonary vasodilators can be delivered either locally by inhalation or systemically by IV infusion or oral delivery.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator frequently used in the critical care setting. Following inhalation, nitric oxide is delivered to ventilated areas of the lungs, where it causes selective pulmonary vasodilation by increasing cyclic guanosine monophosphate, improving ventilation/perfusion matching and reducing PVR.[8,73] iNO is rapidly inactivated by hemoglobin in pulmonary capillaries, so SVR is not affected.[5] It may be delivered continuously by face mask or nasal cannula, but is most commonly used in mechanically ventilated patients.[5] iNO has been demonstrated to decrease PVR in heart transplant recipients and patients with pulmonary hypertension (PH) undergoing mitral valve replacement.[74,75] A small study of critically ill patients with RVF of varying etiologies found iNO improved cardiac output and decreased PVR in 14 (54%) of 26 patients.[76] Studies of iNO in ARDS demonstrate improved oxygenation, but no improvement in clinical end points, including duration of mechanical ventilation or mortality.[77–79] Caution should be exercised when weaning iNO, as rebound pulmonary hypertension may occur.[80] Other potential adverse effects associated with iNO are methemoglobinemia, renal failure, and worsened pulmonary edema in patients with biventricular failure.[46,81,82] iNO requires a specialized delivery system and the cost can be substantial.[45]

Inhaled prostanoids offer a cost-effective alternative to iNO therapy. Prostanoids promote vasodilation through activation of cyclic adenosine monophosphate.[1] Like iNO, inhaled prostanoids improve ventilation/perfusion matching and do not cause systemic hypotension.[8,83] Unlike iNO, they do not require specialized equipment for delivery. Inhaled epoprostenol (iEPO) performed as well as iNO in reducing PVR and improving cardiac output in a randomized, crossover study of 25 transplant recipients.[84] A retrospective study comparing iNO with iEPO found similar improvements in oxygenation in 105 critically ill patients with refractory hypoxemia.[85] Beneficial effects on hemodynamics and/or oxygenation have been demonstrated with inhaled iloprost in patients with ARDS, after cardiac surgery, and after heart transplantation.[86–89]

The role of IV prostanoid therapy in chronic pulmonary hypertension is well-established, but data to guide the use of these agents for RVF in the critically ill are extremely limited. When IV pulmonary vasodilators are used, epoprostenol is the drug of choice given its short half-life (3–6 minutes).[8] IV prostanoids have several side effects, including hypotension, nausea, vomiting, headache, rebound pulmonary hypertension following abrupt discontinuation, and the potential to worsen hypoxemia due to nonselective pulmonary vasodilation.[5] These agents should be avoided in patients with respiratory failure or LV dysfunction.[8] Limited data exist supporting the use of these agents for treatment of pulmonary hypertension following cardiac surgery or heart transplantation.[90,91] Given the paucity of studies supporting their use and the side-effect profile of these medications, we feel the utility of IV prostanoids in the care of acute RVF is limited. The primary role of IV pulmonary vasodilator therapy in the ICU is in the treatment of acutely decompensated PAH and should be done so in consultation with a pulmonary hypertension specialist.[46]

Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators are oral agents used in the chronic care of pulmonary arterial hypertension. Lack of data and long half-lives limit their utility in the care of

acute RVF. Small, nonrandomized studies suggest sildenafil may have a role in weaning inhaled or IV pulmonary vasodilators following cardiac surgery or LVAD implantation.[92,93]

IMPROVE RV CONTRACTILITY: AVOID ISCHEMIA BY ADDRESSING SYSTEMIC HYPOTENSION

Hypotension in RVF may lead to RV ischemia and should be rapidly corrected to prevent cardiovascular collapse. RV dilation leads to increased wall stress, leaving the RV myocardium susceptible to inadequate perfusion. The ratio of PVR to SVR is critical for RV perfusion. If PVR increases beyond SVR, RV perfusion will occur only during diastole, leading to RV myocardial ischemia.[5] This condition can occur through elevations in PVR, decreases in SVR, or some combination of the two. Systemic vasopressor therapy increases SVR and improves coronary perfusion, thereby offsetting RV ischemia.[94] The ideal vasopressor in RVF increases SVR maintaining or decreasing PVR. At a minimum, vasopressors should increase SVR to a greater extent than PVR, thus maintaining a favorable PVR-to-SVR ratio.

Norepinephrine is an α1-adrenergic receptor agonist and β1-adrenergic receptor agonist with potent vasoconstrictor and limited inotropic properties.[5,46] A study of patients with chronic PH with anesthesia-induced hypotension found norepinephrine improved systemic blood pressure and decreased the ratio of pulmonary artery pressure–to–systemic blood pressure without altering cardiac index.[95] Another study of 10 patients with septic shock and RV dysfunction found low to moderate doses of norepinephrine improved the RV oxygen supply/demand ratio, and improved the ratio of PVR to SVR without altering cardiac index.[96] However, high doses of norepinephrine may negatively affect the PVR-to-SVR ratio, leading to worsening of RVF.[97]

Vasopressin is a systemic vasoconstrictor with direct effects on vascular smooth muscle at the vasopressinergic (V1) receptor and increases vascular responsiveness to catecholamines.[5,98] At low doses (0.03–0.067 U/min), vasopressin may reduce PVR and the PVR-SVR ratio through a nitric oxide–mediated mechanism.[99–101] Vasopressin induces fewer tachyarrhythmias than norepinephrine, although it can lead to bradycardia at high doses.[98] Unlike norepinephrine, vasopressin does not augment cardiac contractility.

Phenylephrine is a direct α1 agonist with no β1 effects.[5] It is a potent vasoconstrictor that increases SVR; however, phenylephrine may worsen RV function by increasing PVR.[98] Epinephrine has both α-receptor and β-receptor activity, thus leading to vasoconstriction and increased inotropy.[5] A study of 14 patients with septic shock and RVF found epinephrine improved RV contractility despite increasing mean pulmonary artery pressure.[102] Tachycardia and tachyarrhythmias are common side effects of epinephrine and may be detrimental in RVF.

Based on the limited available data, norepinephrine is generally used as first-line therapy in the hypotensive patient with RVF.[98] Low-dose vasopressin may be a reasonable alternative, particularly in patients with tachycardia, although this recommendation is based on the limited available data.[98] In a patient requiring high-dose norepinephrine to maintain adequate mean arterial pressures, the combination of low-dose vasopressin and norepinephrine is reasonable, although no experimental data confirm this approach.

IMPROVE RV CONTRACTILITY: USE OF INOTROPES

Positive inotropic agents increase the force of myocardial contraction by increasing the force-velocity relationship of cardiac myocytes. Positive inotropes alter SVR,

PVR, and cardiac output. There are 2 primary classes of positive inotropes: the sympathomimetic inotropes, which include dopamine, epinephrine, and dobutamine, and the inodilators, which include phosphodiesterase (PDE) 3 inhibitors and levosimendan. Although commonly used in the critically ill patient, none of these agents has been shown to improve outcomes, and data exist suggesting increased mortality.

Dopamine is a dopaminergic and adrenergic agonist that increases both SVR and cardiac output.[46] Studies demonstrate variable effects of dopamine on the PVR-to-SVR ratio.[96,103,104] Dopamine typically produces significant tachycardia, which may adversely affect LV preload and precipitate RV ischemia.[46] A recent randomized control trial comparing dopamine with norepinephrine found dopamine increased the risk for arrhythmia and worsened mortality in the subgroup of patients with cardiogenic shock.[105]

Dobutamine exerts inotropic effects via the β1 receptor, and variable vasodilatory effects through β2 receptor stimulation.[5] At doses up to 5 μg/kg per minute, dobutamine increases cardiac contractility and reduces PVR and SVR.[98] Higher doses increase myocardial oxygen demand due to tachycardia, and fail to reduce PVR.[8] Use of dobutamine may cause hypotension requiring use of vasopressors, due to β2-mediated systemic vasodilation.[98]

Milrinone, a PDE-3 inhibitor, increases inotropy and causes vasodilation of both the systemic and pulmonary vasculature. Milrinone has been demonstrated to reduce pulmonary pressures and improve RV function in LV systolic heart failure, after cardiac transplantation, and after ventricular assist device implantation.[106–108] Like dobutamine, milrinone often induces systemic hypotension, necessitating the use of vasopressors. The combination of milrinone with vasopressin may be superior to norepinephrine in reducing the PVR-to-SVR ratio.[101]

Levosimendan sensitizes troponin-c to intracellular calcium, increasing contractility without affecting oxygen consumption.[8] The drug also acts as a vasodilator through calcium desensitization and PDE-3 inhibition.[98] Levosimendan reduces PVR and increases cardiac output.[8] Studies have demonstrated clinical improvement in the setting of RV infarction, ARDS, and after cardiac surgery.[109–111] This medication is not currently available for use in the United States.

In the absence of systemic hypotension, milrinone is the inotrope of choice in patients with RVF requiring inotropic support. If dobutamine is used, low-dose therapy is preferred so as to avoid tachycardia and increased myocardial oxygen demand.[98] Use of dopamine should generally be avoided in RVF because of the risk of tachycardia and data demonstrating increased mortality in cardiogenic shock.[98] Clinicians should anticipate the need to use concurrent vasopressor therapy with either milrinone or dobutamine.

MECHANICAL SUPPORT

In cases in which cardiogenic shock persists despite maximal medical therapy, mechanical support of the RV should be entertained. Mechanical support includes intra-aortic balloon pump counterpulsation (IABP), venoarterial extracorporeal membrane oxygenation (VA-ECMO), and RV assist devices (RVADs), and should only be used in carefully selected patients. Each of these therapies provides hemodynamic support in the acute setting, allowing for resolution of a potentially reversible process, definitive treatment of the underlying etiology, or bridging to a more permanent form of support.

IABP, while not directly unloading the RV, augments coronary artery blood flow, decreases myocardial oxygen demand, reduces LV afterload, and increases cardiac

output.[112] Although these effects may benefit patients with RVF due to LV failure, the amount of support is limited.[112] IABP is considered the first line of mechanical support, as it is readily available and may be inserted either at bedside or in a cardiac catheterization laboratory.

In patients requiring full cardiac support, VA-ECMO and RVADs may be considered. VA-ECMO removes blood from the venous system, passes it through a pump head and oxygenator, and returns it to the arterial system, thus providing support of both the cardiac and respiratory systems.[42] Cannulation can be either via the femoral vessels or by direct cannulation of the right atrium and pulmonary artery. VA-ECMO does not fully offload the LV and, depending on the cannulation configuration, may reduce circulation to the pulmonary vessels. VA-ECMO is temporary support only, allowing for either resolution of the underlying process or determination of more permanent mechanical support. VA-ECMO is the mechanical support mode of choice in conditions resulting in severely elevated PVR, such as PAH and massive PE.[1]

Patients with refractory cardiogenic shock or end-stage heart failure may be supported by ventricular assist devices (VADs). Current-generation VADs are continuous-flow axial or centrifugal pumps designed for long-term support of the LV. Most patients require isolated LVAD support, although RVF after LVAD implantation is frequent and a leading cause of morbidity and mortality in this population. RVAD support may be temporary or long-term, although currently there is not a continuous-flow VAD that is approved by the Food and Drug Administration for RV support. There is increasing experience with the Heart Ware ventricular assist system (VAS) (HeartWare Inc, Framingham, MA, USA) in a biventricular configuration in patients awaiting cardiac transplantation. For patients ineligible for transplantation, permanent mechanical support of the RV should not be considered. RVADs should be avoided in the setting of significantly elevated PVR, as the increased flow of blood from the RVAD into the pulmonary circulation will lead to severely elevated pulmonary pressures and lung injury without effectively increasing cardiac output.[113]

TARGETED MANAGEMENT FOR SPECIFIC ETIOLOGIES OF RV FAILURE

We have described general management considerations for critically ill patients with RVF. **Table 2** provides a management "checklist" for providers caring for patients with RVF. In the next section, we briefly review specifics of targeted therapy for 3 specific causes of RVF: decompensated PAH, massive PE, and RV infarction.

DECOMPENSATED PAH

RVF secondary to decompensated PAH is a challenging disorder to manage with high associated mortality.[5] In the past 2 decades, significant progress has been made in treatment of PAH, including the development of 4 new classes of medications providing targeted treatment of PAH. Registry data indicate that patients affected with PAH live longer than before, likely due to improved management strategies.[114] Given an expanding population of patients actively treated with pulmonary vasodilator therapy, intensivists are increasingly likely to encounter patients with PAH in the ICU. Understanding of the nuances of management of this population is important, for many of the typical strategies used in a patient presenting with shock will be detrimental when applied to a decompensated patient with PAH.

Management of decompensated PAH is complex. Likely precipitating factors, such as PE, infection, or arrhythmia, should be actively sought out, as their presence will impact clinical management. Timely, aggressive therapy to restore adequate perfusion and prevent multiorgan system failure is required in decompensated PAH.

Table 2
Management of RVF checklist

Management Consideration	Comments
Does this patient have RVF?	• TTE as initial screening test • TEE may be required if TTE is inadequate • Consider RHC to better define hemodynamics if echocardiography is suggestive
Has the cause of RVF been identified and appropriate treatment initiated?	• Anticoagulation and consideration of thrombolysis vs catheter-directed therapy vs surgical embolectomy for massive PE • Reperfusion if acute RV infarct • Appropriate treatment of left heart failure • Antibiotics and source control in sepsis • If decompensated chronic RVF, rule out PE, systemic infection, arrhythmia
Has RV preload been optimized?	• Avoid fluids if severe RV dilation on TTE • Judicious use of fluids if felt to be volume responsive • Most will be volume overloaded and require diuresis vs hemofiltration
Is the patient in sinus rhythm?	• Rate control is inadequate • Consider anti-arrhythmics (amiodarone) and cardioversion to restore sinus rhythm • Consider AV pacing if medications and cardioversion fail
Has RV afterload been minimized?	• Correct, hypoxia, hypercarbia, and acidosis • Minimize adverse effects of mechanical ventilation (plateau pressures <27; minimal PEEP; low tidal volumes) • Consider pulmonary vasodilators
Has RV contractility been optimized?	• Consider milrinone or low-dose dobutamine to augment contractility • Treat hypotension to maintain coronary perfusion • Norepinephrine is first-line vasopressor • Low-dose vasopressin is a reasonable choice as well
Has this patient failed medical therapy for RVF?	• Consider mechanical support

Abbreviations: AV, atrioventricular; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; RHC, right heart catheterization; RV, right ventricular; RVF, RV failure; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Volume status is a key consideration in decompensated disease and is often assessed and managed incorrectly. In the setting of hypotension, the patients are generally volume overloaded. Fluid loading can be detrimental and precipitate cardiovascular collapse. Continuous IV diuretics and often continuous renal replacement therapy are required for fluid removal.[65] Prerenal acute kidney injury is common and often reversed with restoration of adequate perfusion achieved by diuresis and titration of pulmonary vasodilators. A combination of continuous IV diuretics and pressors is frequently necessary to restore adequate cardiac output. Focused TTE can rapidly confirm RV volume overload. RHC is used commonly to guide therapy and provides vital information, including cardiac output, filling pressures, and pulmonary artery pressures, thus allowing the clinicians to assess response to interventions.

Reduction of RV afterload with pulmonary vasodilator therapy is essential. IV prostanoids are the first-line therapy for treatment of decompensated PAH. Initial dosage and choice of prostanoid should take into consideration prior PAH therapy. Common dose-dependent side effects of prostanoid therapy are hypotension, headache,

nausea, vomiting, and diarrhea.[46] Inhaled pulmonary vasodilators can be used in combination with IV therapy and will not worsen systemic hypotension.[65] New initiation of oral therapies is typically avoided in the critically ill patient with acute RVF, given their long half-life and ability to cause similar side effects to prostanoids. Titration of preexisting oral medications depends on a specific clinical situation. Patients with chronic PAH on IV vasodilator therapy who develop distributive shock may require dose adjustment to avoid high-output failure and systemic hypotension.[5] Consultation with a pulmonary hypertension specialist should be sought and interhospital transfer to an experienced center facilitated when appropriate.

MASSIVE PE

Ten percent of diagnosed cases of PE meet the definition of massive PE.[115] All patients with massive PE should be anticoagulated, barring contraindications. IV unfractionated heparin is typically used in massive PE, as this the preferred agent in patients receiving fibrinolytics or undergoing embolectomy.[116] In patients with suspected massive PE without prohibitive bleeding risk, heparin should be started immediately, rather than waiting for confirmatory testing.[117] Multidetector CT (MDCT) is the most commonly used diagnostic method. If PE is confirmed and the patient is hypotensive, current guidelines suggest thrombolytic therapy should be administered if bleeding risk is acceptable.[117] If hemodynamic instability precludes MDCT, TTE can be performed to assess for evidence of RV dilation.[115] If RV dilation is confirmed, European guidelines suggest consideration of thrombolysis.[118] Very limited randomized controlled trial data on the use of thrombolytic therapy in hypotensive patients exist. Jerjes-Sanchez and colleagues[119] compared heparin plus streptokinase to heparin alone in massive PE. The study was terminated after enrollment of only 4 patients to each arm for ethical reasons. All patients receiving streptokinase lived, whereas all patients in the heparin-only arm died. A meta-analysis of 5 studies that included patients with massive PE concluded that thrombolytic therapy reduces the risk of death or recurrent PE when compared with heparin alone.[120] Recent data suggest that "low-dose" recombinant tissue-type plasminogen activator, the recommended thrombolytic agent, may be as effective as standard doses with decreased risk of bleeding.[121] Supportive care with vasopressors, inhaled pulmonary vasodilators, inotropes, and optimization of volume status should be provided while awaiting hemodynamic improvement following thrombolytic therapy.

For patients with massive PE who have contraindications to thrombolysis, have failed thrombolysis, or who are expected to die from shock before thrombolysis can take effect, the American College of Chest Physicians guidelines recommend consideration of catheter-assisted thrombus removal or surgical embolectomy.[117] No large-scale studies validating catheter-based therapies have been performed, but available studies suggest hemodynamic stability can be restored in 86.5% of patients.[21] Surgical embolectomy was traditionally associated with high mortality rates, although recent studies using modern anesthesia and surgical techniques suggest in-hospital mortality rates as low as 5% to 6%.[122]

RV INFARCTION

The clinical presentation of RV infarction can vary widely, ranging from no hemodynamic effect to severe cardiogenic shock.[123] It is estimated that 25% to 50% of RV infarcts are hemodynamically significant.[123] Classic physical examination findings are hypotension, jugular venous distention, and clear lungs.[124] RV infarct should be entertained in all patients presenting with inferior ST-elevation myocardial infarction,

the typical setting for RV infarction.[124] Larger ST elevations in lead III than in lead II are pathognomonic for RV infarct.[125] ST-elevations in right-sided precordial leads (RV1 through RV6) can be seen as well.[125] TTE reveals a dilated hypokinetic RV and preserved LV function.[123]

Restoration of coronary blood flow is critical when treating RV infarction. This is best accomplished with percutaneous coronary intervention.[126] Studies have demonstrated that successful revascularization is associated with RV recovery, decreased risk for ventricular arrhythmia, and excellent clinical outcomes.[123] Unsuccessful revascularization is associated with poor recovery of RV function and high mortality.[123] While awaiting revascularization, efforts focus on stabilization of hemodynamics. Diuretics and nitrates should be avoided, as they can precipitate significant hypotension. Traditionally, volume loading has been the initial therapy for correction of hypotension following RV infarction, as it was thought to improve RV preload, correct hypotension, and improve cardiac output.[126] Several studies have called this practice into question, reporting that volume loading did not improve cardiac output.[127–129] The disparate results seen in studies are likely due to variability in volume status of patients at the time of presentation. Invasive monitoring is recommended to aid clinicians in volume assessment. Exceeding a RAP or pulmonary capillary wedge pressure of 20 mm Hg is not recommended.[123] In patients with persistent shock after optimization of preload, inotropes are indicated. Dobutamine has been demonstrated to improve cardiac output and RV ejection fraction in RV infarction.[128] In patients with refractory shock despite maximal medical therapy, mechanical support with IABP or RVAD may be beneficial.[128]

SUMMARY

RVF is associated with a number of commonly encountered conditions in critically ill patients. Understanding the pathophysiology of the failing RV is essential to development of an appropriate treatment plan. Medical therapies focus on correction of the underlying cause, optimization of RV preload, and contractility and reduction of RV afterload. Mechanical support is an option for select patients who fail medical management. Given the prevalence of RVF and its association with poor outcomes, further study on optimal therapeutic strategies is warranted.

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