

Chapter 18

Pulmonary Hypertension in Critically Ill Patients

Hooman D. Poor, Corey E. Ventetuolo, and Todd M. Bull

Abstract Pulmonary hypertension (PH) in critically ill patients requiring the intensive care unit (ICU) is a complex and challenging disorder. Whether the elevations of pulmonary arterial pressures are acute or preexisting, significant PH in the setting of acute illness can lead to rapid deterioration of right ventricular (RV) function, precipitating hemodynamic collapse and death. Outcomes of patients with PH who require the ICU are quite poor. In patients with underlying pulmonary arterial hypertension (PAH) or inoperable chronic thromboembolic PH (CTEPH) who are admitted to the ICU, mortality rates between 30 and 41 % have been reported. Given their fragile hemodynamic status, understanding the pathogenesis of RV failure secondary to PH is critical for RV rescue and successful treatment of these patients. In this chapter, we will discuss the pathophysiology of RV failure and management of PH and RV failure in the ICU.

Keywords Pulmonary hypertension • Pulmonary arterial pressures • Right ventricular (RV) function • Pulmonary arterial hypertension • RV dysfunction

Introduction

Pulmonary hypertension (PH) in critically ill patients requiring the intensive care unit (ICU) is a complex and challenging disorder. Whether the elevations of pulmonary arterial pressures are acute or preexisting, significant PH in the setting of acute

H.D. Poor, M.D.

Division of Pulmonary, Critical Care and Sleep, Mount Sinai Hospital, New York, NY, USA

C.E. Ventetuolo, M.D., M.S.

Division of Pulmonary, Sleep and Critical Care Medicine, Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI, USA

T.M. Bull, M.D. (✉)

Division of Pulmonary Sciences and Critical Care Medicine and Cardiology, The University of Colorado, Denver, CO, USA

12505 E. 16th Avenue, 3rd Floor, Aurora, CO 80045, USA

e-mail: Todd.Bull@ucdenver.edu

illness can lead to rapid deterioration of right ventricular (RV) function, precipitating hemodynamic collapse and death. Outcomes of patients with PH who require the ICU are quite poor. In patients with underlying pulmonary arterial hypertension (PAH) or inoperable chronic thromboembolic PH (CTEPH) who are admitted to the ICU, mortality rates between 30 and 41 % have been reported [1–3]. Given their fragile hemodynamic status, understanding the pathogenesis of RV failure secondary to PH is critical for RV rescue and successful treatment of these patients. In this chapter, we will discuss the pathophysiology of RV failure and management of PH and RV failure in the ICU.

Normal Structure and Function of the RV

The RV should not be viewed as simply a smaller and weaker version of the left ventricle (LV). The two ventricles are embryologically, morphologically, and functionally distinct [4, 5]. Although the RV contains helical fibers, unlike the LV, it lacks circumferential constrictor fibers and must therefore rely on longitudinal shortening. This results in a bellows-like contraction beginning near the apex of the heart and moving in a wave toward the outflow tract [6].

The low pressure and high capacitance of the pulmonary vasculature give rise to pressure–volume relationships for the RV that differ markedly from the pressure–volume relationships for the LV. Under normal loading conditions, the RV has only brief periods of isovolumic contraction and relaxation and has sustained ejection during pressure rise and fall. This circuit structure makes for a highly efficient right heart pump. Myocardial energy expenditure in the RV is approximately one-fifth that of the LV despite similar cardiac outputs (COs). This is due primarily to the much lower RV afterload. Increases in RV afterload significantly change this dynamic and lead to the development of prolonged periods of isovolumic contraction and relaxation, ultimately resulting in a decline in RV performance [6, 7] (Fig. 18.1).

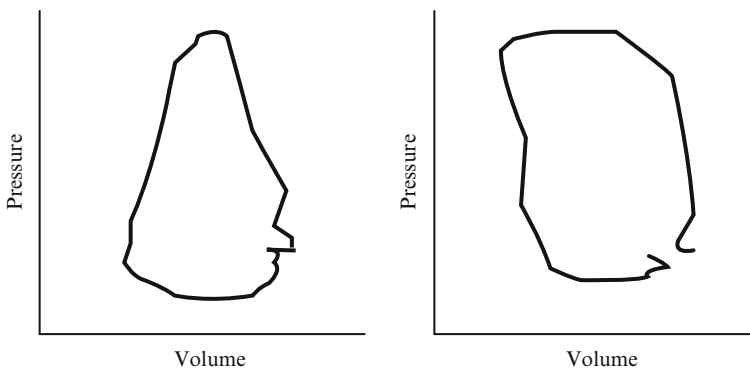


Fig. 18.1 Right ventricular pressure–volume curve from normal subject (a) and from patient with increased right ventricular afterload (b). Adapted from Redington et al. [7]

Coronary perfusion also differs between the two ventricles. Myocardial perfusion in the LV occurs predominantly during diastole, when intra-myocardial tissue pressure falls below aortic root pressure. Because RV intra-myocardial tissue pressure remains below aortic root pressure throughout the cardiac cycle under normal loading conditions, the RV receives continuous coronary flow from the right coronary artery (RCA) [8, 9].

Last, the RV and LV cannot be viewed as isolated chambers because they share the same visceral cavity (the pericardium), common myofibers, and the interventricular septum. As a result of this ventricular interdependence and the contractile relationships noted above, RV systolic function depends significantly on the LV and changes in the condition of one ventricle can significantly impact the function of the other. Importantly, since both ventricles share myofibers in the septum, LV systolic function augments RV pressure generation and RV systolic performance [10, 11]. With these normal anatomical and physiologic characteristics in mind, the pathophysiologic derangements that occur in the ICU setting may be better understood.

Pathophysiology of RV Failure

Right ventricular failure can be defined as low CO and systemic hypoperfusion despite high RV filling pressures [12]. Because the RV is very sensitive to increases in afterload, rapid elevations in RV afterload decrease RV ejection fraction and induce RV dilatation [13]. In contrast, when RV afterload rises more gradually, adaptive RV myocardial hypertrophy may occur, reducing wall stress to maintain adequate stroke volume [14–18]. In the acute setting, a pressure-overloaded RV dilates and RV end-diastolic volumes and pressures rise, increasing RV wall stress and placing the RV on the descending portion of the Frank-Starling curve [19]. The Laplace relation, which states that wall stress is inversely proportional to the thickness of the wall, helps explain why the thinner RV free wall experiences a greater rise in wall tension with incremental elevations in RV pressure compared with the thicker LV free wall [8].

Higher wall stress in the RV increases myocardial oxygen demand and oxygen consumption [20, 21]. As RV wall tension increases, RCA blood flow, normally continuous during both systole and diastole, occurs only during diastole, causing a further decrease in oxygen delivery to the RV [9, 22]. The combination of increased myocardial oxygen demand and decreased oxygen supply leads to RV ischemia and decreased RV contractility [20, 23]. Right ventricular function is further compromised when the tricuspid valve annulus widens in the setting of RV dilatation, with failure of the tricuspid valve leaflets to coapt properly and worsening tricuspid regurgitation [24]. These changes result in a perpetuating cycle of increasing wall stress, worsening ischemia, tricuspid regurgitation, and unfavorable loading conditions that ultimately lead to RV failure [25] (Fig. 18.2).

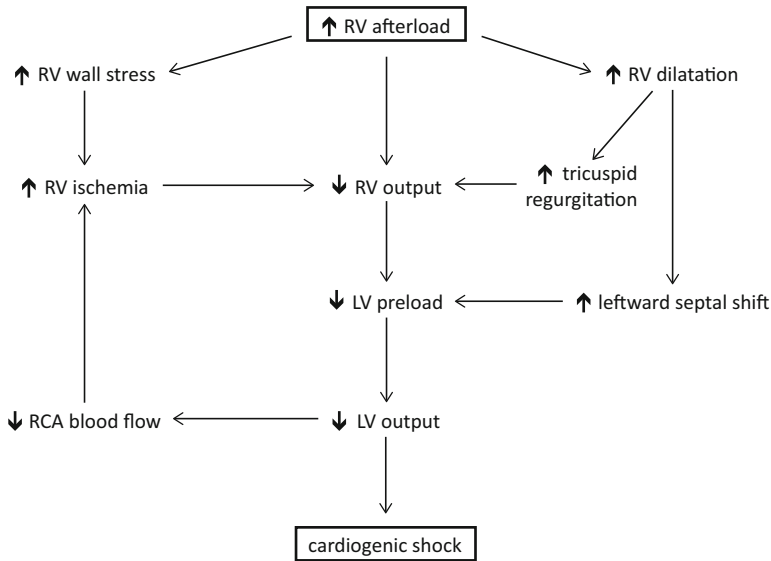


Fig. 18.2 Pathogenesis of right ventricular failure secondary to increased right ventricular afterload. *RV* right ventricle, *LV* left ventricle, *RCA* right coronary artery

Because the RV and LV share the space provided by the pericardium, increases in RV size are at the expense of LV volume. With RV dilatation, the interventricular septum undergoes leftward displacement, impinging upon the LV cavity. The septum's encroachment on the LV impairs LV filling, and the distortion in LV geometry causes a decline in LV systolic performance [26–30]. In addition, the LV is only able to pump the stroke volume received from the right heart, which steadily declines in the failing RV. The resultant decrease in LV stroke volume and CO leads to a fall in RCA blood flow and an exacerbation of RV ischemia, fueling the RV failure cascade (Fig. 18.2).

Acute RV failure from rapid increases in RV afterload can occur in the setting of massive pulmonary embolism (PE). In patients without prior cardiopulmonary disease, good correlation has been observed between hemodynamics and the degree of angiographic obstruction from PE [31–33]. Mean pulmonary artery (PA) pressures of greater than 20 mmHg occur when there is greater than 25–30 % obstruction of the pulmonary vascular bed. When more than 50 % of the pulmonary vascular bed is occluded acutely, patients with are unable to generate mean PA pressures of greater than 40 mmHg, presumably the maximum pressure a normal RV can generate. Thus, when pulmonary vascular obstruction exceeds 50 %, the inability of the RV to generate higher pressures leads to a decrease in CO and the initiation of the RV failure cascade [31, 34]. Mean PA pressures of greater than 40 mmHg suggest that the RV has hypertrophied from chronic increases in afterload such as those caused by underlying cardiopulmonary disease [17]. Patients with poor cardiopulmonary status, manifest a greater deterioration in hemodynamics with a lesser degree of pulmonary

vascular obstruction [35]. In patients with PAH, venous stasis, a sedentary lifestyle, dilated right heart chambers, and sluggish pulmonary blood flow together increase the risk for intrapulmonary thrombosis and thromboembolism.

RV failure can also occur in the absence of increased afterload, as seen in RV infarction. RV infarction results in both decreased RV systolic performance from profound depression of RV free wall contraction as well as RV diastolic dysfunction from ischemia [36, 37]. The culprit vessel for RV infarction is usually the RCA and significant RV infarction nearly always occurs in the setting of acute transmural inferior-posterior LV infarction [38]. When the RCA lesion is proximal to the right atrial (RA) branches, RA ischemia can impair RA function, further worsening right-sided hemodynamics [30, 36, 39]. With RV dilatation and decreased RV output, an RV failure cascade similar to that described above can occur. In the absence of preexisting pulmonary vascular disease or significant LV dysfunction, RV systolic and PA pressures do not rise. As LV septal contraction augments RV systolic pressure, concomitant LV infarction, particularly if the septum is involved, may result in further hemodynamic compromise [36, 40]. The short-term prognosis of patients with RV infarction is poor, owing to a higher incidence of cardiogenic shock, ventricular arrhythmias, and high-grade atrioventricular block. The increase in short-term mortality appears to be related to the actual presence of RV infarction and not total myocardial infarct size [41–46]. On the other hand, for patients who survive the acute period, the long-term prognosis is quite favorable even without successful coronary intervention, as RV function is able to return to near normal both at rest and with exercise [47, 48]. This dramatic improvement in RV function in the absence of reperfusion in survivors may be due to transient RV ischemia and myocardial stunning in the acute period, not true RV infarction [49–51]. The RV is less susceptible to true infarction for several reasons. First, its smaller mass and lower afterload result in lesser oxygen demand; Second, it receives coronary perfusion continuously throughout both diastole and systole; Finally, it has more extensive collateral flow from the left to the right coronary arteries. In fact, chronic RV failure attributable solely to RV infarction is a very rare occurrence [9, 51–53].

Triggers for RV Failure

A patient with preexisting pulmonary vascular and RV dysfunction can deteriorate rapidly when challenged by various insults. The prompt identification of contributing or inciting factors is therefore critical in the successful management of these patients [19]. A broad differential diagnosis should be considered because clinical worsening in these patients may be due to a variety of multisystem derangements and etiologies.

A rigorous search for potential sources of infection should be conducted when patients with PH become acutely ill. In a patient with chronic RV dysfunction and venous congestion, reduced bowel perfusion can impair the function of the intestinal barrier, leading to translocation of bacteria and/or release of endotoxin [54].

Patients with chronic PAH who have indwelling central venous catheters for the administration of vasoactive therapies are at increased risk for developing catheter-related skin and soft tissue infections as well as bacteremia [19]. Chronic PAH therapies, specifically prostacyclins, may also have immunosuppressive effects [55–58]. Pneumonia is particularly problematic in patients with pulmonary vascular disease because the resultant shunt with hypoxia can lead to vasoconstriction and further elevation in pulmonary vascular resistance (PVR).

The hemodynamic perturbations in sepsis can cause profound deterioration in patients with severe PH and RV failure. The increase in capillary leak and venous capacitance observed in sepsis results in decreased venous return and lower RV filling pressures, a condition poorly tolerated by a failing RV. The failing RV relies heavily on elevated end diastolic pressures to maintain cardiac output and is sensitive to abrupt changes in loading conditions [59]. Systemic hypotension from sepsis-induced peripheral vasodilation can result in decreased RCA blood flow, exacerbating RV ischemia and compromising RV function. Even in the absence of preexisting pulmonary vascular disease, sepsis has been shown to cause RV myocardial dysfunction directly through cytokine-mediated myocardial depression, as well as indirectly via hypoxic pulmonary vasoconstriction from associated lung injury [60–63]. As discussed later in the text, the addition of vasopressors and inotropes are fraught with their own difficulties in this hemodynamically fragile patient population. Irrespective of the site of infection, the development of sepsis can be devastating and must be managed aggressively, as described below. For these reasons, when infection is suspected, clinicians should have a low threshold to promptly administer antibiotics.

Acute respiratory distress syndrome (ARDS) can lead to the development of RV dysfunction, primarily via increases in RV afterload [64–70]. A variety of factors contribute to pulmonary vascular dysfunction in ARDS, namely, pulmonary vasoconstriction from hypercapnia and hypoxia, and increased intra-thoracic pressures secondary to mechanical ventilation and high positive end-expiratory pressures [70, 71]. Thrombosis also contributes to the increased RV afterload as postmortem studies have demonstrated thromboemboli in 95 % of patients with ARDS [65, 72]. A sub-study from a large clinical trial of ARDS found that 73 % of patients with ARDS had pulmonary vascular dysfunction, as evidenced by an increase in the transpulmonary gradient (TPG) and pulmonary vascular resistance index. The presence of pulmonary vascular dysfunction was independently associated with increased mortality in a dose-dependent fashion, such that increasing TPG was associated with higher mortality [64]. Although the mortality rates of patients with chronic PH who develop ARDS have not been well studied, it seems likely that PH patients may be particularly susceptible to poor outcomes in the setting of ARDS.

Atrial tachyarrhythmias may contribute to hemodynamic compromise in critically ill patients with pulmonary vascular disease. In a cohort of 231 patients with PAH or inoperable CTEPH, the annual incidence of new-onset supraventricular tachycardia was 2.8 %, most commonly due to atrial fibrillation or atrial flutter [73]. Because patients with PH may already have impaired LV filling, these tachyarrhythmias are poorly tolerated and can lead to clinical decompensation. In addition,

the loss of atrial contractions may be deleterious in the setting of a noncompliant RV [25, 74]. The maintenance or restoration of sinus rhythm may be helpful in the management strategy discussed below, although data supporting this approach are lacking.

Other factors that may contribute to RV failure in the setting of PH include anemia, hypoxemia, hypercapnia, acidosis, PE, and metabolic abnormalities [24]. Iatrogenic causes include the abrupt withdrawal of pulmonary vasodilators leading to rebound PH, the administration of medications with negative inotropic properties such as β -blockers and certain calcium channel blockers, and the use of positive pressure ventilation, especially with high mean airway pressures and volumes [19]. In a study of 46 patients with PAH or inoperable CTEPH admitted to the ICU, 19 patients had an identifiable trigger for RV decompensation, of which 11 had infection, 3 had unplanned modification or withdrawal of pulmonary vasodilator therapy, 1 had unplanned withdrawal of diuretics, 3 had cardiac arrhythmias, and 1 had unplanned pregnancy [1].

Monitoring in the ICU

Close monitoring of patients with PH and RV failure is critical and may incorporate a mix of noninvasive and invasive modalities. The use of cardiac biomarkers may help in risk assessment because natriuretic peptides are secreted in the setting of right atrial and RV myocardial stretching and cardiac troponin is released during myocardial necrosis from RV ischemia [75]. Elevations in troponin and natriuretic peptides are associated with worse outcomes in chronic PH and acute pulmonary embolism [21, 75–82]. In a prospective cohort study examining 46 patients with PAH or inoperable CTEPH high brain natriuretic peptide levels on admission to the ICU were associated with increased mortality, although no statistical link was found between troponin levels and survival [1].

Echocardiography is a noninvasive modality that plays a central role in the management of patients with PH by providing information about RV function and geometry. In addition, it can help elucidate possible precipitating factors of RV failure, including LV dysfunction and valvular disease. Common echocardiographic signs of RV failure include RV dilatation with associated loss of its typical triangular shape and paradoxical motion of the interventricular septum during systole [83]. In chronic PAH, echocardiographic predictors of poor outcomes include RA enlargement, pericardial effusion, low tricuspid annular plane systolic excursion, and septal displacement, although their ability to discriminate between patients who do well and those who deteriorate in the acute care setting remains unclear [84–86].

The presence of a large pericardial effusion in critically ill patients with pulmonary vascular disease and/or RV failure can be alarming, particularly in the setting of decreased cardiac output or hypotension. The question of “silent tamponade” often arises because elevated RVEDP may prevent the normal echocardiographic findings of RV collapse during inspiration. However, drainage of pericardial

effusions in PAH patients traditionally has not been advised due to high reported mortality rates following pericardiocentesis or the placement of a pericardial window [87]. Acute RV decompensation following removal of pericardial fluid likely occurs because of a sudden increase in RV transmural pressure. Under normal conditions the RV is well suited to accommodate this relative increase in RV filling pressure, but in the acutely or chronically overloaded RV, filling pressures have often reached extremely high levels and any further increase may result in a fall in RV contractility. In fact, pericardial effusion in chronic RV failure is often caused by high RVEDP that impedes drainage of pericardial fluid [87]. Gradual removal of fluid may obviate this concern. A more recent single center experience with pericardiocentesis in PAH found low procedural mortality, suggesting that in highly experienced hands there may be a role for this procedure if tamponade is suspected [88]. However, extreme caution is advised.

For patients with PH presenting in shock, it is imperative to obtain adequate central venous access and to perform frequent and blood pressure monitoring. Pulmonary artery catheterization (PAC) may help to differentiate maldistributive from cardiogenic shock as well as guide ICU therapy. For example, the measurement of PA oxygen saturation, a marker of the adequacy of oxygen delivery for the body's oxygen demand, may determine the need for inotropes [83].

The use of PAC in critically ill patients without PH has declined over time because multiple studies have shown that outcomes are not improved with its use [89–92]. However, no studies have been carried out in the acute setting for the “pulmonary vascular” population and obtaining and following pulmonary hemodynamics may be important during acute illness for certain PH patients [90]. As the RV is usually severely dilated in advanced PAH, it is advisable to use fluoroscopy to guide the PA catheter into place in order to avoid excessive ectopy and arrhythmias. It is important to note that the PA diastolic pressure cannot be substituted for the pulmonary capillary wedge pressure in patients with PAH due to the presence of a significant TPG. An accurate pulmonary capillary wedge pressure can be difficult to obtain in patients with PAH but is a critical value and requires due diligence, as the approach to management differs markedly in PAH as compared to pulmonary venous hypertension.

Management

General management goals for patients with PH and RV failure include optimization of RV preload, maintenance of adequate mean systemic arterial pressure, enhancement of RV contractility, and reduction of RV afterload, while treating any potentially reversible causes for the acute decompensation [90]. Unfortunately, PH in the ICU setting has not been robustly studied, and consensus guidelines are lacking. Management strategies therefore rely heavily on the guidance of experienced PH specialists.

Volume Management

Optimizing preload in patients with RV failure is complex because both hypovolemia and hypervolemia can have detrimental effects on CO. In most but not all cases of RV failure, the dilated and stretched RV is operating on the flat portion of the Frank-Starling curve. Volume expansion in this scenario often does not augment CO and can instead exacerbate RV dilatation, increase RV wall tension, worsen tricuspid regurgitation, and displace the inter-ventricular septum toward the LV. These adverse effects on RV function and LV filling contribute to reducing CO and worsening clinical status. The goal, therefore, should be to maintain a negative fluid balance with the use of diuretics and, if necessary, hemofiltration, to decrease the volume load on the distended and failing RV without compromising preload. Adjustments in the rate and amount of volume removal should be made according to hemodynamic response [12, 93–97]. In the case of clear intravascular volume depletion, a conservative strategy of holding diuretics, encouraging oral hydration (if applicable), or judiciously using small fluid boluses is preferred.

Vasopressors

Mean systemic arterial pressure must be maintained to minimize RV ischemia. Increased RV wall stress leads to RCA hypoperfusion as PVR approaches SVR or as SVR falls in mixed shock states (i.e., vasodilatory shock with concomitant RV failure). If PVR exceeds SVR, RCA perfusion will occur only during diastole, exacerbating RV ischemia. With the use of vasopressors, SVR can be increased, leading to augmentation of mean systemic arterial pressure, lowering of the PVR/SVR ratio, and, ultimately, improvement in RV myocardial perfusion [9, 90, 98]. In addition, the use of vasopressors increases LV afterload, helping to normalize distorted LV geometry from a leftward-bowed septum [25]. In choosing a vasopressor agent, it is important to be aware of each drug's effect on PVR because increases in PVR may contribute to clinical decompensation.

Norepinephrine causes vasoconstriction through the α_1 receptor and has limited inotropic properties from β_1 receptor stimulation [99]. It has been shown to improve RV performance and PA/RV coupling in animal models of acute PH and RV dysfunction by way of β_1 effects on contractility [20, 100, 101]. In a study of ten patients with septic shock, PH, and RV dysfunction, norepinephrine increased SVR and improved the RV oxygen supply/demand ratio but also caused an increase in PVR and failed to improve RV ejection fraction [102]. Evidence for the use of norepinephrine in critically ill patients with PH comes from a large randomized trial of ICU patients with shock, in which norepinephrine use, as compared to dopamine use, was associated with decreased mortality at 28 days in the prespecified subgroup of patients with cardiogenic shock and with a decreased rate of arrhythmias in all patients [103].

Phenylephrine, an α_1 receptor agonist with no β_1 receptor activity, improves RCA perfusion in RV failure, but this benefit is offset by its elevation of PVR and lack of β_1 -mediated enhancement of contractility [98, 100, 104]. In addition, reflex bradycardia secondary to phenylephrine may have detrimental effects in the setting of RV failure [105].

Epinephrine, a potent α and β receptor agonist that causes vasoconstriction and increased inotropy, increased CO without altering the PVR/SVR ratio in hypoxic newborn piglets [106]. A small study in patients with RV dysfunction from severe septic shock showed that epinephrine increased RV contractility [107]. The use of epinephrine has not been well studied in patients with PH, however. For these reasons, norepinephrine is a more favorable choice for patients with PH in the ICU than either phenylephrine or epinephrine.

Vasopressin causes vasoconstriction by acting upon V1 receptors on vascular smooth muscle cells and also increases vascular responsiveness to catecholamines [99]. Low doses of vasopressin cause pulmonary vasodilation through endothelium-mediated nitric oxide (NO) production in animals, although high doses cause vasoconstriction through an endothelium-independent mechanism [108]. Vasopressin's effect on the pulmonary vasculature has been inconsistent in human studies [105]. At higher infusion rates, vasopressin may have direct myocardial depressive effects and causes coronary vasoconstriction [109, 110]. Although low-dose (i.e., 0.01–0.03 U min⁻¹) vasopressin may be effective in managing patients with RV failure, higher doses should be used with caution.

Inotropes

Dopamine activates dopaminergic receptors at doses less than 5 $\mu\text{g kg}^{-1} \text{min}^{-1}$, β_1 receptors at doses between 5 and 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$, and α_1 receptors at doses greater than 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$, although actual plasma dopamine levels for a given infusion rate may vary unpredictably in critically ill patients [99, 111]. In a large animal model of hypoxia-induced PH, dopamine did not increase PVR at doses up to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$ [112]. In fact, in patients with PH secondary to left heart disease, dopamine in doses ranging from 2 to 16 $\mu\text{g kg}^{-1} \text{min}^{-1}$ increased CO and heart rate but did not significantly change PVR [113]. Similarly, in a small study of patients with PH and septic shock, dopamine improved CO without increasing PVR but failed to improve RV ejection fraction [102]. As discussed above, although the routine use of dopamine in the critical care setting is not supported by current data, in low doses it may be a reasonable option in patients with PH and RV failure. Aggravation of tachycardia can be a limitation.

Dobutamine has inotropic effects through β_1 receptor stimulation and a variable degree of vasodilatory effects through the β_2 receptor [99]. In an animal model of PH, dobutamine at doses of 5–10 $\mu\text{g kg}^{-1} \text{min}^{-1}$ restored CO and arterial pressure without affecting PA resistance or elastance, improving PA/RV coupling [20]. Doses up to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$ in patients with left heart failure result in improved myocardial

contractility, reduced PVR and SVR, and less tachycardia when compared with dopamine [114]. Dobutamine has been shown to improve hemodynamics in patients with PH at liver transplantation and after severe RV infarction [97, 115]. However, it has significant β_2 -mediated systemic vasodilatory properties and thus, it is important to avoid high doses, anticipate possible systemic hypotension, and be prepared to add systemic vasopressors if systemic hypotension occurs [90].

Milrinone, a selective phosphodiesterase-3 inhibitor, that acts via delaying metabolism of intracellular cAMP has positive inotropic effects and direct-acting vasodilatory properties on the pulmonary circulation [99]. In animal models of both acute and chronic PH, milrinone improved RV function and decreased PVR [116, 117]. In patients with pulmonary vascular dysfunction in the setting of LV failure, post-ventricular assist, or cardiac transplantation, milrinone has been shown to reduce pulmonary pressures and improve RV function and is often the agent of choice in these settings [118–120]. Systemic hypotension often limits the use of milrinone in the treatment of patients with PAH and hemodynamic instability, but it may be effective in patients with PH associated with LV dysfunction. Dopamine, dobutamine, and milrinone therapies are all capable of inducing cardiac tachyarrhythmias that are poorly tolerated in patients with PH and may be a limiting factor in their use in some patients. A few case series suggest that inhaled milrinone may be useful in PH because it minimizes systemic hypotension by delivering the drug directly to the pulmonary vasculature [121–124].

Levosimendan, a novel drug that enhances myocardial contractility by sensitizing troponin C to calcium while also acting as a pulmonary vasodilator, is a promising agent for patients with PH and RV failure but has not yet been thoroughly investigated in this patient population [125–129]. Irrespective of the specific agent, inotropes should generally be considered when there is evidence of inadequate oxygen delivery and/or in the case of volume overload not successfully managed with diuretics alone. It is especially important to avoid “supra-normalization” of oxygen delivery in these patients because this strategy not only is associated with worse outcomes in the general ICU population but may also increase PA pressures and worsen cardiac function in patients with pulmonary vascular disease [130, 131].

Pulmonary Vasodilators

Because increased RV afterload plays a central role in RV failure associated with PH, the use of pulmonary vasodilators to unload the RV is critical. The ability of even a severely dilated and overloaded RV to return to normal size and function is illustrated by the restoration of RV function after pulmonary thromboendarterectomy for CTEPH and lung transplantation in patients with PH [132–134].

Inhaled NO is a potent pulmonary vasodilator with minimal systemic vasodilatory effects because it is rapidly inactivated by hemoglobin within the pulmonary capillaries. Because of its short half-life, continuous administration through a face mask, a nasal cannula, or, a ventilator circuit is required [135]. In patients with

chronic PAH, NO reduces PVR and improves CO without a drop in SVR [136–138]. In 26 patients admitted to the ICU with acute RV failure, NO administration resulted in a greater than 20 % increase in CO and/or decrease in PVR in half of the patients [139]. With prolonged use at high concentrations, methemoglobinemia may develop, necessitating periodic surveillance of methemoglobin levels and routine assessment for cyanosis [140]. Nitrogen dioxide (NO₂) will accumulate when NO is delivered with high FiO₂ and needs to be monitored continuously in the ventilator circuit. Care must be taken in the discontinuation of NO because abrupt withdrawal has been associated with rebound PH and hemodynamic collapse [141–143]. After prolonged use, complete discontinuation of even low-dose inhaled NO may necessitate bridging therapy with another targeted pulmonary vasodilator.

Prostacyclins, including epoprostenol, treprostinil, and iloprost, are potent, short-acting agents that cause pulmonary vasodilation and inhibit platelet aggregation. In chronic PAH, these medications improve exercise capacity, hemodynamics, and, in the case of continuous infusion epoprostenol, survival [144–149]. In the critical care setting, prostacyclins have been mainly studied in patients with PH after cardiac surgery or transplantation, where they have been shown to reduce PVR and improve RV function [150–156]. The use of intravenous prostacyclins and up-titration of their dose in the ICU is usually limited by systemic hypotension and other systemic adverse effects including nausea, flushing, headache, and diarrhea [55]. Prostacyclins should be avoided in patients with significant left heart dysfunction and elevated pulmonary venous pressures because their use in this setting can generate further increases in left-sided filling pressures, leading to the development of pulmonary edema, pleural effusions and/or the deterioration of LV function [157].

Importantly, vasodilation of the pulmonary vasculature by systemic prostacyclin or prostacyclin analogues is nonselective and can exacerbate ventilation-perfusion mismatch, leading to worsened gas exchange and hypoxemia. These effects may be particularly problematic in patients with intrinsic lung disease and hypoxic PH. This phenomenon maybe circumvented with the use of inhaled preparations whereby pulmonary blood flow to well-ventilated regions in the lung is increased, thereby decreasing intra pulmonary shunt [158]. The inhaled prostacyclins iloprost and treprostinil are approved for outpatient use with specific devices (the I-neb Adaptive Aerosol Delivery device and the Optineb-ir, respectively). Iloprost is increasingly being used “off-label” in the postoperative and ICU setting with an ultrasonic nebulizer, although dosing and drug absorption are not standardized. Drug delivery and pharmacokinetics using alternative systems (i.e., conventional nebulizers and ventilator circuits) have also not been studied. Finally, abrupt discontinuation of prostacyclin infusions in chronically treated patients should be avoided because this may precipitate severe rebound PAH and even death [159]. Patients with PAH on chronic prostacyclin therapies who develop vasodilatory or mixed shock may require dose reductions during their acute illness, so as to not exacerbate systemic hypotension and/or create (relative) high-output failure, but this should be done under the guidance of a PH specialist.

The endothelin receptor antagonists and phosphodiesterase-5 (PDE5) inhibitors are proven oral medications for the management of chronic PAH, but they have not been investigated in critically ill patients with RV failure [160–163]. An intravenous formulation of the PDE5 inhibitor sildenafil has recently become available and may prove useful in the acute setting, although future studies in this patient population are needed [164]. By increasing downstream cyclic guanosine monophosphate signaling, PDE5 inhibitors reduce PVR and may also augment RV function by exerting a milrinone-like effect through inhibition of phosphodiesterase-3 [165–168]. With a rapid onset of action and a relatively prolonged half-life of 3–4 h, intravenous sildenafil must be used cautiously in critically ill patients to avoid systemic hypotension and exacerbation of ventilation-perfusion mismatch [164, 169]. Anecdotally, intravenous dosing should be approximately one third to one half that of the anticipated oral sildenafil dose.

Supportive Care

Maintaining peripheral oxygen saturations greater than 90 % in PAH; this is critically important in the acute setting, to prevent or reverse any contributing hypoxic pulmonary vasoconstriction [170]. Oxygen inhalation has been shown to reduce PVR and improve CO in patients with PH [171, 172]. Hypercapnia and acidemia worsen hypoxic pulmonary vasoconstriction and RV contractility and should be avoided [173, 174]. Although no studies have been performed to determine the optimal hemoglobin level for patients with PH and RV failure, many experts recommend maintaining a hemoglobin level of greater than 10 g dL⁻¹ to optimize oxygen-carrying capacity and minimize RV ischemia [25]. Volume status should be monitored carefully and diuretics adjusted appropriately with transfusion. As mentioned previously, patients with PH and RV failure are intolerant of electrolyte disturbances, metabolic derangements, and vagal stimuli, and care must be taken to normalize these imbalances if present.

Mechanical Ventilation

Endotracheal intubation of patients with PH and RV failure should be avoided when at all possible. If intubation is necessary, etomidate is generally the preferred induction sedative because it has minimal effects on SVR, PVR, and cardiac contractility. Propofol should be avoided given its propensity to cause systemic hypotension. Systemic vasopressors should be readily available or started preemptively to maintain SVR and counteract peri-intubation hypotension, which, if occurs in a patient with severe PH and RV failure, can be catastrophic and result in cardiac arrest [175, 176].

Because elevated intrathoracic pressures decrease RV and LV preload and increase PVR, ventilator strategies that use high inflation lung volumes and pressures should be avoided to prevent these detrimental effects [90, 177]. High positive end-expiratory pressures may, in theory, increase pulmonary vascular resistance and should be avoided, as should atelectasis or reduced lung volumes. In general, ventilation strategies should aim to keep lung volumes close to Functional Residual Capacity (FRC) while maintaining adequate oxygenation and ventilation while avoiding high peak inspiratory or end expiratory pressures.

Mechanical Support

When conventional support for the RV is ineffective in severe cases of PH and RV failure, mechanical support, including RV-assist devices and venoarterial extracorporeal membrane oxygenation (VA-ECMO), may be considered. The use of intra-aortic balloon counterpulsation in isolated RV failure has been reported, and improves CO by augmenting coronary blood flow [178, 179]. Although RV-assist devices are effective in primary RV dysfunction or RV failure secondary to LV failure, thus far, they have not been shown to be successful in patients with significantly elevated PVR. In this setting, the increase in pulmonary blood flow, particularly if pulsatile, gives rise to markedly elevated pulmonary vascular pressures, which can damage the pulmonary microcirculation and lead to intraparenchymal pulmonary hemorrhage, hemoptysis, and death [180, 181].

VA-ECMO has been used successfully in patients with massive PE, in patients with PH and RV failure as a bridge to lung transplantation, and in patients with CTEPH as a bridge to or for complications arising after pulmonary thromboendarterectomy [182–189]. By unloading the RV and providing additional blood flow to the systemic circulation, VA-ECMO improves the hemodynamics of patients with PH and RV failure. In addition, it can help reverse hypoxic pulmonary vasoconstriction by performing gas exchange and has been successfully used in awake, spontaneously breathing patients (a number of whom had PAH) as a bridge to lung transplantation [190]. VA-ECMO is not without potentially serious complications, however, and may include bleeding, infection, thromboembolism, and neurologic sequelae [180]. More recently, pumpless lung-assist devices have been developed and used in patients with PAH as a bridge to lung transplantation, connecting the PA to the left atrium with a low-resistance membrane oxygenator. With the blood flow through the circuit powered by the patient's own RV, these devices unload the RV and enhance LV filling in a manner similar to balloon atrioseptostomy; however, in contrast to septostomy, these devices improve instead of impair gas exchange [191, 192].

Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) in patients with PH and RV failure is largely unsuccessful. In a retrospective, multicenter study, 132 patients with PAH had circulatory arrest and implementation of CPR, of which only 8 patients (6 %) survived for more than 90 days. In addition, seven of these eight surviving patients had correctable causes of their cardiopulmonary arrest, including vasovagal reactions, digitalis toxicity, and pericardial tamponade [193]. One explanation for the lack of efficacy of CPR in this patient population is that high PVR makes it unlikely that chest compressions will achieve adequate pulmonary blood flow and LV filling. In addition, the use of epinephrine during CPR causes even further increases in PVR [194]. In light of the poor outcomes of CPR in patients with severe PH and RV failure, having timely discussions about the possibility of “Do Not Resuscitate” orders with these patients and their families is crucial, particularly in patients in whom a reversible cause for decompensation cannot be determined.

Conclusion

Patients with PH and RV failure who require ICU admission are at significant risk for worsening morbidity and mortality. In the setting of PH, RV failure can be triggered by various factors, giving rise to a vicious cycle of worsening RV function, profound shock, and death. Given their tenuous hemodynamics, these patients must be monitored closely with indicators of end-organ perfusion, cardiac biomarkers, echocardiography, and, in select situations, PAC. Management goals include optimizing RV preload with diuretics or hemofiltration, maintaining mean systemic arterial pressure with systemic vasopressors, augmenting RV contractility with inotropes, decreasing RV afterload with selective pulmonary vasodilators, and reversing any identifiable inciting factors. In severe cases, VA-ECMO or other forms of mechanical support may be considered. Although there have been marked advances in therapeutic strategies for PAH over the last several decades, acute care of patients with pulmonary vascular and RV dysfunction remains largely unstudied and guided by clinical expertise.

References

1. Sztymf B, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;35(6):1286–93.
2. Kurzyna M, et al. Characteristics and prognosis of patients with decompensated right ventricular failure during the course of pulmonary hypertension. *Kardiol Pol*. 2008;66(10):1033–9. discussion 1040–1.
3. Huynh TN, et al. Prognostic factors and outcomes of patients with pulmonary hypertension admitted to the intensive care unit. *J Crit Care*. 2012;27(6):739e7–13.

4. Greyson CR. Pathophysiology of right ventricular failure. *Crit Care Med.* 2008;36(1 Suppl):S57–65.
5. Zaffran S, et al. Right ventricular myocardium derives from the anterior heart field. *Circ Res.* 2004;95(3):261–8.
6. Sheehan F, Redington A. The right ventricle: anatomy, physiology and clinical imaging. *Heart.* 2008;94(11):1510–5.
7. Redington AN, et al. Changes in the pressure-volume relation of the right ventricle when its loading conditions are modified. *Br Heart J.* 1990;63(1):45–9.
8. Greyson CR. The right ventricle and pulmonary circulation: basic concepts. *Rev Esp Cardiol.* 2010;63(1):81–95.
9. Lowensohn HS, et al. Phasic right coronary artery blood flow in conscious dogs with normal and elevated right ventricular pressures. *Circ Res.* 1976;39(6):760–6.
10. Damiano Jr RJ, et al. Significant left ventricular contribution to right ventricular systolic function. *Am J Physiol.* 1991;261(5 Pt 2):H1514–24.
11. Hoffman D, et al. Left-to-right ventricular interaction with a noncontracting right ventricle. *J Thorac Cardiovasc Surg.* 1994;107(6):1496–502.
12. Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. *Chest.* 1997;111(1):218–24.
13. Brent BN, et al. Physiologic correlates of right ventricular ejection fraction in chronic obstructive pulmonary disease: a combined radionuclide and hemodynamic study. *Am J Cardiol.* 1982;50(2):255–62.
14. Sharma S, et al. Dynamic changes of gene expression in hypoxia-induced right ventricular hypertrophy. *Am J Physiol Heart Circ Physiol.* 2004;286(3):H1185–92.
15. Simon MA. Right ventricular adaptation to pressure overload. *Curr Opin Crit Care.* 2010;16(3):237–43.
16. Baandrup JD, et al. Pressure load: the main factor for altered gene expression in right ventricular hypertrophy in chronic hypoxic rats. *PLoS One.* 2011;6(1):e15859.
17. Badano LP, et al. Right ventricle in pulmonary arterial hypertension: haemodynamics, structural changes, imaging, and proposal of a study protocol aimed to assess remodelling and treatment effects. *Eur J Echocardiogr.* 2010;11(1):27–37.
18. Dias CA, et al. Reversible pulmonary trunk banding. II. An experimental model for rapid pulmonary ventricular hypertrophy. *J Thorac Cardiovasc Surg.* 2002;124(5):999–1006.
19. Matthews JC, McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. *Curr Cardiol Rev.* 2008;4(1):49–59.
20. Kerbaul F, et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Crit Care Med.* 2004;32(4):1035–40.
21. Torbicki A, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. *Circulation.* 2003;108(7):844–8.
22. Gibbons Kroeker CA, et al. Compression induced by RV pressure overload decreases regional coronary blood flow in anesthetized dogs. *Am J Physiol Heart Circ Physiol.* 2006;290(6):H2432–8.
23. Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. *Coron Artery Dis.* 2005;16(1):13–8.
24. Chemla D, et al. Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J.* 2002;20(5):1314–31.
25. Hoepfer MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med.* 2011;184(10):1114–24.
26. Gan CT, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol.* 2006;290(4):H1528–33.
27. Mahmud E, et al. Correlation of left ventricular diastolic filling characteristics with right ventricular overload and pulmonary artery pressure in chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2002;40(2):318–24.

28. Stojnic BB, et al. Left ventricular filling characteristics in pulmonary hypertension: a new mode of ventricular interaction. *Br Heart J*. 1992;68(1):16–20.
29. Marcus JT, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol*. 2008;51(7):750–7.
30. Brookes C, et al. Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. *Circulation*. 1999;100(7):761–7.
31. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. *Am J Cardiol*. 1971;28(3):288–94.
32. McIntyre KM, Sasahara AA. Hemodynamic alterations related to extent of lung scan perfusion defect in pulmonary embolism. *J Nucl Med*. 1971;12(4):166–70.
33. Azarian R, et al. Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. *J Nucl Med*. 1997;38(6):980–3.
34. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest*. 2002;121(3):877–905.
35. McIntyre KM, Sasahara AA. Determinants of right ventricular function and hemodynamics after pulmonary embolism. *Chest*. 1974;65(5):534–43.
36. Goldstein JA, et al. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation*. 1990;82(2):359–68.
37. Toldo S, et al. Right ventricular dysfunction following acute myocardial infarction in the absence of pulmonary hypertension in the mouse. *PLoS One*. 2011;6(3):e18102.
38. Bowers TR, et al. Patterns of coronary compromise resulting in acute right ventricular ischemic dysfunction. *Circulation*. 2002;106(9):1104–9.
39. Goldstein JA, et al. Right atrial ischemia exacerbates hemodynamic compromise associated with experimental right ventricular dysfunction. *J Am Coll Cardiol*. 1991;18(6):1564–72.
40. Goldstein JA, et al. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. *J Am Coll Cardiol*. 1992;19(3):704–11.
41. Zehender M, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med*. 1993;328(14):981–8.
42. Bowers TR, et al. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med*. 1998;338(14):933–40.
43. Bueno H, et al. In-hospital outcome of elderly patients with acute inferior myocardial infarction and right ventricular involvement. *Circulation*. 1997;96(2):436–41.
44. Mehta SR, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol*. 2001;37(1):37–43.
45. Gumina RJ, et al. Strong predictive value of TIMI risk score analysis for in-hospital and long-term survival of patients with right ventricular infarction. *Eur Heart J*. 2002;23(21):1678–83.
46. Shiraki H, et al. Acute impact of right ventricular infarction on early hemodynamic course after inferior myocardial infarction. *Circ J*. 2010;74(1):148–55.
47. Lim ST, et al. Right ventricular performance at rest and during stress with chronic proximal occlusion of the right coronary artery. *Am J Cardiol*. 2003;92(10):1203–6.
48. Dell'Italia LJ, et al. Hemodynamically important right ventricular infarction: follow-up evaluation of right ventricular systolic function at rest and during exercise with radionuclide ventriculography and respiratory gas exchange. *Circulation*. 1987;75(5):996–1003.
49. Ramzy IS, et al. Right ventricular stunning in inferior myocardial infarction. *Int J Cardiol*. 2009;136(3):294–9.
50. Ketikoglou DG, et al. Echocardiographic evaluation of spontaneous recovery of right ventricular systolic and diastolic function in patients with acute right ventricular infarction associated with posterior wall left ventricular infarction. *Am J Cardiol*. 2004;93(7):911–3.
51. Goldstein JA. Acute right ventricular infarction: insights for the interventional era. *Curr Probl Cardiol*. 2012;37(12):533–57.

52. Kusachi S, et al. Right and left ventricular oxygen metabolism in open-chest dogs. *Am J Physiol.* 1982;243(5):H761–6.
53. Haupt HM, Hutchins GM, Moore GW. Right ventricular infarction: role of the moderator band artery in determining infarct size. *Circulation.* 1983;67(6):1268–72.
54. Krack A, et al. The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur Heart J.* 2005;26(22):2368–74.
55. Papierniak ES, Lowenthal DT, Mubarak K. Pulmonary arterial hypertension: classification and therapy with a focus on prostaglandin analogs. *Am J Ther.* 2012;19(4):300–14.
56. Oudiz RJ, et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. *Chest.* 2004;126(1):90–4.
57. Rich JD, et al. The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension. *Chest.* 2012;141(1):36–42.
58. Kallen AJ, et al. Bloodstream infections in patients given treatment with intravenous prostanooids. *Infect Control Hosp Epidemiol.* 2008;29(4):342–9.
59. Zanotti Cavazzoni SL, Dellinger RP. Hemodynamic optimization of sepsis-induced tissue hypoperfusion. *Crit Care.* 2006;10 Suppl 3:S2.
60. Sharma AC. Sepsis-induced myocardial dysfunction. *Shock.* 2007;28(3):265–9.
61. Court O, et al. Clinical review: Myocardial depression in sepsis and septic shock. *Crit Care.* 2002;6(6):500–8.
62. Kimchi A, et al. Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. *J Am Coll Cardiol.* 1984;4(5):945–51.
63. Parker MM, et al. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. *Chest.* 1990;97(1):126–31.
64. Bull TM, et al. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med.* 2010;182(9):1123–8.
65. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med.* 1977;296(9):476–80.
66. Sibbald WJ, et al. Biventricular function in the adult respiratory distress syndrome. *Chest.* 1983;84(2):126–34.
67. Schulman DS, Matthay RA. The right ventricle in pulmonary disease. *Cardiol Clin.* 1992;10(1):111–35.
68. Vieillard-Baron A, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med.* 2001;29(8):1551–5.
69. Vieillard-Baron A, et al. Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care Med.* 2002;166(10):1310–9.
70. Vieillard-Baron A, Jardin F. Why protect the right ventricle in patients with acute respiratory distress syndrome? *Curr Opin Crit Care.* 2003;9(1):15–21.
71. Jardin F, et al. Relation between transpulmonary pressure and right ventricular isovolumetric pressure change during respiratory support. *Cathet Cardiovasc Diagn.* 1989;16(4):215–20.
72. Tomaszefski Jr JF, et al. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol.* 1983;112(1):112–26.
73. Tongers J, et al. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. *Am Heart J.* 2007;153(1):127–32.
74. Goldstein JA, et al. Hemodynamic importance of systolic ventricular interaction, augmented right atrial contractility and atrioventricular synchrony in acute right ventricular dysfunction. *J Am Coll Cardiol.* 1990;16(1):181–9.
75. Henzler T, et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. *Eur Respir J.* 2012;39(4):919–26.
76. Fijalkowska A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest.* 2006;129(5):1313–21.

77. Mauritz GJ, et al. Usefulness of serial N-terminal pro-B-type natriuretic peptide measurements for determining prognosis in patients with pulmonary arterial hypertension. *Am J Cardiol.* 2011;108(11):1645–50.
78. Leuchte HH, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. *J Am Coll Cardiol.* 2004;43(5):764–70.
79. Nagaya N, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation.* 2000;102(8):865–70.
80. Mehta NJ, Jani K, Khan IA. Clinical usefulness and prognostic value of elevated cardiac troponin I levels in acute pulmonary embolism. *Am Heart J.* 2003;145(5):821–5.
81. La Vecchia L, et al. Increased cardiac troponin I on admission predicts in-hospital mortality in acute pulmonary embolism. *Heart.* 2004;90(6):633–7.
82. Lega JC, et al. Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis. *Thorax.* 2009;64(10):869–75.
83. Gayat E, Mebazaa A. Pulmonary hypertension in critical care. *Curr Opin Crit Care.* 2011;17(5):439–48.
84. Ghio S, et al. Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension. *Int J Cardiol.* 2010;140(3):272–8.
85. Lopez-Candales A, et al. Apical systolic eccentricity index: a better marker of right ventricular compromise in pulmonary hypertension. *Echocardiography.* 2010;27(5):534–8.
86. Raymond RJ, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol.* 2002;39(7):1214–9.
87. Hemnes AR, Gaine SP, Wiener CM. Poor outcomes associated with drainage of pericardial effusions in patients with pulmonary arterial hypertension. *South Med J.* 2008;101(5):490–4.
88. Fenstad ER, Le RJ, Sinak LJ, Maradit-Kremers H, et al. Pericardial effusions in pulmonary arterial hypertension: characteristics, prognosis, and role of drainage. *Chest.* 2013;144(5):1530–8.
89. Hadian M, Pinsky MR. Evidence-based review of the use of the pulmonary artery catheter: impact data and complications. *Crit Care.* 2006;10 Suppl 3:S8.
90. Price LC, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care.* 2010;14(5):R169.
91. Harvey S, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet.* 2005;366(9484):472–7.
92. Sandham JD, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med.* 2003;348(1):5–14.
93. Belenkie I, et al. Effects of volume loading during experimental acute pulmonary embolism. *Circulation.* 1989;80(1):178–88.
94. Forrest P. Anaesthesia and right ventricular failure. *Anaesth Intensive Care.* 2009;37(3):370–85.
95. Ghignone M, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. *Anesthesiology.* 1984;60(2):132–5.
96. Mebazaa A, et al. Acute right ventricular failure—from pathophysiology to new treatments. *Intensive Care Med.* 2004;30(2):185–96.
97. Ferrario M, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol.* 1994;74(4):329–33.
98. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. *Circulation.* 1981;63(1):87–95.
99. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med.* 2011;183(7):847–55.

100. Hirsch LJ, et al. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. *Chest*. 1991;100(3):796–801.
101. Ducas J, et al. Treatment of canine pulmonary hypertension: effects of norepinephrine and isoproterenol on pulmonary vascular pressure-flow characteristics. *Circulation*. 1987;75(1):235–42.
102. Schreuder WO, et al. Effect of dopamine vs. norepinephrine on hemodynamics in septic shock. Emphasis on right ventricular performance. *Chest*. 1989;95(6):1282–8.
103. De Backer D, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779–89.
104. Rich S, Gubin S, Hart K. The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. *Chest*. 1990;98(5):1102–6.
105. Zamanian RT, et al. Management strategies for patients with pulmonary hypertension in the intensive care unit. *Crit Care Med*. 2007;35(9):2037–50.
106. Cheung PY, Barrington KJ. The effects of dopamine and epinephrine on hemodynamics and oxygen metabolism in hypoxic anesthetized piglets. *Crit Care*. 2001;5(3):158–66.
107. Le Tulzo Y, et al. Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. *Intensive Care Med*. 1997;23(6):664–70.
108. Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. *Chest*. 1993;103(4):1241–5.
109. Leather HA, et al. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med*. 2002;30(11):2548–52.
110. Indrambarya T, et al. Low-dose vasopressin infusion results in increased mortality and cardiac dysfunction following ischemia-reperfusion injury in mice. *Crit Care*. 2009;13(3):R98.
111. Juste RN, et al. Dopamine clearance in critically ill patients. *Intensive Care Med*. 1998;24(11):1217–20.
112. Lejeune P, et al. Effects of dopamine and dobutamine on hyperoxic and hypoxic pulmonary vascular tone in dogs. *Am Rev Respir Dis*. 1987;136(1):29–35.
113. Holloway EL, Polumbo RA, Harrison DC. Acute circulatory effects of dopamine in patients with pulmonary hypertension. *Br Heart J*. 1975;37(5):482–5.
114. Leier CV, et al. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation*. 1978;58(3 Pt 1):466–75.
115. Acosta F, et al. Effects of dobutamine on right ventricular function and pulmonary circulation in pulmonary hypertension during liver transplantation. *Transplant Proc*. 2005;37(9):3869–70.
116. Chen EP, et al. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. *Ann Thorac Surg*. 1997;63(3):814–21.
117. Deb B, Bradford K, Pearl RG. Additive effects of inhaled nitric oxide and intravenous milrinone in experimental pulmonary hypertension. *Crit Care Med*. 2000;28(3):795–9.
118. Oztekin I, et al. Effects of low-dose milrinone on weaning from cardiopulmonary bypass and after in patients with mitral stenosis and pulmonary hypertension. *Yakugaku Zasshi*. 2007;127(2):375–83.
119. Kihara S, et al. Effects of milrinone for right ventricular failure after left ventricular assist device implantation. *Heart Vessels*. 2002;16(2):69–71.
120. Eichhorn EJ, et al. Differential effects of milrinone and dobutamine on right ventricular preload, afterload and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1987;60(16):1329–33.
121. Singh R, et al. Inhaled nitroglycerin versus inhaled milrinone in children with congenital heart disease suffering from pulmonary artery hypertension. *J Cardiothorac Vasc Anesth*. 2010;24(5):797–801.
122. Sablotzki A, et al. Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates. *Can J Anaesth*. 2005;52(10):1076–82.

123. Wang H, et al. Comparison of inhaled and intravenous milrinone in patients with pulmonary hypertension undergoing mitral valve surgery. *Adv Ther.* 2009;26(4):462–8.
124. Haraldsson sA, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg.* 2001;93(6):1439–45. table of contents.
125. Kerbaul F, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Crit Care Med.* 2006;34(11):2814–9.
126. Kleber FX, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study. *J Clin Pharmacol.* 2009;49(1):109–15.
127. Kerbaul F, et al. Effects of levosimendan on acute pulmonary embolism-induced right ventricular failure. *Crit Care Med.* 2007;35(8):1948–54.
128. Missant C, et al. Levosimendan improves right ventriculovascular coupling in a porcine model of right ventricular dysfunction. *Crit Care Med.* 2007;35(3):707–15.
129. Yontar OC, Yalta K, Yilmaz MB. Superiority of levosimendan over dobutamine in right ventricle failure. *Crit Care Med.* 2010;38(1):342–3. author reply 343–4.
130. Hayes MA, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330(24):1717–22.
131. Gattinoni L, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO₂ Collaborative Group. *N Engl J Med.* 1995;333(16):1025–32.
132. Kramer MR, et al. Recovery of the right ventricle after single-lung transplantation in pulmonary hypertension. *Am J Cardiol.* 1994;73(7):494–500.
133. Reesink HJ, et al. Reverse right ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. *J Thorac Cardiovasc Surg.* 2007;133(1):58–64.
134. D'Armini AM, et al. Reverse right ventricular remodeling after pulmonary endarterectomy. *J Thorac Cardiovasc Surg.* 2007;133(1):162–8.
135. Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med.* 2005;353(25):2683–95.
136. Pepke-Zaba J, et al. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet.* 1991;338(8776):1173–4.
137. Vizza CD, et al. Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension. *Crit Care.* 2001;5(6):355–61.
138. Cockrill BA, et al. Comparison of the effects of nitric oxide, nitroprusside, and nifedipine on hemodynamics and right ventricular contractility in patients with chronic pulmonary hypertension. *Chest.* 2001;119(1):128–36.
139. Bhorade S, et al. Response to inhaled nitric oxide in patients with acute right heart syndrome. *Am J Respir Crit Care Med.* 1999;159(2):571–9.
140. Weinberger B, et al. The toxicology of inhaled nitric oxide. *Toxicol Sci.* 2001;59(1):5–16.
141. Christenson J, et al. The incidence and pathogenesis of cardiopulmonary deterioration after abrupt withdrawal of inhaled nitric oxide. *Am J Respir Crit Care Med.* 2000;161(5):1443–9.
142. Cueto E, et al. Life-threatening effects of discontinuing inhaled nitric oxide in children. *Acta Paediatr.* 1997;86(12):1337–9.
143. Lavoie A, et al. Life-threatening effects of discontinuing inhaled nitric oxide in severe respiratory failure. *Am J Respir Crit Care Med.* 1996;153(6 Pt 1):1985–7.
144. Olschewski H, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 2002;347(5):322–9.
145. Simonneau G, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med.* 2002;165(6):800–4.
146. Benza RL, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary

- Arterial Hypertension (TRIUMPH) study open-label extension. *J Heart Lung Transplant*. 2011;30(12):1327–33.
147. Hoepfer MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. *J Am Coll Cardiol*. 2000;35(1):176–82.
 148. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351(14):1425–36.
 149. Barst RJ, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296–301.
 150. Ocal A, et al. Efficiency of prostacyclin in the treatment of protamine-mediated right ventricular failure and acute pulmonary hypertension. *Tohoku J Exp Med*. 2005;207(1):51–8.
 151. Schmid ER, et al. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. *Anesth Analg*. 1999;89(5):1108–15.
 152. Elliott CG, Palevsky HI. Treatment with epoprostenol of pulmonary arterial hypertension following mitral valve replacement for mitral stenosis. *Thorax*. 2004;59(6):536–7.
 153. Lowson SM, et al. Inhaled prostacyclin for the treatment of pulmonary hypertension after cardiac surgery. *Crit Care Med*. 2002;30(12):2762–4.
 154. De Wet CJ, et al. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. *J Thorac Cardiovasc Surg*. 2004;127(4):1058–67.
 155. Rex S, et al. Inhaled iloprost to control pulmonary artery hypertension in patients undergoing mitral valve surgery: a prospective, randomized-controlled trial. *Acta Anaesthesiol Scand*. 2008;52(1):65–72.
 156. Yurtseven N, et al. A comparison of the acute hemodynamic effects of inhaled nitroglycerin and iloprost in patients with pulmonary hypertension undergoing mitral valve surgery. *Ann Thorac Cardiovasc Surg*. 2006;12(5):319–23.
 157. Califf RM, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134(1):44–54.
 158. Walmrath D, et al. Effects of inhaled versus intravenous vasodilators in experimental pulmonary hypertension. *Eur Respir J*. 1997;10(5):1084–92.
 159. Badesch DB, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest*. 2007;131(6):1917–28.
 160. Galie N, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119(22):2894–903.
 161. Galie N, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148–57.
 162. Rubin LJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12):896–903.
 163. Galie N, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010–9.
 164. Vachiery JL, et al. Safety, tolerability and pharmacokinetics of an intravenous bolus of sildenafil in patients with pulmonary arterial hypertension. *Br J Clin Pharmacol*. 2011;71(2):289–92.
 165. Preston IR, et al. Acute and chronic effects of sildenafil in patients with pulmonary arterial hypertension. *Respir Med*. 2005;99(12):1501–10.
 166. Michelakis E, et al. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation*. 2002;105(20):2398–403.
 167. Nagendran J, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. *Circulation*. 2007;116(3):238–48.

168. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N Engl J Med*. 2009;361(19):1864–71.
169. Cornet AD, et al. Sildenafil attenuates pulmonary arterial pressure but does not improve oxygenation during ARDS. *Intensive Care Med*. 2010;36(5):758–64.
170. McLaughlin VV, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119(16):2250–94.
171. Moloney ED, Evans TW. Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome. *Eur Respir J*. 2003;21(4):720–7.
172. Roberts DH, et al. Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with pulmonary hypertension. *Chest*. 2001;120(5):1547–55.
173. Balanos GM, et al. Human pulmonary vascular response to 4 h of hypercapnia and hypocapnia measured using Doppler echocardiography. *J Appl Physiol*. 2003;94(4):1543–51.
174. Mekontso Dessap A, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med*. 2009;35(11):1850–8.
175. Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. *Curr Opin Anaesthesiol*. 2010;23(3):411–6.
176. Gordon C, Collard CD, Pan W. Intraoperative management of pulmonary hypertension and associated right heart failure. *Curr Opin Anaesthesiol*. 2010;23(1):49–56.
177. Feihl F, Broccard AF. Interactions between respiration and systemic hemodynamics. Part II: practical implications in critical care. *Intensive Care Med*. 2009;35(2):198–205.
178. Darrah WC, et al. Intraaortic balloon counterpulsation improves right ventricular failure resulting from pressure overload. *Ann Thorac Surg*. 1997;64(6):1718–23. discussion 1723–4.
179. Arafa OE, et al. Intraaortic balloon pumping for predominantly right ventricular failure after heart transplantation. *Ann Thorac Surg*. 2000;70(5):1587–93.
180. Keogh AM, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl):S67–77.
181. Berman M, et al. Life-threatening right ventricular failure in pulmonary hypertension: RVAD or ECMO? *J Heart Lung Transplant*. 2008;27(10):1188–9.
182. Maggio P, et al. Extracorporeal life support for massive pulmonary embolism. *J Trauma*. 2007;62(3):570–6.
183. Kolvekar SK, et al. Extracorporeal membrane oxygenator for pulmonary embolism. *Ann Thorac Surg*. 1997;64(3):883–4.
184. Deehring R, et al. Extracorporeal membrane oxygenation as a bridge to surgical embolectomy in acute fulminant pulmonary embolism. *Am J Emerg Med*. 2006;24(7):879–80.
185. Olsson KM, et al. Extracorporeal membrane oxygenation in nonintubated patients as bridge to lung transplantation. *Am J Transplant*. 2010;10(9):2173–8.
186. de Perrot M, et al. Impact of extracorporeal life support on outcome in patients with idiopathic pulmonary arterial hypertension awaiting lung transplantation. *J Heart Lung Transplant*. 2011;30(9):997–1002.
187. Gregoric ID, et al. Extracorporeal membrane oxygenation as a bridge to emergency heart-lung transplantation in a patient with idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant*. 2008;27(4):466–8.
188. Berman M, et al. Successful extracorporeal membrane oxygenation support after pulmonary thromboendarterectomy. *Ann Thorac Surg*. 2008;86(4):1261–7.
189. Mydin M, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary endarterectomy. *Ann Thorac Surg*. 2011;92(5):e101–3.
190. Fuehner T, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med*. 2012;185(7):763–8.

191. Strueber M, et al. Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. *Am J Transplant*. 2009;9(4):853–7.
192. Schmid C, et al. Bridge to lung transplantation through a pulmonary artery to left atrial oxygenator circuit. *Ann Thorac Surg*. 2008;85(4):1202–5.
193. Hoepfer MM, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2002;165(3):341–4.
194. Smith AM, et al. The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension. *QJM*. 2006;99(3):127–33.