

Sepsis and Pulmonary Arterial Hypertension in the ICU

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The management of sepsis in the patient with pulmonary arterial hypertension (PAH) is dependent on 2 primary principles: 1) optimizing right ventricular (RV) function, and 2) reducing pulmonary vascular resistance. In this review, we will discuss the major challenges that health care providers face in trying to achieve these goals. We will start with an overview of normal RV function and modulators of pulmonary vascular tone. A general approach to managing RV failure and hemodynamic instability will be provided, along with a discussion of how modern therapies for the treatment of PAH can best be used in the setting of sepsis.

The inflammatory response to sepsis results in increased vascular permeability and vasodilation, leading to decreased intravascular volume and a fall in systemic vascular resistance (SVR) that must be compensated for by an increase in cardiac output (CO). Unfortunately for patients who suffer from pulmonary arterial hypertension (PAH), the ability to acutely increase CO may be severely limited, and significant pulmonary hypertension (PH) in the setting of acute illness can lead to rapid deterioration of right ventricular (RV) function, hemodynamic instability, and death. As a result, the management of critically ill PAH patients can be extremely challenging. As a group, these patients have a poor prognosis, with intensive care unit (ICU) mortality rates between 30% and 41%.¹⁻³ Whereas a considerable number of studies have examined left ventricular (LV) and systemic circulatory responses to sepsis,⁴⁻⁶ relatively little attention has been directed at the RV and pulmonary circulation. This is unfortunate because the pulmonary and systemic circulations are connected in series, and despite its smaller size, nearly the entire circulation must pass through the right heart and

pulmonary vasculature before it reaches the systemic circulation.

Normally, vascular resistance in the lungs is low and the pulmonary circulation is able to accommodate large increases in CO by recruiting unused or underperfused vessels. As a result, impairment of pulmonary blood flow or RV function rarely limits CO and oxygen delivery (DO_2) to peripheral tissues. However, when pulmonary vascular resistance (PVR) is high, as occurs in patients with PAH, pulmonary blood flow and RV function may become the primary determinants of adequate circulation.

THE NORMAL PULMONARY CIRCULATION AND RV

Although the CO generated by the RV and LV is essentially the same, the vascular bed they pump it through is considerably different. In the healthy adult, PVR is remarkably low, considering the drop in pressure across the pulmonary circulation [mPAP (15 mm Hg) – PCWP (8 mm Hg) = 7 mm Hg, where mPAP = mean pulmonary artery pressure and PCWP = pulmonary capillary wedge pressure] is less than a tenth

of that across the systemic circulation [MAP (90 mm Hg) – CVP (5 mm Hg) = 85 mm Hg, where MAP = mean systemic arterial pressure and CVP = central venous pressure. Despite a rise in CO during heavy exertion that may be 4-fold above baseline, PAP increases minimally and PVR falls. In the systemic circulation, increased CO during exercise is associated with an increase in MAP . The difference between the 2 circulations is the relatively low degree of vascular motor tone in the proximal pulmonary vascular bed, and the ability of the lung to recruit partially collapsed or unused vessels as CO increases. In the systemic circulation, muscularized resistor vessels allow for marked alterations in SVR via sympathetic stimulation or the release of endogenous catecholamines or vasodilators such as nitric oxide (NO) and prostaglandins. A variety of vasoactive drugs can also be used to sharply increase or decrease systemic vascular tone. In contrast, the pulmonary circulation has relatively low vascular tone, making it difficult to acutely increase or decrease PVR.

During fetal life, PVR is higher in the uninflated lung than it is in adult life, and the elevated pressure helps direct right-sided blood flow across the foramen ovale and into the left atrium. After birth, lung inflation reduces PVR considerably, and blood from the RV is redirected to the low resistance of the

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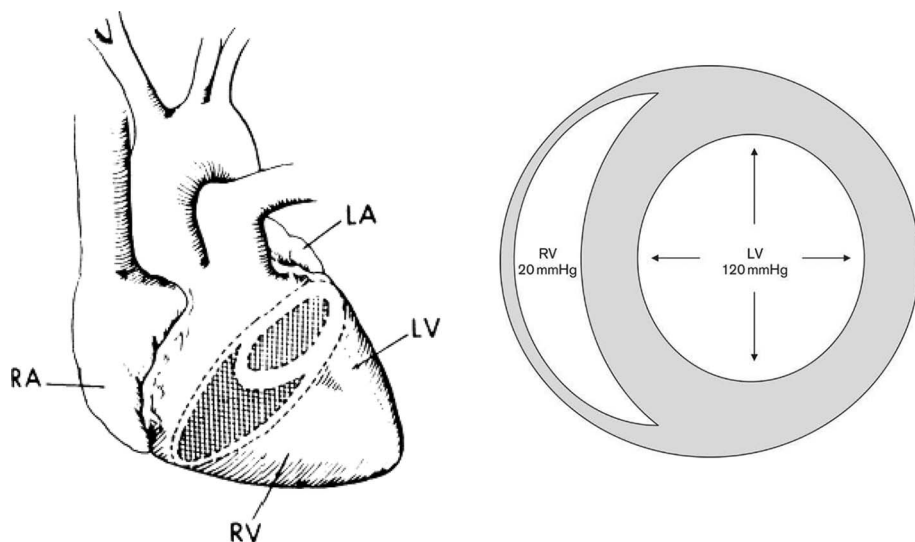


Figure 1: Structure and shape of the adult right and left ventricles. (Reprinted from Chan CM, Klinger JR. The right ventricle in sepsis. *Clin Chest Med*. 2008;29(4):661-676, with permission from Elsevier.)

pulmonary circulation. During normal development, the ventricles take on distinct structural characteristics designed to compensate for the marked differences in afterload they work against. The unique structural and functional characteristics of the RV and LV result in different responses to afterload and preload.

The LV has a thick muscular wall and global shape. High systolic pressures are achieved by circumferential contraction, resulting in the lateral free wall and interventricular septum (IVS) moving toward each other. In contrast, the RV is a crescent-shaped chamber formed by a thin, triangular-shaped piece of myocardial tissue wrapped around the IVS (Figure 1). At end diastole, the normal RV free wall is only 2 to 3 mm in thickness, compared to 8 to 11 mm in the LV.⁷ The CO from the RV is achieved by longitudinal contraction of the apex up toward the lateral leaflet of the tricuspid valve in a peristaltic pattern. Dilatation of the outflow region causes an initial expansion of the pulmonary artery (PA), thereby increasing its compliance and priming it to receive the RV stroke volume. The high compliance of the proximal PA facilitates RV output. In fact, blood has been observed to flow from the RV into the proximal PA even during diastole.⁸

Its high compliance allows the RV to accommodate large increases in venous return, with only a small increase in RV

end-diastolic pressure (RVEDP) or stroke work (Figure 2A).⁹⁻¹¹ RV output is well preserved over a range of volumes until dilatation of the ventricle is limited by the IVS septum and pericardium.¹² At that point, further increases in RV filling pressure overdistend myocardial fibers, increasing RV stroke work and decreasing CO.^{13,14} The structural properties of the RV that allow it to accommodate large increases in preload make it highly sensitive to increases in

afterload. Its smaller muscle mass and peristaltic contraction is poorly suited to increasing pressure when PVR is acutely increased. In healthy animals, RV stroke volume and output decline dramatically as resistance is increased by constricting the main PA (Figure 2B). In contrast, the LV tolerates increased afterload fairly well, but is sensitive to increases in preload (Figures 2A-2B).

The RV is also more affected by changes in intrathoracic pressure than the LV. Deep inhalation increases RV transmural filling pressure because intrathoracic pressure falls while systemic venous pressure is unaffected. Conversely, even a small rise in intrathoracic pressure, as occurs during positive-pressure ventilation, can substantially reduce RV filling pressure. Normally, the fall in RV filling caused by increased intrathoracic pressure is compensated for by increasing systemic venous tone and elevating CVP, but this can be difficult to achieve in patients with sepsis because of decreases in vascular tone and intravascular volume and because of the use of sedatives and analgesics.

The RV and LV share a common septum, and changes in pressures of one ventricle can be transmitted across the septum and affect the compliance of the other ventricle. Normally, LV end-

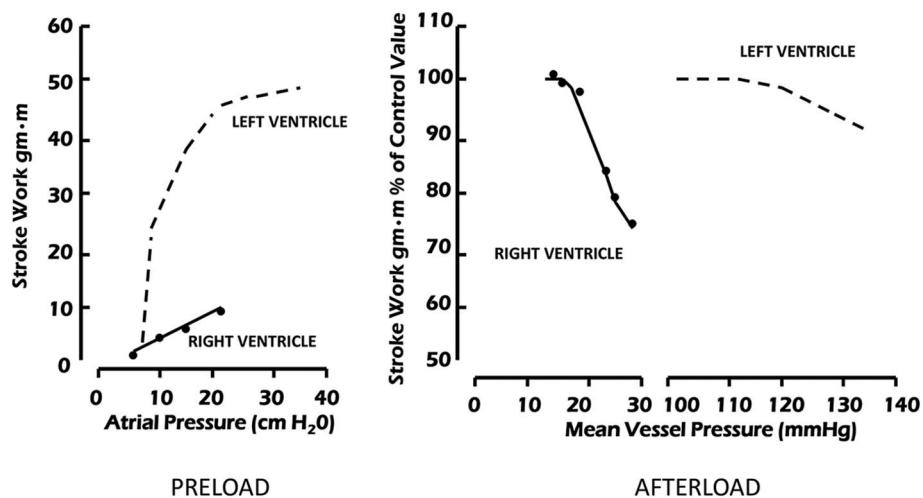
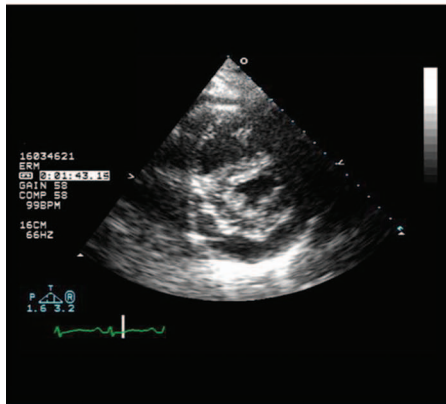


Figure 2: Differences between right and left ventricular response to increasing afterload (left panel) and increasing preload (right panel). Right ventricular stroke volume falls sharply as mean vascular pressure is increased from 20 to 30 mm Hg in the pulmonary artery, but left ventricular stroke volume remains fairly constant as mean aortic pressure is increased from 100 to 140 mm Hg. In contrast, left ventricular stroke work increases rapidly as left atrial pressure is raised from 10 to 20 cm H₂O, while the increase in RV stroke work in response to the same elevation of right atrial pressure is much more modest. (Reprinted with permission from Braunwald E. Pathophysiology of heart failure. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine*. Philadelphia, PA: Saunders, 1980;453-471.)



Diastole



Systole

Figure 3: The position of the interventricular septum during the cardiac cycle is determined by the difference between right and left ventricular pressure. Under normal conditions, left ventricular end-diastolic pressure is greater than right ventricular end-diastolic pressure and the septum bows toward the right ventricle during diastole. As the right ventricle fails, right ventricular end-diastolic pressure begins to exceed that of the left ventricle and the septum bows toward the left ventricle during diastole, forming a “D”-shaped pattern and impaired left ventricular filling (left panel). When right ventricular failure occurs due to elevated pulmonary vascular resistance, the combination of high right ventricular systolic pressure and decreased left ventricular filling may lead to near obliteration of the left ventricle at end systole (right panel). (Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Ventetuolo CE, Klingler JR. Management of acute right ventricular failure in the intensive care unit. *Ann Am Thorac Soc*. 2014;11(5):811-822. The *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.)

diastolic pressure (LVEDP) is greater than RVEDP, allowing the IVS to move toward the RV during diastole. This motion allows for maximal chamber enlargement in the concentric LV. However, as RVEDP exceeds LVEDP, the IVS can move paradoxically toward the LV lumen during diastole. This is best seen on 2-dimensional echocardiography as a flattening of the normal concave shape of the septum or a bowing of the septum toward the LV (Figure 3). As the IVS shifts toward the LV, compliance decreases and LVEDP rises resulting in decreasing LV output. The ability of RV filling pressures to affect LV filling pressure via the IVS is referred to as ventricular interdependence, and represents one of the greatest challenges to fluid management in septic patients with PAH. The lungs normally contain only about a tenth of the total

intravascular volume, or approximately 500 mL in an average-sized adult,¹⁵ and LV filling is largely dependent on blood flow through the lungs determined by RV output. Intravascular volume expansion must improve RV output enough to increase transpulmonary blood flow and increase blood return to the LV. If not, the increase in RVEDP transmitted through the IVS will decrease LV transmural filling pressure and can impede CO.

APPROACH TO MANAGEMENT OF THE PAH PATIENT WITH SEPSIS

The key to managing sepsis is to maintain adequate tissue perfusion until its cause can be eradicated. This is normally achieved by expanding intravascular volume and maintaining the increase in CO that sepsis demands. As

mentioned earlier, for the patient with PAH, achieving these goals centers on maximizing RV function while reducing PVR. These 2 goals are closely interrelated. Maximizing RV function requires optimizing RV preload, improving RV contractility, and reducing RV afterload. The latter, of course, is achieved primarily by reducing PVR. In general, the pulmonary vascular disease of PAH is relatively fixed, and acute reduction in PVR is difficult. Management, therefore, is usually directed at optimizing RV function and making sure that PVR does not increase in response to metabolic derangements caused by sepsis or vasoactive medications administered during resuscitation.

RV Preload

Proper fluid management is critical for successful management of the septic patient with PAH. In the early phase of sepsis, CVP is reduced due to a fall in intravascular volume from increased vascular permeability and a decrease in venous vascular tone. Adequate right-sided filling pressure is essential in maintaining CO in patients with acute RV failure.¹⁶ Therefore, volume resuscitation should be initiated if low intravascular volume is suspected. However, RV preload requirements differ substantially based on whether RV afterload is normal or increased. When RV failure occurs in the setting of normal PVR, RVEDP often needs to be increased above normal levels to maintain CO. However, when RV failure occurs in the setting of increased RV afterload, as occurs in the septic patient with PAH, volume loading can result in displacement of the IVS toward the LV and impair LV diastolic filling. In this setting, intravascular volume may need to be decreased.

Initial attempts at volume reduction may have little effect, because the RV has a relatively flat pressure volume curve, meaning there is less of a change in RV contractility over a wide range of filling pressures. Hence, a considerable amount of volume unloading may be necessary before any improvement in RV function is seen. At the same time, care must be exercised not to allow RV preload to become too low, because RV

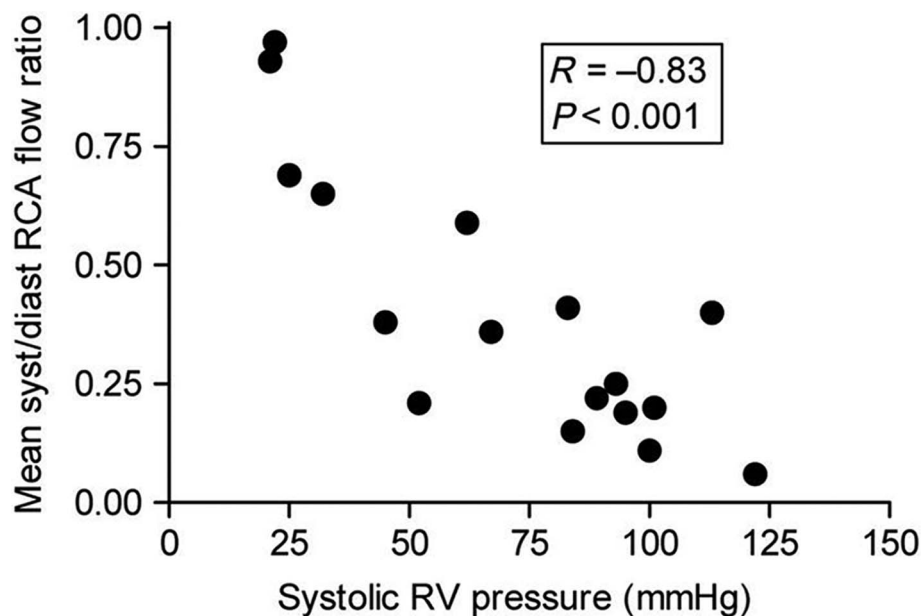


Figure 4: Ratio of blood flow during systole to blood flow during diastole in the right coronary artery (RCA) as a function of right ventricular (RV) systolic pressure in patients with pulmonary hypertension. When RV systolic pressure is near normal levels, the amount of RCA blood flow is similar during systole and diastole. As RV systolic pressure increases, RCA blood flow during systole falls. Blood flow in the RCA during systole is inversely proportional to RV systolic pressure such that RCA blood flow during systole approaches zero as RV systolic pressure approaches systemic levels. (Reprinted with permission from van Wolferen SA, et al. *Eur Heart J.* 2008;29(1):120-127.²³)

output is particularly dependent on adequate RV filling when RV afterload is high. In general, RV filling pressures should be kept moderately elevated in the 8 to 12 mm Hg range. The use of positive-pressure ventilation should be avoided if at all possible as it has a marked effect on reducing right-sided filling pressures.

Measurement of RV filling pressure can be challenging in the critically ill patient with PAH. A central venous line can measure CVP and provides access to superior vena cava oxygen saturation (SvO₂) that can help assess oxygen delivery. Normal SvO₂ is 70% to 80%, and lower values in the setting of normal arterial oxygenation can be suggestive of reduced CO. If RV preload is too high, reductions in CVP via diuresis or dialysis should be accompanied by improvement in CO as assessed by SvO₂ or systemic organ perfusion. Echocardiography may also be helpful. Evidence of RV dilation and impingement on LV filling suggest that further reduction in preload may be necessary. Ultrasound assessment of inferior vena caval filling can also be used to assess RV preload. If these assessments of RV function are inadequate,

placement of a PA catheter may be necessary. Although the routine use of a PA catheter has not been found to improve outcome in the management of severe sepsis^{17,18} and has not been well studied in the management of acute RV failure,¹⁹ there are times when measurement of pulmonary hemodynamics may be helpful in guiding clinical decision making. In our practice, we do not typically place Swan-Ganz-style catheters for continuous monitoring of RVEDP, CO, or PAP in septic patients with PAH, but do not hesitate to catheterize patients when we are uncertain of their filling pressures or afterload.

RV Contractility

RV function becomes critically important to the maintenance of adequate CO in the patient with PAH and sepsis. RV failure can occur because of insufficient or excess preload or an increase in afterload from worsening PH. But even when these factors have been corrected, RV function can be reduced from baseline due to a fall in myocardial contractility. Reduced RV contractility occurs due to 3 interrelated factors: 1) derangements in cellular metabolism

leading to decreased myocardial contractile forces, 2) insufficient oxygen delivery due to decreased coronary arterial perfusion, and 3) overstretching of the RV free wall placing the myocytes at a mechanical disadvantage.

A variety of metabolic derangements including acid/base disturbances, generation of reactive oxygen species, and inflammatory cytokines impair oxygen utilization and contribute to decreased RV contractility.^{20,21} These derangements should be minimized whenever possible, but are often difficult to correct in patients with sepsis.

Insufficient coronary artery perfusion is often the most important contributor to decreased RV function. Increases in RV preload and/or afterload increase RV free wall tension and oxygen demand while impeding LV filling. This results in reduced LV output that in turn can decrease coronary artery pressure. Perfusion of the RV free wall is determined by the difference in RV free wall tension and coronary artery pressure.²² Normally, coronary artery pressure is greater than RV pressure throughout the cardiac cycle, and the RV receives blood from the coronary arteries during systole and diastole. As RV systolic pressure approaches systemic levels in advanced cases of PAH, coronary perfusion of the RV decreases during systole (Figure 4).²³ The lack of RV perfusion in patients with PAH is only made worse in the setting of systemic hypotension that may occur during sepsis. In this situation, it becomes critical to keep systemic arterial pressure at least as high as RV systolic pressure.^{24,25} Excessive fluid resuscitation can increase RV size and free wall tension without improving systemic arterial pressure and can actually decrease RV perfusion.^{26,27} Drugs that increase myocardial contractility should be held until this first goal is achieved, because they increase RV oxygen demand and can worsen RV ischemia if systemic arterial pressure is not increased.

Vasopressors

Several vasoactive drugs have been used to manage PAH patients with sepsis (Table 1). The ideal agent should increase systemic arterial pressure and RV contractility without raising PVR. In

Table 1: Vasoactive Drugs for Management of Pulmonary Hypertension in Sepsis and their Mechanism of Action

Agent	Receptor Binding					Notes
	α_1	β_1	β_2	D	V1	
Norepinephrine	++	+				Improves PA/RV coupling in animals
Phenylephrine	++					Increases PVR; may induce reflex bradycardia
Epinephrine	++	++	+			
Vasopressin					+	Dose-dependent pulmonary vasodilatation (0.01–0.03 U/min) and vasoconstriction
Dopamine						Risk of arrhythmias
Low (<5 $\mu\text{g}/\text{kg}/\text{min}$)		+		++		
Medium (>10 $\mu\text{g}/\text{kg}/\text{min}$)	+	++		++		
High (>10 $\mu\text{g}/\text{kg}/\text{min}$)	++	++		++		
Dobutamine		++	+			β_2 mediated drop in SVR; risk of arrhythmias
Milrinone						Phosphodiesterase-3 inhibitor; inotropy and pulmonary vasodilatation; drop in LVEDP and SVR; risk of arrhythmias

D=dopaminergic receptor; V1=vasopressin receptor 1; PA=pulmonary artery; RV=right ventricle; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance; LVEDP=left ventricular end-diastolic pressure.

theory, such an agent would have β_1 activity to enhance cardiac contractility and selective activity for systemic vascular α_1 receptors to increase blood pressure and RV perfusion. Norepinephrine primarily targets the α_1 receptor, causing vasoconstriction with limited cardiac inotropy.²⁸ However, the β_1 effects on contractility have been shown to improve PA/RV coupling in animal models of RV dysfunction.^{29–31} In a small study of septic patients with right heart failure, norepinephrine use was associated with improved RV myocardial oxygen delivery due to an increase in SVR, but PVR increased and no change was seen in RV ejection fraction.³² Phenylephrine is a pure α_1 receptor agonist that augments right coronary artery perfusion, but also increases PVR and does not improve RV contractility.^{30,33} Reflex bradycardia can also result in decreased CO. Epinephrine is a mixed α/β receptor agonist that can induce vasoconstriction and increase inotropy. In one animal study, it improved CO without increasing PVR, and in a small study of patients with septic shock was found to increase RV contractility.³⁴ Vasopressin increases SVR by activating V1 receptors on vascular smooth muscle cells.²⁸ At lower doses (eg, 0.01–0.03 U/min) it causes pulmonary vasodilatation via stimulation of endothelial NO, but at higher doses it increases responsiveness to catecholamines and

causes pulmonary and coronary artery vasoconstriction.^{16,34–36} Taken together, norepinephrine is a reasonable agent in hypotensive patients with acute RV failure.

Inotropes

Low-dose dopamine is a reasonable option to improve RV contractility in patients with RV failure. Dopamine has dose-dependent effects on various receptors, activating dopaminergic receptors at low doses (<5 $\mu\text{g kg}^{-1} \text{min}^{-1}$), β_1 receptors at medium doses (5 to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$), and α_1 receptors at high doses (>10 $\mu\text{g kg}^{-1} \text{min}^{-1}$). At doses below 16 $\mu\text{g kg}^{-1} \text{min}^{-1}$, dopamine increases CO without worsening PVR.^{37,38} Dobutamine is another inotrope that acts via β_1 receptor stimulation, but may also cause vasodilatation due to β_2 effects. At low doses (5 to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$), dobutamine improves PA/RV coupling in animal studies and improves myocardial contractility and PVR in patients with left heart failure.^{29,39} Dobutamine has been shown to improve hemodynamics in patients with PH at liver transplantation and after RV infarction.⁴⁰ Higher doses should be avoided because of the risk of β_2 -mediated vasodilatation and hypotension.

Milrinone, a selective phosphodiesterase type 3 (PDE3) inhibitor that slows intracellular cAMP metabolism, is an appealing agent for use in pulmonary

vascular disease because it can improve inotropy and pulmonary vasodilatation.^{28,41} Milrinone is frequently the agent of choice in patients with PH from biventricular failure, and in those recovering postventricular assist or following cardiac transplantation. Several small studies have also examined the use of inhaled milrinone in patients with pulmonary vascular disease to avoid systemic hypotension.^{42,43}

The use of inotropes to improve RV contractility increases the risk of tachyarrhythmias, and their use in sepsis has been controversial. At the same time, it is important to avoid increasing CO above normal levels because this can increase PAP and thereby increase RV workload. In general, they should not be used in PAH patients with sepsis unless there is evidence of inadequate oxygen delivery despite the correction of abnormalities in RV preload, afterload, and ischemia. Calcium sensitizers such as levosimendan enhance myocardial contractility without increasing cytosolic calcium and thereby have less effect on increasing oxygen demand. Clinical trials have shown improvement in RV systolic and diastolic function in patients with left heart failure, and recent reports describe improved RV function in RV failure associated with chronic thromboembolic PH and heart transplantation.⁴⁴ These agents may be another option for improving RV contractility in PAH patients with sepsis.

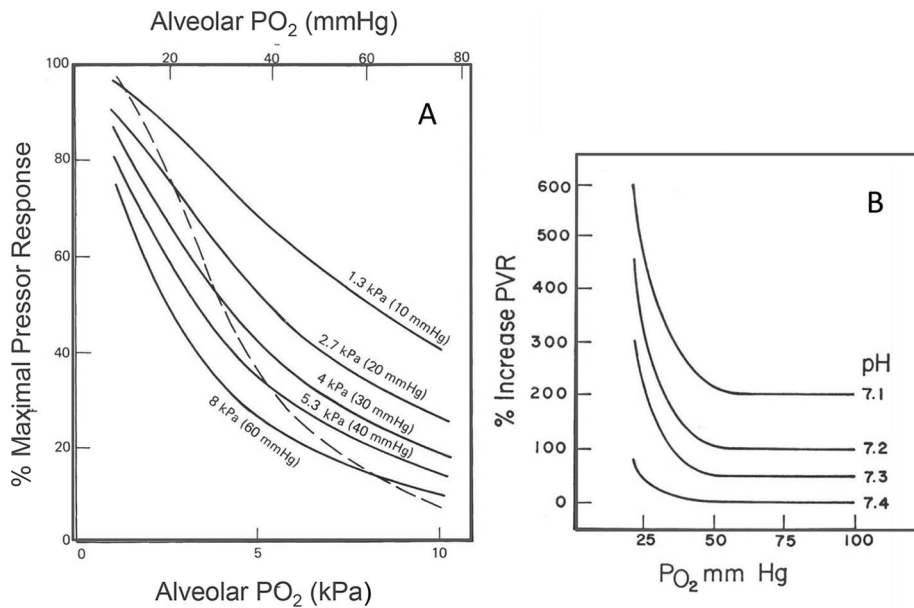


Figure 5: Effect of oxygen tension and acidemia on pulmonary vasoconstriction. (A) Pulmonary vasoconstriction increases as alveolar O₂ tension (P_AO₂) falls while keeping mixed venous oxygenation constant (mixed venous PO₂ indicated for each solid line from 60 to 10 Torr, panel A). The combined effect of allowing P_AO₂ and mixed venous PO₂ to fall is shown by the dashed line, where P_AO₂ and mixed venous oxygen saturation O₂ are the same.³⁴ (B) Pulmonary vasoconstriction in newborn calves as a function of inspired PO₂ under conditions of different levels of arterial blood pH. Hypoxic pulmonary vasoconstriction is increased and occurs at a higher level of inspired O₂ as arterial pH is decreased. Maximal pulmonary vasoconstrictor response was defined as the difference between baseline pulmonary artery pressure when ventilating with F_IO₂ = 0.21 and perfusate F_O2 = 0.06, and the pulmonary artery pressure when both the inspired and the perfusate F_O2 = 0. The pressure response at all other combinations of inspired and perfusate F_O2 were expressed as a percent of this maximum (%Rmax). Adapted from Marshall BE, Marshall C. Anesthesia and the pulmonary circulation. In: Covino BG, Fozzard HA, Rehder K, Strichartz G, eds. *Effects of anesthesia*. Bethesda, MD: American Physiological Society, 1983.

Pulmonary Vascular Resistance

For most patients with PAH, the majority of the increase in PVR is caused by fixed remodeling of the pulmonary vascular bed. Thus, it can be difficult if not impossible to acutely reduce PVR. However, most patients with PAH have increased muscularization of proximal pulmonary vessels, and some are capable of a heightened pulmonary vasoconstrictive response. Therefore, it is imperative to avoid any factors that can increase pulmonary vascular tone while at the same time attempting to administer maximal pulmonary vasodilator therapy.

A number of factors can contribute to increased PVR during sepsis. Hypoxic pulmonary vasoconstriction can occur in response to decreases in alveolar oxygen tension (P_AO₂) or decreased oxygen in pulmonary arterial or bronchial arterial blood, and is enhanced by hypercapnea or acidemia (Figure 5).⁴⁵ The pulmonary vasoconstrictive response is greater when

P_AO₂ falls than when pulmonary artery oxygen saturation falls, but for any degree of alveolar hypoxia, hypoxic pulmonary vasoconstriction is greater in the presence of decreased pulmonary artery oxygen. Adequate systemic arterial oxygen saturation (SaO₂) routinely monitored by pulse oximetry in the ICU effectively excludes alveolar hypoxia, but is not a reliable indicator of pulmonary arterial oxygenation.

Lung volume also affects PVR. Overdistension of alveolar vessels at high lung volume increases PVR, as does the collapse of extra-alveolar pulmonary vessels at low lung volume. PVR is lowest at functional residual capacity (FRC), and this should be kept in mind in septic patients with PAH who require mechanical ventilation. Although, as mentioned earlier, the use of positive-pressure ventilation should be avoided if possible.

Several vasoactive factors that have been implicated in the pathogenesis of

PAH such as endothelin and thromboxane are elevated during sepsis and have been shown to correlate inversely with CO.⁴⁶ Other mediators of PH such as serotonin and interleukin-6 are also upregulated in sepsis and the acute respiratory distress syndrome (ARDS).^{47,48} Endotoxin can suppress NO synthesis and has been shown to increase PVR in sepsis.^{49,50} Finally, just as disseminated intravascular coagulation can impede perfusion in the systemic circulation, sepsis can cause thrombosis in situ in the pulmonary circulation and raise PVR.⁵¹

Prior to the use of pulmonary vasodilators, every attempt should be made to lower PVR by reversing any of the above factors that are known to increase pulmonary vascular tone. Alveolar hypoxia and hypoxemia should be corrected as much as possible, and hypercapnea and acidemia reversed. Ideally, SaO₂ should be raised to 92% or greater and pCO₂ and pH should be kept as close to normal as possible.

Several classes of drugs that target cellular pathways that are abnormally regulated in PAH have been developed over the last 2 decades (Table 2). These drugs have been shown to improve functional capacity and reduce PVR in patients with PAH, but their ability to improve pulmonary hemodynamics in PAH patients with sepsis has not been studied. Despite the lack of clinical evidence showing efficacy in this situation, it is reasonable to use these drugs in PAH patients with sepsis in an attempt to lower PVR and improve CO. It should be remembered, however, that in addition to their pulmonary vasorelaxant properties, most of these drugs have significant effects on the systemic circulation and are capable of causing hypotension. Furthermore, pulmonary vasodilators can worsen gas exchange by blunting hypoxic pulmonary vasoconstriction and impairing ventilation perfusion (V/Q) matching.⁵²

By virtue of their route of administration, inhaled agents have the most selective effect on the pulmonary circulation. Inhaled NO (iNO) is a potent pulmonary vasodilator with a rapid onset of action and an extremely short half-life, making it an ideal agent for unloading the RV in the septic patient.

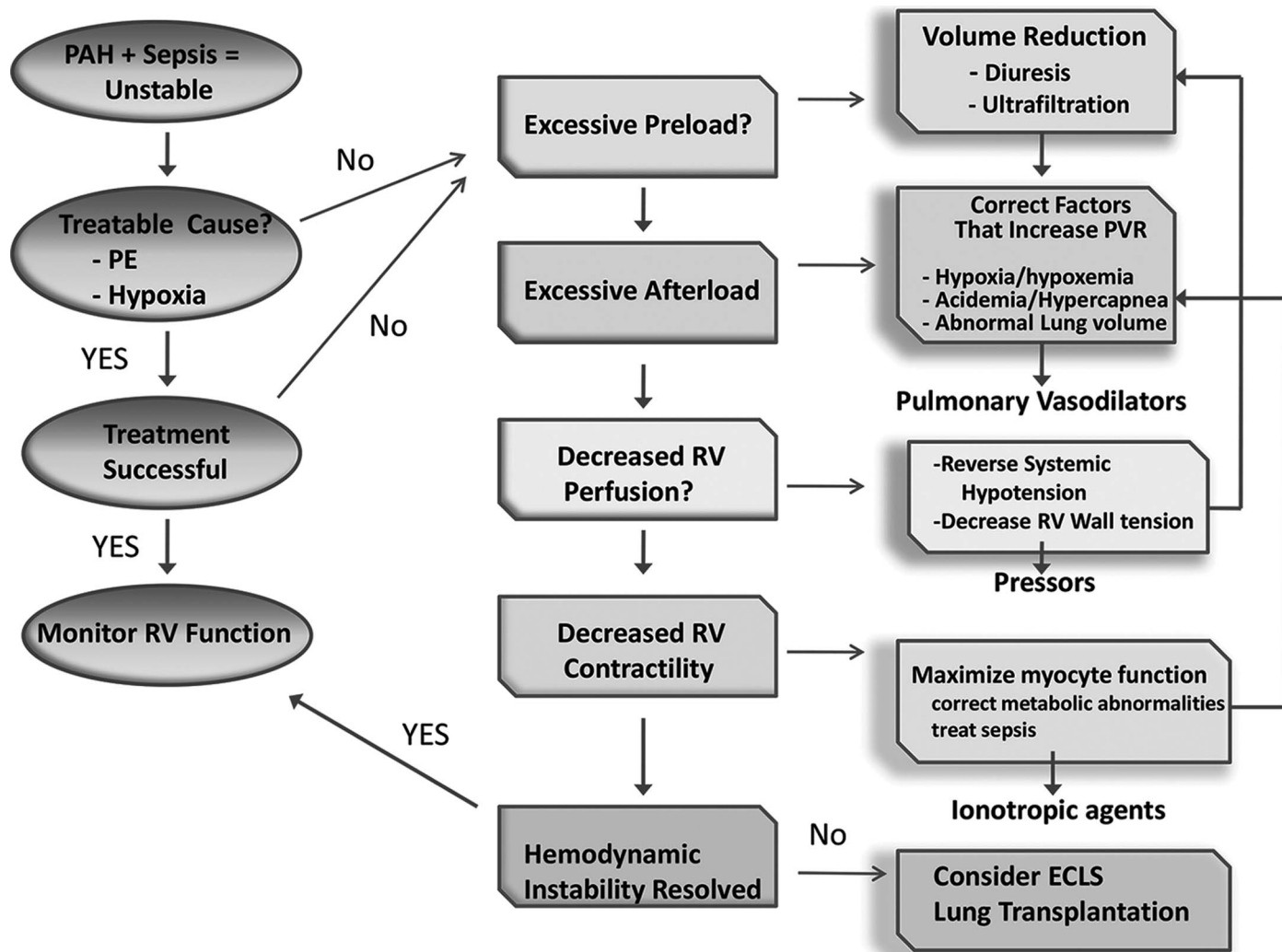


Figure 6: Schematic approach to the treatment of sepsis in the patient with PAH. Management should start with treating any reversible causes of acute right heart failure and increased pulmonary artery pressure. If systemic perfusion is inadequate, right ventricular preload should be adjusted to optimize RV function. Right ventricular afterload should be reduced by removing causes of pulmonary vasoconstriction and the administration of selective, short-acting pulmonary vasodilators. If these measures prove inadequate, RV function can be improved by using vasopressors to enhance RV perfusion and inotropes to improve contractility. Patients who do not respond may need extracorporeal life support. (Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Ventetuolo CE, Klingler JR. Management of acute right ventricular failure in the intensive care unit. *Ann Am Thorac Soc*. 2014;11(5):811-822. The *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.)

Furthermore, its greater effect in well-ventilated lungs prevents the increase in A-a gradient that can occur with pulmonary vasodilators administered via oral or intravenous routes. Also, in some patients, iNO can improve oxygenation by reducing intrapulmonary shunt. Although the use of iNO in PAH patients with sepsis has not been studied, it has been shown to improve RV ejection fraction and end-diastolic volume in patients with ARDS⁵³ and improve pulmonary hemodynamics in patients with acute RV failure.⁵⁴

Three prostacyclin derivatives are currently available for treatment of PAH in the United States, and all can be admin-

istered by inhalation, making them reasonable alternatives when iNO is not available. Like iNO, these drugs have rapid onset of action with short half-lives and have potent vasodilator properties on the pulmonary circulation. Inhaled epoprostenol has been used successfully to manage patients with RV failure after cardiac surgery and to improve gastric mucosal pH in septic patients with PH.^{55,56}

Phosphodiesterase type 5 (PDE5) inhibitors are effective pulmonary vasodilators that reduce pulmonary vascular tone by inhibiting the metabolism of cGMP. Interesting studies in animal models of PH suggest that they can also

improve contractility in the setting of RV hypertrophy,⁵⁷ but little is known about their use in critical illness. The PDE5 inhibitors should be used cautiously in septic patients with PAH and any patient who is hemodynamically unstable because of their systemic hypotensive effects and extended half-life. The considerably shorter half-life of sildenafil, compared to tadalafil, makes it the drug of choice if PDE5 inhibitors are considered. An intravenous form of sildenafil is also available if the enteral route cannot be used.

The use of other currently available pulmonary vasodilators, such as the endothelin receptor antagonists and the

Table 2: Currently Available Pulmonary Vasodilator Medications

Name	Drug Class	Action	Route of Administration	Terminal Half-life
Ambrisentan	Endothelin receptor antagonist	Blocks endothelin receptor-A	Oral	15 hours
Bosentan	Endothelin receptor antagonist	Blocks endothelin receptor –A and –B	Oral	5.4 hours
Macitentan	Endothelin receptor antagonist	Blocks endothelin receptor –A and –B	Oral	14-18
Sildenafil	Phosphodiesterase type-5 inhibitor	Slows metabolism of intracellular cGMP	Oral or intravenous	4 hours orally
Tadalafil	Phosphodiesterase type-5 inhibitor	Slows metabolism of intracellular cGMP	Oral	17.5 hours
Epoprostenol	Prostacyclin	Increases intracellular cAMP	Intravenous or Inhaled*	<6 minutes
Treprostinil	Prostacyclin derivative	Increases intracellular cAMP	Intravenous, subcutaneous, or inhaled	4 hours
Iloprost	Prostacyclin derivative	Increases intracellular cAMP	Inhaled	20-30 minutes
Nitric Oxide	Soluble guanylate cyclase stimulator	Increases intracellular cGMP	Inhaled	Seconds
Riociguat	Soluble guanylate cyclase stimulator	Increases intracellular cGMP	Oral	7-12 hours

*Not FDA-approved for this route of administration.

cAMP=cyclic adenosine monophosphate; cGMP=cyclic guanosine monophosphate.

recently approved soluble guanylate cyclase stimulator riociguat, should probably be avoided in the septic patient with PAH unless the patient was taking these medications prior to becoming septic. Endothelin receptor antagonists have less acute pulmonary hemodynamic effects and greater potential to affect liver function and the metabolism of other drugs. Riociguat is a soluble guanylate cyclase stimulator and may have significant systemic vasodilator effects, especially under conditions such as sepsis where endogenous NO production may be increased. Calcium channel blockers should also be avoided because they have negative inotropic effects and have been shown to increase RV stroke work index.⁵⁸

MECHANICAL SUPPORT

When medical therapy for acute RV failure in the ICU is ineffective, mechanical support may be considered. Extracorporeal life support, specifically veno-venous and veno-arterial extracorporeal membrane oxygenation have been used in PAH patients as a bridge to endarterectomy or lung transplantation, and recent reports have described their use to support patients with PAH through critical illness.⁵⁹ The use of extracorporeal life support in the critically ill patient with PAH is described in a later section of this issue of *Advances in Pulmonary Hypertension*.

CONCLUSION

The management of sepsis in patients with PAH is challenging. The limited ability of the RV to augment cardiac output in the PAH patient makes it difficult to compensate for vasodilatory shock. There must be careful assessment of intravascular volume and vasoactive drugs should be used judiciously. One must weigh the risk:benefit ratio of initiating a pulmonary vasodilator to augment the RV and reduce PVR with its potential effects on systemic hemodynamics. Lastly, mechanical ventilation should be avoided as much as possible given how small shifts in intrathoracic pressure can dramatically affect PVR and CO.

References

1. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;35(6):1286-1293.
2. Kurzyna M, Zytowska J, Fijalkowska A, et al. Characteristics and prognosis of patients with decompensated right ventricular failure during the course of pulmonary hypertension. *Kardiologia Pol*. 2008;66(10):1033-1039; discussion 1040-1041.
3. Huynh TN, Weigt SS, Sugar CA, Shapiro S, Kleerup EC. Prognostic factors and outcomes of patients with pulmonary hypertension admitted to the intensive care unit. *J Crit Care*. 2012;27(6):739.e7-739.e13.
4. Rackow EC, Kaufman BS, Falk JL, Astiz ME, Weil MH. Hemodynamic response to fluid repletion in patients with septic shock: evidence for early depression of cardiac performance. *Circ Shock*. 1987;22(1):11-22.
5. Weisel RD, Vito L, Dennis RC, Valeri CR,

- Hechtman HB. Myocardial depression during sepsis. *Am J Surg*. 1977;133(4):512-521.
6. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock. *Crit Care Clin*. 2000; 16(2):251-287.
7. Dell'Italia LJ. The right ventricle: anatomy, physiology, and clinical importance. *Curr Probl Cardiol*. 1991;16(10):653-720.
8. Pouleur H, Lefevre J, Van Mechelen H, Charlier AA. Free-wall shortening and relaxation during ejection in the canine right ventricle. *Am J Physiol*. 1980;239(5):H601-H613.
9. Maughan WL, Shoukas AA, Sagawa K, Weisfeldt ML. Instantaneous pressure-volume relationship of the canine right ventricle. *Circ Res*. 1979;44(3):309-315.
10. Hurtford WE, Barlai-Kovach M, Strauss HW, Zapol WM, Lowenstein E. Canine biventricular performance during acute progressive pulmonary microembolization: Regional myocardial perfusion and fatty acid uptake. *J Crit Care*. 1987; 2(4):270-281.
11. Hurford WE, Zapol WM. The right ventricle and critical illness: a review of anatomy, physiology, and clinical evaluation of its function. *Intensive Care Med*. 1988;14 Suppl 2:448-457.
12. Janicki JS, Weber KT. The pericardium and ventricular interaction, distensibility, and function. *Am J Physiol*. 1980;238(4):H494-H503.
13. Szabó G, Soós P, Bährle S, et al. Adaptation of the right ventricle to an increased afterload in the chronically volume overloaded heart. *Ann Thorac Surg*. 2006;82(3):989-995.
14. de Vroomen M, Cardozo RH, Steendijk P, van Bel F, Baan J. Improved contractile performance of right ventricle in response to increased RV afterload in newborn lamb. *Am J Physiol Heart Circ Physiol*. 2000;278(1):H100-H105.
15. De Freitas FM, Faraco EZ, De Azevedo DF, Zaduchliver J, Lewin I. Behavior of normal pulmonary circulation during changes of total blood volume in man. *J Clin Invest*. 1965;44: 366-378.

16. Zamanian RT, Haddad F, Doyle RL, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. *Crit Care Med.* 2007;35(9):2037-2050.
17. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA.* 1996;276(11):889-897.
18. Harvey S, Harrison DA, Singer M, 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):472-477.
19. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. 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.
20. Hoffman MJ, Greenfield LJ, Sugerman HF, Tatum JL. Unsuspected right ventricular dysfunction in shock and sepsis. *Ann Surg.* 1983;198(3):307-319.
21. Mitsuo T, Shimazaki S, Matsuda H. Right ventricular dysfunction in septic patients. *Crit Care Med.* 1992;20(5):630-634.
22. Urabe Y, Tomoike H, Ohzono K, Koyanagi S, Nakamura M. Role of afterload in determining regional right ventricular performance during coronary underperfusion in dogs. *Circ Res.* 1985;57(1):96-104.
23. van Wolferen SA, Marcus JT, Westerhof N, et al. Right coronary artery flow impairment in patients with pulmonary hypertension. *Eur Heart J.* 2008;29(1):120-127.
24. Lowensohn HS, Khouri EM, Gregg DE, Pyle RL, Patterson RE. Phasic right coronary artery blood flow in conscious dogs with normal and elevated right ventricular pressures. *Circ Res.* 1976;39(6):760-766.
25. 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.
26. Kleinman WM, Krause SM, Hess ML. Differential subendocardial perfusion and injury during the course of gram-negative endotoxemia. *Adv Shock Res.* 1980;4:139-152.
27. Gold FL, Bache RJ. Transmural right ventricular blood flow during acute pulmonary artery hypertension in the sedated dog. Evidence for subendocardial ischemia despite residual vasodilator reserve. *Circ Res.* 1982;51(2):196-204.
28. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med.* 2011;183(7):847-855.
29. Kerbaul F, Rondelet B, Motte S, et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. *Crit Care Med.* 2004;32(4):1035-1040.
30. Hirsch LJ, Rooney MW, Wat SS, Kleinmann B, Mathru M. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. *Chest.* 1991;100(3):796-801.
31. Ducas J, Duval D, Dasilva H, Boiteau P, Prewitt RM. Treatment of canine pulmonary hypertension: effects of norepinephrine and isoproterenol on pulmonary vascular pressure-flow characteristics. *Circulation.* 1987;75(1):235-242.
32. Schreuder WO, Schneider AJ, Groeneveld AB, Thijs LG. Effect of dopamine vs norepinephrine on hemodynamics in septic shock. Emphasis on right ventricular performance. *Chest.* 1989;95(6):1282-1288.
33. Rich S, Gubin S, Hart K. The effects of phenylephrine on right ventricular performance in patients with pulmonary hypertension. *Chest.* 1990;98(5):1102-1106.
34. Le Tulzo Y, Seguin P, Gacouin A, 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):664-670.
35. 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):1241-1245.
36. Leather HA, Segers P, Berends N, Vandermeersch E, Wouters PF. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med.* 2002;30(11):2548-2552.
37. Lejeune P, Naeije R, Leeman M, Melot C, Deloof T, Delcroix M. Effects of dopamine and dobutamine on hyperoxic and hypoxic pulmonary vascular tone in dogs. *Am Rev Respir Dis.* 1987;136(1):29-35.
38. Holloway EL, Polumbo RA, Harrison DC. Acute circulatory effects of dopamine in patients with pulmonary hypertension. *Br Heart J.* 1975;37(5):482-485.
39. Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation.* 1978;58(3 Pt 1):466-475.
40. Acosta F, Sansano T, Palenciano CG, et al. Effects of dobutamine on right ventricular function and pulmonary circulation in pulmonary hypertension during liver transplantation. *Transplant Proc.* 2005;37(9):3869-3870.
41. Chen EP, Bittner HB, Davis RD Jr, Van Trigt P 3rd. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. *Ann Thorac Surg.* 1997;63(3):814-821.
42. Wang H, Gong M, Zhou B, Dai A. Comparison of inhaled and intravenous milrinone in patients with pulmonary hypertension undergoing mitral valve surgery. *Adv Ther.* 2009;26(4):462-468.
43. Haraldssons A, 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):1439-1445.
44. Pitsiou G, Paspala A, Bagalas V, Boutou AK, Stanopoulos I. Inhaled iloprost plus levosimendan to compensate right heart failure due to chronic thromboembolic pulmonary hypertension. *Anaesth Intensive Care.* 2013;41(4):554-556.
45. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxia and H⁺ ion concentration changes. *J Clin Invest.* 1966;45(3):399-411.
46. Pittet JF, Morel DR, Hemsén A, et al. Elevated plasma endothelin-1 concentrations are associated with the severity of illness in patients with sepsis. *Ann Surg.* 1991;213(3):261-264.
47. Sibbald W, Peters S, Lindsay RM. Serotonin and pulmonary hypertension in human septic ARDS. *Crit Care Med.* 1980;8(9):490-494.
48. Hack CE, De Groot ER, Felt-Bersma RJ, et al. Increased plasma levels of interleukin-6 in sepsis. *Blood.* 1989;74(5):1704-1710.
49. Ogata M, Ohe M, Katayose D, Takashima T. Modulatory role of EDRF in hypoxic contraction of isolated porcine pulmonary arteries. *Am J Physiol.* 1992;262(3 Pt 2):H691-H697.
50. Myers PR, Wright TF, Tanner MA, Adams HR. EDRF and nitric oxide production in cultured endothelial cells: direct inhibition by E. coli endotoxin. *Am J Physiol.* 1992;262(3 Pt 2):H710-H718.
51. Aihara M, Nakazawa T, Dobashi K, et al. A selective pulmonary thrombosis associated with sepsis-induced disseminated intravascular coagulation. *Intern Med.* 1997;36(2):97-101.
52. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med.* 2010;181(3):270-278.
53. Rossaint R, Slama K, Steudel W, et al. Effects of inhaled nitric oxide on right ventricular function in severe acute respiratory distress syndrome. *Intensive Care Med.* 1995;21(3):197-203.
54. Bhorade S, Christenson J, O'connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. *Am J Respir Crit Care Med.* 1999;159(2):571-579.
55. Muzaffar S, Shukla N, Angelini GD, Jeremy JY. 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;128(6):949-950.
56. Eichelbrönnner O, Reinelt H, Wiedeck H, et al. Aerosolized prostacyclin and inhaled nitric oxide in septic shock—different effects on splanchnic oxygenation? *Intensive Care Med.* 1996;22(9):880-887.
57. Nagendran J, Archer SL, Soliman D, 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):238-248.
58. Packer M, Medina N, Yushak M. Adverse hemodynamic and clinical effects of calcium channel blockade in pulmonary hypertension secondary to obliterative pulmonary vascular disease. *J Am Coll Cardiol.* 1984;4(5):890-901.
59. Rosenzweig EB, Brodie D, Abrams DC, Agerstrand CL, Bacchetta M. Extracorporeal membrane oxygenation as a novel bridging strategy for acute right heart failure in group 1 pulmonary arterial hypertension. *ASAIO J.* 2014;60(1):129-133.