Pharmacologic Management of Perioperative Pulmonary Hypertension

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Abstract: Perioperative pulmonary hypertension can originate from an established disease or acutely develop within the surgical setting. Patients with increased pulmonary vascular resistance are consequently at greater risk for complications. Despite the various specific therapies available, the ideal therapeutic approach in this patient population is not currently clear. This article describes the basic principles of perioperative pulmonary hypertension and reviews the different classes of agents used to promote pulmonary vasodilation in the surgical setting.

Key Words: pulmonary hypertension, perioperative care, pulmonary vasodilators

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INTRODUCTION

Patients with pulmonary hypertension (PH) experience increased morbidity and mortality after cardiac, noncardiac, and transplant surgeries. Patients more frequently experience complications, such as acute right heart failure, delayed extubation, and early postoperative death.^{1–7} Despite important therapeutic advances in the management of PH, there is still a marked delay between the start of PH symptoms and the diagnosis of the disease by right heart catheterization. A multicenter registry demonstrated a delay in disease diagnosis of 2.8 ± 5 years.⁸ This suggests that PH may remain undiagnosed or underestimated at the time of surgery, and as a result, these patients would be at risk for developing associated complications before proper evaluation or intervention. Although studies have evaluated the efficacy of various forms of therapy within the surgical setting, guidelines for perioperative management in the adult population are limited and

unclear. The purpose of this review is to discuss the principles of management, focusing on the currently available pharmacologic options.

PERIOPERATIVE PULMONARY HYPERTENSION

Perioperative PH can be attributed to an established disease or acute development within the operative setting. Because patients present with nonspecific clinical manifestations, such as dyspnea or fatigue, PH is diagnosed based on hemodynamic criteria through a pulmonary arterial pressure (PAP) of ≥ 25 mm Hg at rest. Echocardiography provides a noninvasive means of estimating PAP and assessing right ventricular (RV) function. Right heart catheterization, however, provides accurate measurement of PAP in addition to other pulmonary hemodynamic parameters. Measurements of pulmonary artery occlusion pressure, cardiac index, and pulmonary vascular resistance (PVR) can aid in distinguishing the etiology of PH and provide a more accurate assessment of disease severity.

Pre-existing PH can be idiopathic or arise secondary to underlying cardiac or pulmonary diseases (Table 1).⁹ Because chronic PH can result from multiple etiologic mechanisms, the pathogenesis of each condition can vary and ultimately determine the preoperative assessment, operative course, and clinical outcomes of these patients. Patients with previously diagnosed PH who undergo surgery should be evaluated preoperatively for PH severity and comorbid conditions. In addition to baseline hemodynamic parameters, patients should also be assessed by their response to inhaled pulmonary vasodilators. This can provide a predictive measure of a patient's potential to respond to perioperative management with pulmonary vasodilators. Despite the risk for complications, patients with these conditions often undergo surgical procedures and subsequently require management for perioperative PH. In addition to the clinical condition of the patient, multiple factors can influence the development and progression of PH within the operative setting.

Perioperative PH can develop acutely as a result of iatrogenic interventions or operative events that lead to pulmonary vasoconstriction (Table 2). As a result, an increase in PAP is required to overcome this resistance to maintain blood flow within the pulmonary vasculature. This increase in afterload, however, can ultimately lead to potentially fatal complications, such as pulmonary hypertensive crisis (defined as a PAP equal to or greater than systemic arterial pressure) or RV dysfunction (Fig. 1).

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TABLE 1. Updated Classification of Pulmonary Hypertension by the World Health Organization⁹

Group	Description	Examples
Group 1	Pulmonary arterial hypertension	Primary <ul style="list-style-type: none"> • Idiopathic • Heritable: BMPR2, ALK1/endoglin, unknown Secondary <ul style="list-style-type: none"> • Connective tissue disease • Congenital disease (left-to-right shunt) • Portal hypertension • Infection: HIV or schistosomiasis • Chronic hemolytic anemia • Persistent pulmonary hypertension of the newborn
Group 1'		Drugs and toxins Pulmonary vaso-occlusive disease Pulmonary capillary hemangiomatosis
Group 2	Pulmonary venous hypertension secondary to left heart dysfunction	Systolic dysfunction Diastolic dysfunction Valvular disease
Group 3	Pulmonary hypertension associated with lung disease or hypoxemia	Chronic obstructive pulmonary disease Interstitial lung disease Sleep-disordered breathing Alveolar hypoventilation disorders Chronic high altitude
Group 4	Pulmonary hypertension secondary to chronic obstruction	Developmental abnormalities Thromboembolic obstruction of proximal pulmonary arteries Thromboembolic obstruction of distal pulmonary arteries
Group 5	Pulmonary hypertension due to unclear multifactorial mechanisms	Nonthrombotic obstruction: tumor, parasites, foreign material <ul style="list-style-type: none"> • Hematologic: myeloproliferative disorders, splenectomy, myoglobinopathy • Systemic: sarcoidosis, pulmonary Langerhans cell • Metabolic: glycogen storage disease, Gaucher disease, thyroid disorder • Other: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Because cardiogenic shock secondary to RV failure can result in mortality rates of approximately 53% that are comparable to those of LV failure,¹⁰ this is a primary concern of perioperative PH management.

Iatrogenic interventions, including cardiopulmonary bypass (CPB) or mechanical ventilation, have resulted in a perioperative increase in resistance and pressure within the pulmonary vessels. Both cardiac and noncardiac thoracic surgery have been associated with perioperative PH, as these procedures may require CPB to temporarily replace heart and lung function. However, exposure to CPB has been shown to result in myocardial and pulmonary injury, significantly increased PVR and decreased pulmonary compliance.^{11,12} Mechanical ventilation can acutely increase PVR by overdistending alveoli or increasing the risk for developing respiratory acid-base disturbances. Increased PaCO₂ levels and acidotic conditions directly increase in PAP and PVR within the operative setting.^{13–15} As a slight hypocarbic alkalosis

seems to be beneficial in minimizing resistance,¹⁵ blood gas levels should be closely monitored.

General surgical complications can also increase afterload. In addition to contributing to the chronic form of this condition,⁹ pulmonary emboli have been associated with acute development of PH.⁴ Obstruction secondary to a thrombotic event reduces the cross-sectional area of pulmonary vasculature and results in an increase in pressure. Furthermore, wound infections and anemia secondary to blood loss contribute to perioperative PH through altered acid–base balance and limited oxygen delivery, respectively. RV afterload should therefore be minimized through the immediate recognition and treatment of these complications.

Although it does not directly impact pulmonary vasculature, altered RV preload can affect RV function through a loss of fluid balance. Neurohormonal imbalance, underlying conditions, or exogenously administered fluids can lead to fluid overload. Not only could this exacerbate RV

TABLE 2. Factors Leading to an Acute Increase in PVR and Risk of RV Dysfunction

	Pulmonary	Vascular	Cardiac
Chronic PH	Pulmonary hypertension associated with lung disease or hypoxemia	Pulmonary hypertension secondary to chronic vascular obstruction Pulmonary arterial hypertension	Pulmonary hypertension secondary to left heart dysfunction
Perioperative factors acutely increasing PVR	Mechanical ventilation <ul style="list-style-type: none"> • Alveoli overdistention • Respiratory acid-base disturbances • CPB-related injury 	Mechanical obstruction <ul style="list-style-type: none"> • Thromboembolus • Air, fat, or tumor emboli Acute vasoconstriction <ul style="list-style-type: none"> • Hypoxemia • Hypercapnia • Acidosis <ul style="list-style-type: none"> • Pain • Hypothermia 	Fluid overload <ul style="list-style-type: none"> • Left heart dysfunction • Tricuspid regurgitation • Pulmonary valve regurgitation Myocardial dysfunction <ul style="list-style-type: none"> • RV myocardial infarct • Anesthesia-related decrease in myocardial contractility
Perioperative factors increasing risk of RV dysfunction	Changes in intrathoracic pressure limiting coronary blood flow	Systemic hypotension <ul style="list-style-type: none"> • Anesthesia • Sepsis Hypovolemia <ul style="list-style-type: none"> • Acute blood loss • Fluid depletion • Fluid shifts 	Reduced coronary perfusion <ul style="list-style-type: none"> • Inadequate preload • LV dysfunction

dysfunction, but it may also compromise LV filling and cardiac output through interventricular dependence. However, volume depletion from blood loss, fluid shifts, or excessive diuresis can decrease the LV preload and cardiac output.

Subsequent hypotension and limited systemic perfusion may decrease coronary perfusion and place the heart at risk for ischemia. Within the context of chronic PH, the RV has undergone structural remodeling that predisposes it to an

FIGURE 1. Operative factors affecting pulmonary hypertension and associated RV failure.

imbalance between oxygen supply and demand.¹⁶ Increased wall stress and coronary compression results in an increase in oxygen consumption and limited oxygen delivery.¹⁶ In addition to maintaining proper fluid balance, blood pressure should be carefully monitored and appropriate diuretics or vasopressors should be administered as necessary.

Pulmonary hypertension may be suspected within the operative or perioperative setting by signs of systemic congestion suggestive of acute right heart dysfunction or evidence of RV strain and structural change, such as tricuspid regurgitation or right axis deviation and bundle branch block on electrocardiogram. Prompt recognition and diagnosis through echocardiography or right heart catheterization can help optimize management.

PULMONARY VASODILATORS

Pulmonary hypertension can be managed directly by the judicious use of pulmonary vasodilator therapy within the perioperative setting (Table 3). Endothelial injury and dysfunction cause an imbalance between vasodilators and vasoconstrictors that ultimately results in increased PVR. Decreased production of endogenous pulmonary vasodilators results in the loss of vascular compliance, platelet aggregation inhibition, and dysregulation of smooth muscle proliferation. The goal of perioperative PH therapy is to maximize pulmonary vasodilation and reduce PVR. This decrease in RV afterload subsequently improves cardiac output. However, agents that cause pulmonary vasodilation can also decrease systemic

vascular resistance (SVR) and mean arterial pressure (MAP). As discussed above, this would decrease systemic perfusion and increase the risk of cardiac ischemia.

Because treatment for PH is limited by untoward reduction in SVR, inhaled pulmonary vasodilators have become the preferred method of management over their oral and intravenous counterparts. Inhaled agents, such as nitric oxide (NO) and nebulized iloprost, are inactivated before reaching systemic circulation and therefore have lesser impact on systemic hemodynamics. Furthermore, by reaching well-ventilated regions of the lung, these agents may improve ventilation-perfusion matching and subsequently improve oxygenation. Although inhaled agents demonstrate greater pulmonary specificity than those with systemic administration, the risk of causing systemic hypotension, although lower, nevertheless remains. A disadvantage of continuous nebulization is that only an indeterminate proportion of aerosolized medication actually reaches the alveoli and pulmonary vessels during the inspiratory phase. Regardless of the dosage, this ultimately results in an imprecise delivery of medication that makes it difficult to monitor.

Treatment should ideally be tailored to the etiology of PH and the clinical condition of the patient. There are instances in which pulmonary vasodilators can exacerbate clinical conditions. As pulmonary vasodilation increases blood flow through arteriolar and capillary circulation, an increase in pulmonary venous pressure can worsen left heart congestion and result in pulmonary edema in patients with left heart failure and other forms of pulmonary

TABLE 3. Summary Table of Pulmonary Vasodilators Used Within the Perioperative Setting

	Advantages	Disadvantages
Inhaled NO	Selective pulmonary vasodilation	Specialized equipment required Short duration of action Toxic metabolites Potential contribution to pathogenesis of sepsis Rebound PH on withdrawal
NO donors	Induce venodilation to enable management of PH secondary to left heart disease	
• SNP	Selective pulmonary vasodilation (low doses of nebulized form)	Systemic hypotension (reported with intravenous administration or high doses of nebulized form)
• Nitroglycerin	Selective pulmonary vasodilation (nebulized form)	Reduction in cardiac output
Prostacyclin and analogs		
• Inhaled prostacyclin	Minimal systemic effects (even at high doses)	Short duration of action Rebound PH on withdrawal Platelet aggregation inhibited in vitro
• Inhaled iloprost	Selective pulmonary vasodilation Longer duration of action Protection against perfusion injury No reports of rebound PH	No devices available to deliver to patients on mechanical ventilation
PDE inhibitors		
• Milrinone	Decrease in pulmonary capillary wedge pressure	Systemic hypotension (reported with intravenous administration)
• Sildenafil	Selective pulmonary vasodilation Limit effects of NO withdrawal Easy to administer (oral or intravenous) Combination therapy	Reported cases of systemic hypotension May worsen oxygenation status

veno-occlusive disease. These patients may subsequently require treatment with agents that promote venodilation, such as sodium nitroprusside (SNP) or nitroglycerin. Furthermore, increasing blood flow to poorly ventilated regions can result in ventilation–perfusion mismatch and worsen hypoxemia in patients with parenchymal lung disease.

When individual agents are ineffective, combination therapy provides an additional option for managing perioperative PH. This can augment the effect of individual pulmonary vasodilator agents, particularly when there are different mechanisms of action involved. For example, the effects of a pharmacologic NO donor, such as SNP, can be augmented when administered with a phosphodiesterase-5 inhibitor that suppresses NO metabolism, such as sildenafil. The integration of separate mechanisms of action, however, must be used carefully as an inappropriate combination of pulmonary vasodilators may produce or aggravate systemic hypotension. For example, the contraindicated use of nitroglycerin and phosphodiesterase-5 inhibitors, such as sildenafil, should be considered when determining appropriate agents. Furthermore, combination therapy can be complicated with regard to the method and timing of drug administration, which is already challenging with a single agent alone.

Inhaled NO

NO produced endogenously by the vascular endothelium increases cyclic guanosine monophosphate (cGMP) production, which promotes relaxation of vascular tone and reduces smooth muscle proliferation. Endothelial dysfunction results in diminished NO production and contributes to the pathophysiology of PH. Inhaled NO targets this deficiency. The short half-life of this agent necessitates continuous administration using specialized equipment.

The Food and Drug Administration has approved this agent for the management of PH in the pediatric population. NO has also been used for preventative PH management and rescue therapy from pulmonary hypertensive crisis. Because it is inactivated quickly by hemoglobin, NO has limited systemic effects and more specific action on the pulmonary vasculature. As a result, there is an improvement in pulmonary hemodynamics without systemic side effects, such as reduced SVR or diminished cardiac output.¹⁷

NO has been demonstrated to be effective postoperatively in children undergoing congenital heart surgery. Patients with preoperative PH exhibited significant decreases in mean PAP and PVR compared with control groups undergoing hyperventilation¹⁷ or receiving placebo nitrogen gas.^{18,19} Incidence of pulmonary hypertensive crisis, time to extubation, and length of postoperative course were also significantly reduced when using NO to manage postoperative PH.¹⁹ Inhaled NO has also been effective for treatment in the adult population.^{20–23} Inhaled NO significantly reduced PAP and increased cardiac index and systemic blood pressure in high-risk cardiac surgery patients.^{20–22} It was also effective in improving RV ejection fraction and reducing the need for vasopressor treatment.^{22,23}

Despite reducing PAP and PVR in patients who developed perioperative PH, NO did not decrease intensive care stay or reduce mortality compared with inhalation of

placebo gas.¹⁹ A separate study found that NO induced similar hemodynamic changes and did not significantly decrease the incidence of pulmonary hypertensive crisis compared with other forms of conventional treatment selected by the treating physicians.²⁴

A concern with NO inhalation is the formation of toxic metabolites, including methemoglobin, nitrogen dioxide, and peroxynitrite free radicals.²⁵ These compounds cause tissue hypoxia or directly damage the respiratory tract.²⁵ NO administered with a high fraction of inspired oxygen can lead to free radical formation and subsequent peroxynitrite-mediated oxidative cell death.²⁶ It has also been shown to damage surfactant apoproteins and limit the ability of pulmonary surfactant to reduce alveolar surface tension.²⁷

It should be noted that modifying the NO pathway could also complicate the management of patients with impending or established sepsis. Increased levels of NO have been demonstrated in patients with sepsis and hypothesized to contribute to its pathogenesis.^{28–30} There is also an increased cardiac demand during infection that may not be met by the limited RV contractile reserve of patients with PH. As a result, the potential systemic effects of inhaled NO, though minimal, may compound the systemic effects (hypotension) and associated complications of sepsis.

NO poses additional complications during withdrawal, when patients can experience rebound PH with life-threatening increases in PAP and decreases in oxygenation.^{31,32} Various mechanisms have been proposed to contribute to rebound PH. These include transient decreases in endogenous NO synthase activity, guanylate cyclase levels, and cGMP concentrations^{33,34} with maintained activity of phosphodiesterases in plasma and lung tissue.³⁴ Both these processes would be expected to lead to NO deficiency and lessened intrinsic ability to dilate the pulmonary vasculature.

NO may also transiently increase endothelin-1 (ET-1) levels, which can stimulate vasoconstriction. In one study examining patients undergoing congenital heart disease repair, plasma ET-1 levels significantly increased during NO administration and remained elevated until therapy was discontinued, although levels decreased in controls not receiving postoperative NO.³⁵ The same authors found similar ET-1 elevations in patients receiving NO for acute respiratory distress syndrome.³⁵

Because patients successfully weaned from NO experience lower postoperative morbidity,³⁶ factors influencing NO withdrawal have been carefully scrutinized. Successful discontinuation is associated with longer duration of inhalation and lower dose at discontinuation.³⁶ Complications associated with NO withdrawal may be managed through the use of sildenafil.^{37,38} Through phosphodiesterase-5 inhibition, sildenafil maintains cGMP availability. In one study, there was no incidence of rebound PH in children after a single dose of sildenafil 1 hour before planned NO withdrawal.³⁷ These patients also required a shorter duration of mechanical ventilation compared with those receiving placebo interventions. In addition to preventing rebound PH, sildenafil was also beneficial for patients who had already failed NO weaning by enabling subsequent weans to occur without increased PAP or altered systemic pressure.³⁸

An additional drawback of NO is its increased cost in relation to other commonly utilized agents. Although this is not a sole factor in determining an appropriate therapeutic agent, rebound PH after withdrawal and its toxic metabolites may not justify the routine use of NO. Alternatives to NO do not require special equipment and can be administered through infusion and continuous nebulization. These agents have been compared with NO with regard to efficacy and tolerability and are described below.

NO Donors

SNP and nitroglycerin are classified as NO donors that induce enzymatic release of this vasodilator. Because they preferentially induce venodilation, these agents are most commonly used to treat PH resulting from chronic pulmonary venous obstruction, such as in left heart and valve dysfunction. The pulmonary vascular bed can be specifically targeted by these drugs through aerosolized administration.

SNP increases cGMP levels by promoting direct NO release from the vascular endothelium. As SNP promotes arterial vasodilation in addition to venodilation, this agent can also reduce afterload and improve cardiac output. Although treatment with intravenous SNP results in severe systemic hypotension in patients undergoing mitral valve replacement,²¹ the inhaled version of this drug has been found to promote local NO release at pulmonary vasculature.³⁹ Nebulized SNP was effective in selectively decreasing PAP and PVR in animal models of PH.^{39–41} Although PVR was selectively reduced without systemic effects at lower doses, higher doses of inhaled SNP did result in systemic hypotension.⁴² Unfortunately, no recommended dosing for adults has been published. Although clinical studies of inhaled SNP are currently limited, this agent nevertheless exhibits dose-dependent pulmonary specificity that may vary with the underlying etiology of PH.⁴¹

Nitroglycerin also increases levels of NO to induce vasodilation. Nitroglycerin acts as a prodrug that is metabolized to NO and preferentially exerts its actions on the venous circulation. By decreasing ventricular preload, this agent reduces right-sided cardiac output and relieves the pulmonary congestion that results from left heart dysfunction. This agent has also been found to induce selective pulmonary vasodilation when administered in aerosolized form.^{43,44} Inhaled nitroglycerin significantly reduced mean PAP without significant changes in systemic resistance or cardiac index in children with congenital heart disease^{45,46} and adults undergoing mitral valve surgery.^{44,47,48} Although neither SNP or nitroglycerin are as commonly used as NO, inhaled versions of these drugs nevertheless demonstrate pulmonary specificity and offer attractive alternative options for PH management.

Prostacyclin and Prostacyclin Analogues

Prostacyclin is produced by prostacyclin synthase via the arachidonic pathway at the vascular endothelium. By activating adenylate cyclase and increasing cAMP production, prostacyclin inhibits platelet aggregation and promotes smooth muscle relaxation to lower PAP. Patients with PH exhibit a loss of prostacyclin synthase that results in decreased prostacyclin production. Similar to NO, prostacyclin and prostacyclin analogues (epoprostenol, iloprost and

treprostinil) have been administered exogenously to treat PH. The pulmonary specificity of these agents varies by the method of administration. Intravenous prostacyclin was shown to decrease SVR in patients undergoing orthotopic heart transplantation but can result in severe hypotension.⁴⁹ In contrast, inhaled prostacyclin and prostacyclin analogues exhibit pulmonary specificity and inhalation has subsequently become the preferred method of perioperative administration.

Inhaled Prostacyclin

Limited studies have shown that inhalational prostacyclin is safe and effective in treating acute intraoperative PH and RV failure.^{50,51} It significantly reduced PAP and PVR and improved RV performance with minimal systemic effects in patients undergoing cardi thoracic surgery or heart transplantation.^{21,50–53} This agent has also been effective in treating perioperative portopulmonary hypertension secondary to liver failure.⁵⁴ Unlike SNP, increased administration consistently results in dose-dependent pulmonary vasodilation without any significant impact on systemic resistance.⁵¹ Despite the expectation of selected pulmonary delivery, hypotension with inhaled prostacyclin administration has been reported, suggesting systemic provision.⁵⁵ As the hypotension was limited mainly to patients with systemic hypotension before surgery, confounding factors cannot be excluded as the cause.

Comparison studies have shown that inhaled prostacyclin seems as effective as NO in reducing PAP and improving cardiac index and mixed venous oxygen saturation.^{21,56} Heart and lung transplant recipients receiving inhaled NO or inhaled prostacyclin demonstrated similar degrees of PAP reduction and cardiac output increase.⁵⁶ Furthermore, oxygenation index and systemic blood pressure were unaffected by both agents.⁵⁶ Another study demonstrated that inhaled prostacyclin may actually be more effective than NO in acutely managing primary and secondary PH. Nebulized prostacyclin resulted in significantly greater reduction in mean PAP than inhaled NO without any significant change in systemic pressure.⁵⁷

Additional studies will be required comparing the efficacy and complications of inhaled NO and prostacyclin before the latter can be considered an adequate alternative for managing perioperative PH. Compared with NO, however, inhaled prostacyclin seems to be significantly more cost-effective. Furthermore, prostacyclin does not produce the toxic metabolites or exhibit the same rate of potential complications as NO. Although prostacyclin inhibits platelet aggregation *in vitro*, this has not to date demonstrated a prolongation in bleeding time or increase in chest tube drainage when utilized in cardiac surgery.^{53,58} Rebound PH after prostacyclin use has, however, been reported in a high-risk patient who experienced increased RV afterload and developed cardiogenic shock after its withdrawal.⁵⁹ Because NO and prostacyclin exhibit half-lives lasting seconds to minutes, withdrawal of either agent can cause an acute loss of vasodilation that results in rebound PH.⁵⁹

Inhaled Iloprost

Iloprost is a prostacyclin analogue that offers a more stable molecule with a longer duration of action. This agent has

also been shown to significantly decrease PAP and PVR and improve cardiac index when administered after cardiac surgery^{48,60,61} or heart transplantation.⁶² Iloprost was also effective in optimizing pulmonary hemodynamics in patients undergoing pulmonary thromboendarterectomy for chronic thromboembolic PH.⁶³ In addition to preventing acute RV failure,⁶⁰ iloprost therapy improved indices of RV function as measured by echocardiography.⁶¹ This agent also significantly decreased pulmonary pressures and improved oxygen saturation when it was used as rescue therapy for pulmonary hypertensive crises after congenital heart surgery.⁶⁴ Additionally, there were no significant changes in MAP, SVR, bleeding complications, or incidence of bronchospasm after treatment.^{62–65} Because iloprost is not as rapidly inactivated as NO or inhaled prostacyclin, there have been no reports of rebound PH.⁶⁶

Although iloprost is as effective as inhaled NO in preventing pulmonary hypertensive crises,⁶⁷ studies have shown that iloprost may be more effective than NO when used for management of PH.^{66,68,69} Within the nonsurgical context of pulmonary arterial hypertension, NO and iloprost led to significant increases in cardiac output and mixed-venous oxygen saturation, as well as significant reductions in PAP and PVR.⁶⁶ However, patients treated with iloprost exhibited more pronounced hemodynamic changes in each parameter.⁶⁶ Inhaled iloprost also induces greater levels of pulmonary vasodilation than NO within the perioperative setting.^{68,69} Cardiac surgery patients treated with iloprost exhibited greater improvements in cardiac output in addition to better PAP and PVR reduction when weaned from CPB.⁶⁸ Heart transplant patients treated with iloprost demonstrated a more reliable reduction in PAP and improvement in cardiac index compared with a small proportion of patients who actually experienced an increase in PVR with NO administration.⁶⁹

Iloprost also exhibited a protective effect against ischemia–reperfusion injury in an animal model.⁷⁰ Treatment with iloprost before mechanical injury completely prevented pulmonary edema, maintained vasoconstrictor ET-1 balance, and significantly decreased PVR.⁷⁰ Although further studies are needed, these data suggest that iloprost may find a role in preventing the development or worsening of perioperative PH by reducing injury from surgical vascular manipulation.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors slow metabolism of the second messengers cAMP and cGMP to promote acute vasodilation. By maintaining these substrates, phosphodiesterase inhibitors ultimately potentiate the effects of prostacyclins and NO.

Milrinone

Milrinone is a type 3 phosphodiesterase inhibitor that maintains cAMP concentrations in myocardial and smooth muscle cells. As a result, milrinone promotes cardiac contractility and vasodilation at the pulmonary vasculature. A comparison between intravenous milrinone and inhaled NO revealed that milrinone required greater vasopressor support to maintain systemic pressures in cardiac surgery patients.²³ These results suggest that the ability of this agent to treat

perioperative PH is limited by its systemic effects. However, milrinone has demonstrated effectiveness in promoting selective pulmonary vasodilation in heart transplant candidates with baseline PH when administered through inhalation.⁷¹ The decrease in PVR only occurred in patients who exhibited PH and did not lead to complications in patients with normal hemodynamic values.⁷¹ When used in combination with inhaled prostacyclin, milrinone potentiated pulmonary vasodilation after cardiac surgery.⁷² Although stroke volume increased and there was prolonged PVR reduction, SVR and MAP were unaffected.⁷² Compared with NO or prostacyclin analogues, milrinone was also able to uniquely reduce pulmonary capillary wedge pressure and may provide an additional means of managing patients with pulmonary venous hypertension and preserved ejection fractions.⁷¹ Because selective pulmonary vasodilator therapy in such patients may lead to clinical aggravation through increased left ventricular loading, milrinone's unique properties may provide more ideal therapy.

Sildenafil

By inhibiting type 5 phosphodiesterases, sildenafil maintains cGMP levels, promotes the action of NO, and has been administered in various contexts of PH management. As oral sildenafil is easy to administer and exhibits pulmonary specificity by reducing PAP without affecting systemic pressure, this agent has also been utilized as monotherapy to treat perioperative PH. Sildenafil has been used to treat PH in both pediatric and adult patients who have undergone cardiac surgery. Hemodynamic monitoring has revealed significant decreases in PAP and PVR without any reported incidence of systemic hypotension, pulmonary hypertensive crisis, or rebound PH.^{73–75} Sildenafil has also been found to have a potentially protective effect in managing moderate-to-severe PH in congenital heart surgery. Sildenafil administered before and after CPB not only lowers mean PAP, but patients also experienced shorter CPB and mechanical ventilation times and decreased lengths of intensive care unit admission.⁷⁵

Sildenafil has also been used in combination with other agents to augment their vasodilatory effects or to limit the impact of their withdrawal. In addition to facilitating NO discontinuation, sildenafil has been administered with inhaled NO to treat PH after valve replacement surgery. This combination produced a greater degree of selective pulmonary vasodilation compared with either agent alone.⁷⁶ Combination therapy with oral sildenafil and inhaled iloprost was more effective than either agent alone in treating severe PH as well.⁷⁷ Sildenafil has also been used as adjunctive therapy in managing adult cardiac surgery patients who experience persistent PH despite treatment with isoproterenol, milrinone, SNP, nitroglycerin, or NO. Hemodynamic data collected before and after sildenafil administration demonstrated reductions in mean PAP and PVR.⁷⁸ Regular dosing enabled these patients to be successfully weaned from vasodilators without rebound PH, in-hospital mortality, or significant systemic effects on cardiac index, MAP, or SVR.⁷⁸

It is important to note that some studies have suggested that sildenafil may have limited pulmonary specificity and can

even worsen morbidity and mortality. When infants at risk for PH were treated with NO and intravenously administered sildenafil after septal defect closure, PVR reduction was augmented, but patients also experienced hypotension and significant decreases in arterial O₂ levels that were not ameliorated with additional NO administration.⁷⁹ Furthermore, the FDA recently issued a warning on the safety of long-term sildenafil use in children with pulmonary arterial hypertension as high doses have been associated with increased rates of mortality.⁸⁰

CONCLUSIONS

Patients with PH should undergo thorough preoperative assessment and careful perioperative monitoring to ensure optimal systemic perfusion, RV preload, and RV contractility. At our institution, perioperative PH is pharmacologically managed through the use of continuously nebulized pulmonary vasodilators, such as prostacyclins. Due to its costs, NO is rarely used. Agents such as sildenafil are used either as prophylactic treatment for suspected or anticipated PH or as an adjunct to pulmonary vasodilators when combination therapy is considered.

Pulmonary hypertension complicates the operative course of patients undergoing various surgical procedures. However, there is currently a lack of consistent recommendations for perioperative management in the adult population. This can be partially attributed to the multiple pathogenic causes of pulmonary hypertension, which can present within various contexts in either the acute or chronic setting, and the underrecognition of PH before surgery. Although studies on the variety of available treatment options reveal promising results, specific guidelines are needed to identify which treatments would best benefit specific patient populations.

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