Pharmacology of the Pulmonary Circulation

9

Cara Reimer and John Granton

Abbreviations

(m)PAP	(mean) Pulmonary artery pressure
CI	Confidence interval
CO	Cardiac output
LAP	Left atrial pressure
PHTN	Pulmonary hypertension
PVB	Paravertebral block
PVR(I)	Pulmonary vascular resistance (index)
SVR(I)	Systemic vascular resistance (index)
TEA	Thoracic epidural analgesia

Key Points

- The pulmonary vasculature is a complex system, and studies of the effects of anesthetic drugs on this system are often contradictory.
- A balanced anesthetic technique with adherence to the hemodynamic goals of maintenance of right ventricular preload and right coronary perfusion is the safest choice for patients with PHTN.
- There are no absolute contraindications to most anesthetic drugs in patients with pulmonary hypertension.
- Inhaled pulmonary vasodilators can be used to optimize hemodynamic variables perioperatively, although effects on gas exchange are variable.

C. Reimer (✉)
Department of Anesthesiology and Perioperative Medicine, Kingston Health Sciences Centre, Kingston, ON, Canada
e-mail: cara.reimer@kingstonhsc.ca

J. Granton
Division of Respirology, Department of Medicine, University of Toronto and University Health Network, Mount Sinai Hospital, Women's College Hospital, Toronto, ON, Canada

Introduction

Drugs affecting the pulmonary vascular bed are routinely administered perioperatively in thoracic anesthesia, and their effects are of particular interest in patients with pulmonary hypertension (PHTN). In addition, the increase in right ventricular (RV) afterload afforded by positive pressure ventilation may have adverse effects on patients with more advanced PHTN and reduced RV function.

Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥25 mmHg at rest. PHTN is classified according to the recent international guidelines into five groups: pulmonary arterial hypertension (PAH; group 1), PHTN secondary to left-sided heart or valvular disease (group 2), PHTN secondary to parenchymal or hypoxic/hypercapnic respiratory disease (group 3), chronic thromboembolic pulmonary hypertension (CTEPH; group 4), and miscellaneous causes of PHTN (group 5) [1, 2]. Group 1 PHTN embraces idiopathic, heritable, congenital cardiac, connective tissue disease, HIV, portal hypertension, and schistosomiasis-related pulmonary arterial hypertension. The rational for differentiation of PAH from other forms of PHTN relates to the distinctive arteriopathy that characterizes this condition as well as response to pulmonary vasodilator therapies. Irrespective of the etiology, patients with PHTN are high-risk candidates for cardiothoracic and non-cardiothoracic surgery. Although defined as an increase on pulmonary pressure, the consequence and severity of PHTN are likely best judged by the degree of right ventricular function [3]. Although the studies to date have not systematically evaluated the degree of RV function and outcome in patients with PHTN undergoing surgery, data from mixed populations of patients undergoing cardiac surgery supports the notion that RV function is associated with short- and longer-term outcomes [4]. Owing to the influence of afterload on the thinner walled RV, these patients have poor cardiorespiratory reserve and are at risk of having perioperative complications including pulmonary hypertensive crises with resultant heart failure, respiratory failure, and dysrhythmias [5, 6]. In

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patients undergoing valve repair or coronary artery bypass surgery, the presence of preoperative PHTN is associated with worse perioperative and long-term outcomes [7–9]. Management of these patients should not focus on pulmonary arterial pressure rather the goals should be centered on improving RV function and oxygen delivery [10]. Owing to the limited reserve of the RV, however, anesthetic management of these patients can be complex and challenging.

Drugs can interact with the pulmonary vascular bed both directly, through receptor binding, and indirectly, by changes in cardiac output. The effects of anesthetic, vasopressor, and vasodilator drugs on the pulmonary vessels will be reviewed in this chapter, with a special emphasis on perioperative drug choices in patients with pulmonary hypertension.

Anesthetic Drugs

Introduction

Evaluating the effects of anesthetic drugs on the pulmonary vasculature is challenging. In clinical practice, these drugs are rarely administered in isolation. Their administration can lead to concurrent changes in non-pulmonary hemodynamic parameters such as cardiac output (CO) that ultimately affect pulmonary artery pressure (PAP). An increase in PAP may be the result of increased PVR, increased CO, or an increase in LAP (PAP = (PVR × CO) + LAP). In addition, general anesthesia involves manipulation of variables that affect PVR, including FiO_2, carbon dioxide (CO_2), and positive pressure ventilation (PPV). Issues that arise in interpreting studies and making useful conclusions include reliance on and extrapolation from animal data, small study sample sizes, the questionable application of results in normal patients to patients with PHTN, children to adults and vice versa, and a vast supply of contradictory results. It is with acknowledgment of these limitations that we will review the effects of routinely administered anesthetic drugs on the pulmonary system.

Ketamine

Ketamine has occupied a controversial position in anesthesia for patients with PHTN [11]. Despite its current widespread use in these challenging patients, it has been classically taught that ketamine causes pulmonary vasoconstriction and should be used with extreme caution in this group.

The mechanism of action of ketamine is complex and not fully elucidated. It is an N-methyl-D-aspartic acid (NMDA) receptor antagonist and also binds to opioid receptors and muscarinic receptors [12]. It appears to stimulate release [13] as well as inhibit neuronal uptake of catecholamines [14] which may account for its cardiostimulatory and bronchodilatory effects. Some animal studies have shown an endothelium-independent vasodilatory response to ketamine in the pulmonary bed [15, 16]. NMDA receptor subunits have been demonstrated in human pulmonary vascular cells, and antagonism of NMDA receptors prevents glutamate-mediated lung injury and reverses pulmonary hypertension in rats [17].

The effects of ketamine on the human pulmonary vasculature appear to be complex, and, indeed, review of the clinical literature reveals heterogeneity in regard to results. Factors known to affect pulmonary vasoreactivity such as FiO_2, CO_2, presence of PHTN, and presence of premedicants are not reported or acknowledged in many studies. The hemodynamic effects of a bolus of ketamine can be attenuated or abolished with premedicants like droperidol [18], dexmedetomidine [19], or benzodiazepines [20].

Early study of the drug's hemodynamic profile in adult patients showed increases of PAP and PVR in the range of 40–50% [21, 22]. This, combined with increases in variables contributing to myocardial oxygen consumption, raised concern about the use of ketamine in patients with CAD and PHTN. In the pediatric literature, Williams et al. [23] showed no change in PVR or mPAP after ketamine administration in spontaneously breathing children with severe pulmonary hypertension undergoing cardiac catheterization. In another pediatric study, ketamine maintained pulmonary to systemic blood flow and did not affect pulmonary pressure or resistance in children with intracardiac shunt undergoing cardiac catheterization [24]. Propofol, on the other hand, decreased SVR leading to increased right to left shunting in this study. More recently, a bolus of ketamine (2 mg/kg) has been shown to increase mPAP by a negligible amount clinically (mean 2 mmHg [95% CI 0.2, 3.7]) in pediatric patients with pulmonary hypertension with no change in PVRI or SVRI [25]. As part of a balanced anesthetic induction for open lung biopsy, ketamine has been used in Eisenmenger syndrome with good results [26]. In adult patients undergoing OLV for lung resection, ketamine did not significantly increase PAP or PVR compared to enflurane [27]. Other case reports highlight the value of the cardiostability of the drug in patients with minimal cardiorespiratory reserve [28–30]. Many clinicians, including those at our institutions, incorporate this drug into their routine inductions for patients with severe pulmonary hypertension. The advantages, in particular maintenance of stable hemodynamics and coronary artery perfusion pressure, seem to outweigh the potential disadvantages.

Propofol

Propofol is ubiquitously used in anesthesia, including for patients with pulmonary hypertension. It is frequently used to maintain anesthesia during and after lung transplantation.

The effects of propofol are thought to be primarily mediated by GABA receptors [31]. GABA inhibits peripheral sympathetic neurotransmission, and chronic treatment with GABA has been shown to decrease extent of pulmonary artery medial thickening and decrease right ventricular hypertrophy in mice with induced pulmonary hypertension [32].

As mentioned in the discussion on ketamine, the concerning hemodynamic effect of propofol in the context of pulmonary hypertension is a decrease in SVR, which can not only have effects on intracardiac shunting if present, but can lead to decreased coronary artery perfusion of the right ventricle and resultant right ventricular dysfunction. In regard to direct effects on the pulmonary vasculature, animal studies have shown that during increased tone conditions in the pulmonary vasculature, propofol may act as a pulmonary vasoconstrictor [33, 34]. Propofol has also been shown to interfere with acetylcholine-induced pulmonary vasodilation in dogs [35]. On the other hand, in isolated pulmonary arteries from human and chronically hypoxic rats, etomidate and (to a lesser extent) propofol showed vessel relaxation [36]. The clinical significance of these contradictory results is unknown. It has been suggested that to avoid hypotension, a vasopressor should be used at the time of anesthetic induction with propofol, etomidate, or volatile gas in patients with Eisenmenger syndrome [37].

Etomidate

Etomidate is an imidazole that mediates its clinical actions primarily at GABA A receptors. As mentioned above, it appears to have vasorelaxant properties in isolated pulmonary arteries [36]. Its major attribute as an induction agent is its stable hemodynamic profile. In patients with cardiac disease, an induction dose of etomidate increased MAP, decreased SVR, and decreased PAP [38]. In pediatric patients without pulmonary hypertension presenting for cardiac catheterization, there were no significant changes in any hemodynamic parameters, including PAP, after a bolus dose of etomidate (0.3 mg/kg) [39].

The drug has successfully been used in patients with pulmonary hypertension in obstetrics [40] and other procedures requiring general anesthesia or sedation [37].

Dexemedetomidine

An α2 adrenergic agonist, dexmedetomidine acts at preganglionic sites in the central nervous system and the autonomic nervous system to inhibit norepinephrine release, in addition to acting on postsynaptic receptors to cause vasoconstriction and vasodilation [41, 42]. Whereas the sympathetic nerve fibers of the human pulmonary artery possess presynaptic α2 receptors [43], there is minimal evidence for postsynaptic α2 receptors in the arterial system of the lung [44]. However, this data is from canine pulmonary arteries which may have a different α2 receptor distribution than humans [45].

The drug has been shown to cause transient increases in MAP and a dose-dependent persistent decrease in noninvasively measured CO and increase in SVR at higher bolus doses (>1 mcg/kg over 2 min) in healthy volunteers [45]. These higher bolus doses caused small increases (~5 mmHg) in CO_2 and decrease in minute ventilation by approximately 30% [46]. Dose-dependent increases in dexmedetomidine cause increases in PAP, PVRI, and SVRI in healthy volunteers with pulmonary artery catheters [47]. While a bolus dose of 0.5–1 mcg/kg dexmedetomidine over 10 min caused an increase in MAP and SVRI, there were minimal changes in PAP and PVRI in children with pulmonary hypertension undergoing cardiac catheterization [48]. The increase in SVRI was theorized to take place via stimulation of postsynaptic α1 receptors in the peripheral vessels. A 1 mcg/kg bolus followed by 0.4 mcg/kg/h infusion prior to surgical incision in patients with pulmonary hypertension undergoing mitral valve replacement surgery caused significant decreases in HR, MAP, CI, and mPAP with no significant increases in PVRI or SVRI. The decrease in heart rate seen with dexmedetomidine is thought to occur via decreased inhibition of cardiac vagal neurons [49]. It would appear that (as with most drugs used in patients with pulmonary hypertension) titrated lower bolus doses of dexmedetomidine (<1 mcg/kg) with subsequent infusion titration would be appropriate for patients with pulmonary hypertension given the widespread hemodynamic effects of the drug. Dexmedetomidine used during one-lung ventilation decreased volatile and opioid requirements and increased phenylephrine requirements in a randomized trial [50].

Opioids

Mu, delta, and kappa opioid receptors have been shown to exist in the pulmonary artery of rats [51]. The number of kappa opioid receptors in rat pulmonary artery is increased under hypoxic conditions [52]. Kappa receptor agonism attenuates proliferation of pulmonary artery smooth muscle cells and lowers mean pulmonary artery pressure in these animals [53].

In anesthetized cats, administration of histamine, morphine, fentanyl, remifentanil, and sufentanil causes a vasodilatory response under elevated tone conditions in isolated lobar artery [54]. The mechanism seems to involve histamine- and opioid-mediated receptor pathways. Morphine causes a prostanoid-dependent vasodilation in isolated dog pulmonary arteries and veins [55].

The presence of opioid receptors and their significance in human pulmonary arteries are unknown as per the author's literature search. Clinical experience would echo the cardiostability of judicious opioid administration in hemodynamically fragile patients.

Neuromuscular Blockers

Pancuronium increases PAP in dogs with lung injury [56]. It is theorized to do so indirectly by increases in cardiac output and directly by increasing PVR, possibly by its antagonist actions at muscarinic receptors in the pulmonary vasculature. The drug has been shown to be an antagonist at acetylcholine M3 receptors in transfected hamster cells [57]. Rocuronium and succinylcholine also were antagonists at M3 receptors in this study, but not at clinically relevant concentrations. In human pulmonary arteries, M3 receptors present on endothelial cells are involved in vasodilation, and M3 receptors on smooth muscle cells mediate vasoconstriction [58].

In humans, rocuronium, cisatracurium, and vecuronium have little to no effect on most cardiac indices in patients undergoing CABG [59, 60].

Vasopressors and Inotropes

Vasopressors and inotropes are commonly required in thoracic anesthesia to counteract the effects of cardiodepressant and vasodilating drugs. Treatment of hypotension in these patients can be difficult to manage given the typical cautious fluid administration in this patient population. Neurotransmitter receptors in this system include those from the adrenergic, cholinergic, and dopaminergic families as well as histamine, serotonin, adenosine, purines, and peptides [61]. The pulmonary vasculature's response to sympathetic activation will generally result in an increase in PVR [62]. In human pulmonary artery, administration of acetylcholine induces pulmonary relaxation at the endothelial level [58, 63].

The response of the pulmonary system to exogenous vasoinopressor administration is dependent on the clinical situation. Consequently, results of studies are heterogeneous. In anesthetized dogs without pulmonary hypertension, dopamine, epinephrine, norepinephrine, and phenylephrine all increase PAP to varying degrees by varying mechanisms but with no drug is there a significant increase in PVR [64]. Dopamine does not increase PVR after lung transplantation in pigs [65]. In anesthetized patients with chronic secondary pulmonary hypertension undergoing cardiac surgery, both norepinephrine and phenylephrine increase PAP and PVRI with minimal change in CI [66]. Within the clinically relevant MAP target in this study, norepinephrine decreased the mPAP to MAP ratio, but phenylephrine did not, suggesting it (norepinephrine) may be a better choice in this patient cohort. In a dog model of acute pulmonary hypertension, however, phenylephrine restored perfusion to the ischemic right ventricle and therefore increased CO [67]. This is a relevant observation, as it illustrates the importance of coronary artery perfusion in the setting of right ventricular strain and that maintenance of systemic pressure by whatever method may be the most important guiding principle in this subset of patients.

Vasopressin has also been studied. In a chronic hypoxic rat model, vasopressin administration resulted in a V1 receptor-mediated pulmonary vasodilation [68]. In an acute PHTN model in dogs, vasopressin increased PVR and resulted in a substantial decrease in right ventricular contractility [69]. Human studies of the effects of vasopressin on the pulmonary vasculature are limited. Vasopressin has been used successfully after cardiac surgery in patients with pulmonary hypertension and resistant hypotension [70]. The use of vasopressin to treat acute right ventricular failure in patients with IPPH has been described in obstetric anesthesia [71]. In isolated human pulmonary arteries, both norepinephrine and phenylephrine cause vasoconstriction, whereas vasopressin does not [72]. In dogs, phenylephrine and vasopressin have been shown to increase pulmonary artery pressure "passively" by increasing pulmonary blood volume. This is associated with minimal increases in PVR, increases in left atrial pressure, and SVR and is worse during left ventricular dysfunction [73].

Magnesium

Magnesium is a vasodilator in both the systemic and pulmonary circulations. The mechanism of action of magnesium's effects on vasodilation is likely through its effects on membrane channels involved in calcium flux and through its action in the synthesis of cyclic AMP [74]. It would appear to be an important cofactor for endothelial-dependent pulmonary vasodilation [75]. It has been used successfully to wean nitric oxide in pulmonary hypertension [76]. Increasing doses of magnesium in piglets with acute embolic pulmonary hypertension decreased mean PAP, increased CO, and decreased PVR [77]. Magnesium has been used to treat persistent pulmonary hypertension of the newborn, but controversy surrounds its use here, and a systematic review concluded that there is a lack of evidence to support its use in this population [78].

Volatile Anesthetics

At clinically relevant concentrations, modern volatile anesthetics likely have little to no direct vasodilating effect on the pulmonary vasculature. At MAC levels of 1.5, neither sevoflurane

nor desflurane had an effect on the relationship between the pulmonary artery pressure-left atrial pressure gradient and pulmonary blood flow in healthy dogs [79]. In a dog model (without PHTN), isoflurane decreased right ventricular function more than left ventricular function with no effect on PVR [80]. Likewise in pigs, sevoflurane administration depressed right ventricular function with no change in PVR [81]. This suggests that the decreases in PAP observed with volatile anesthetics [82] may partially occur secondary to the decreases in cardiac output seen with these agents. Nitrous oxide is typically avoided in patients with pulmonary hypertension as it is believed to cause pulmonary vasoconstriction, perhaps via release of catecholamines from sympathetic nerves supplying the pulmonary vasculature [83]. In patients with mitral stenosis and pulmonary hypertension presenting for cardiac surgery, administration of nitrous oxide after fentanyl anesthesia (7.5–10 mcg/kg) increased PVR, PAP, and CI [84]. However, a subsequent study showed that in the presence of high-dose fentanyl (50–75 mcg/kg), 70% nitrous oxide actually was associated with a decrease in PAP and CO in patients with secondary PHTN, with no echocardiographic changes in right ventricular function [85]. Interestingly, in univariate analysis in one retrospective cohort study, *not* using nitrous oxide was associated with postoperative mortality and increased length of stay in patients with PHTN presenting for non-cardiac surgery [5]. The ENIGMA-II international randomized trial demonstrated the safety of nitrous oxide use in a large group of patients with coronary artery disease undergoing non-cardiac surgery [86]. The incidence of pulmonary hypertension in this cohort of patients was not indicated, but thoracic procedures were excluded given the usual requirement for higher FiO_2 in these patients. Death and cardiovascular complications occurred with equal frequencies in both intervention and control groups. In addition, the risk of postoperative nausea was only slightly increased in the nitrous oxide group (15% vs 11%). Similarly at 1-year follow-up, nitrous oxide did not increase the risk of death or complications [87].

Perioperative Analgesia

Pain can increase PVR [88]. Perioperative thoracic epidural analgesia (TEA) and paravertebral blockade (PVB) are used routinely in thoracic surgery. TEA may decrease PAP through decreases in CO or via attenuation of the pulmonary sympathetic outflow [89]. In humans without pulmonary hypertension, TEA during one-lung ventilation depresses right ventricular contractility but maintains cardiac output by increases in right diastolic function and a decrease in pulmonary artery elastance [90]. In this study, right ventricular contractility increased in response to pulmonary artery clamping. Unilateral thoracic paravertebral block with lidocaine has been shown to decrease myocardial contractility up to 30% and significantly decrease systemic pressure, an effect that may be attenuated by epinephrine [91]. In general, the potential benefits of regional anesthesia in thoracic surgery probably outweigh the risks of hypotension and right ventricular dysfunction. As with most anesthetic interventions in patients with PHTN, careful titration and monitoring are paramount. Indeed, case reports illustrate successful use of epidural analgesia in this patient population [92–94].

Conclusion

In general, no anesthetic drug is contraindicated in patients with PHTN. The aim of any anesthetic intervention in these patients is hemodynamic neutrality, which can be accomplished by a variety of agents and techniques. An awareness of the potential advantages and disadvantages of drugs is key to proper decision-making. In the PHTN population, the general principles remain the same: adequate anesthesia and analgesia, maintenance of gas exchange to the best extent possible, and support of the right ventricle. In reality, most clinicians who deal with these patients regularly use a wide variety of medications with success.

Support of the Right Ventricle

RV failure can occur acutely when the right ventricular afterload suddenly increases. Unlike the left ventricle, the naïve right ventricle is not capable of generating flow against a high afterload. In the setting of chronic pulmonary hypertension, RV failure can occur following arrhythmias, sepsis, pulmonary embolism, pregnancy, surgery/anesthesia, or progression of their primary disease [95]. The mainstay to supporting the right ventricle includes ensuring an adequate systemic blood pressure (to preserve coronary perfusion), optimizing RV volumes (to reduce RV wall tension and myocardial work and improve RV–LV interaction), and reducing RV afterload [10, 96]. Inotropes may not be effective in acute RV failure owing to the relatively small muscle mass of the right ventricle or the presence of RV ischemia. Additionally, inotropes may lead to an increase in heart rate and a reduction in RV and LV filling time. In addition to avoiding agents that may have a direct adverse effect on cardiac function or those that may adversely increase RV afterload, agents that can reduce RV afterload can be used acutely. Although not systematically studied in the context of acute RV failure, the anesthetist should have an understanding of the agents used to treat chronic pulmonary arterial hypertension and how to manage these agents in the perioperative setting.

Pulmonary Vasodilators (PO/IV/Inhaled)

Pulmonary vascular resistance (PVR) is commonly considered clinically as reflective of the degree of right ventricular afterload. However, afterload to the right ventricle also includes pulmonary vascular compliance and impedance as well as RV wall tension [97, 98]. The naïve and decompensated RV is exquisitely sensitive to increases in its afterload. Consequently, even small changes in RV afterload may have profound effects on RV function. There are three main pathways that have been exploited acutely and more commonly chronically to reduce right ventricular afterload and increase cardiac output and oxygen delivery to metabolically active tissues. The various agents, pathway, and route of administration are provided in Table 9.1. Therapies directed toward the nitric oxide/guanylate cyclase pathway, the endothelin pathway, and the prostanoid/adenylate cyclase pathway have been the subject of several randomized controlled trials in patients with WHO group I pulmonary hypertension (pulmonary arterial hypertension – PAH). The use of these agents in the acute setting however is based more on biological plausibility and often small case series. In the acute setting, the ideal pulmonary vasodilator would have a rapid onset, short half-life, and selectivity for the pulmonary (as opposed to systemic) vasculature. In general, the only way to confer pulmonary vascular selectivity is by delivering the drug by inhalation. However, many agents administered by inhalation may be absorbed and "spill over" producing systemic effects. Systemic agents are also limited by possible increase in ventilation perfusion mismatching (shunt) owing to dilation of blood vessels to alveolar units that are not effectively participating in gas exchange.

Table 9.1 Comparison of currently available pulmonary vasodilators used to treat pulmonary hypertension and RV failure

Pathway	Agent/therapy	Route
Prostanoids		
Prostaglandin analogues	Epoprostenol sodium	IV, Inhaled
	Treprostinil	IV, SC, Inhaled
	Beraprost sodium	Oral
Prostaglandin receptor agonist	Selexipag	Oral
Endothelin		
Endothelin receptor blockers	Bosentan, ambrisentan, macitentan	Oral
Nitric oxide/cGMP		
	Nitric oxide	Inhaled
Inhibition of phosphodiesterase	Sildenafil	Oral, IV
	Tadalafil	Oral
Guanylate cyclase agonist	Riociguat	Oral

Nitric Oxide/Cyclic-GMP Pathway

Nitric oxide (NO) exerts its vasodilatory effects, in part, by binding to soluble guanylate cyclase (sGC) leading to the production of cyclic GMP (cGMP) that in turn activates protein kinase G [99–101]. The ensuing reduction in cytosolic calcium causes smooth muscle dilation by inhibition of phosphorylation and subsequent cross-linking of myosin or through activation of myosin light chain phosphatases that dephosphorylate myosin light chains. Direct activation of calcium-dependent potassium channels is another mechanism and leads to hyperpolarization of cells/reduced contraction [100].

Nitric Oxide

Inhaled nitric oxide (iNO) leads to an improvement in perfusion to alveoli that can participate in gas exchange. This "selective effect" leads to a decrease in intrapulmonary shunt [102, 103]. Nitric oxide may be administered either noninvasively or through a ventilator circuit using a device that can regulate the concentration of NO and monitor levels of nitrogen dioxide – a byproduct of NO when it combines with oxygen. Although there is controversy about a dose response relationship for NO and pulmonary vasodilation, the typical dose ranges from 10 to 40 ppm [104, 105]. The effect of NO on gas exchange and hemodynamics may be increased when used in combination with phosphodiesterase inhibitors [106–108]. Methemoglobin levels need to be monitored when NO is administered for more than 24 h. At present iNO is only approved for infants with respiratory distress syndrome. This approval stems from two large prospective placebo controlled studies demonstrating that NO reduced the need for ECMO and reduced the requirement for oxygen therapy following ICU discharge [109, 110]. However, iNO is still used for patients with refractory hypoxemia, acute pulmonary hypertension and RV failure, primary graft dysfunction, and acute RV failure following heart transplant [111, 112]. The acute right ventricular failure complicating heart transplantation may be attenuated with the use of a pulmonary vasodilator. Although several studies suggest that NO may be useful preoperatively in risk stratifying patients scheduled for cardiac transplant, only case series support the use of inhaled NO to reverse the right ventricular dysfunction following cardiac transplant [111, 113]. However, based on clinical experience, inhaled NO has become a standard of care in many transplant centers for the management of primary graft dysfunction (PGD). The beneficial immune-modulating effects of inhaled NO in addition to its vasodilating properties were felt to be responsible for preliminary studies of using inhaled NO to prevent PGD after lung transplantation [114, 115]. Although a randomized clinical trial failed to

show benefit in preventing PGD, it is commonly used to treat the hypoxemia and pulmonary hypertension seen in established, severe PGD [116]. Owing to the inherent cost of using inhaled NO, other pulmonary vasodilators have been evaluated.

In non-transplant thoracic surgery, NO has been studied as a potential treatment for the gas exchange abnormalities associated with OLV. Its effects are controversial, but it would appear that it exerts its maximal benefits in patients with elevated PVRI and the poorest gas exchange before administration [117–120]. There is no evidence for the routine use of this expensive drug in otherwise normal patients undergoing routine thoracic surgery.

cGMP/cAMP Pathway

Phosphodiesterase (PDE) inhibitors prevent the degradation of cyclic guanosine monophosphate (cGMP) and adenosine monophosphate (cAMP). Owing to the relatively higher expression of PDE_5 in the pulmonary circulation relative to the systemic circulation, PDE_5 inhibitors have a relative selective effect on PVR as opposed to SVR [121, 122]. In addition to their relatively selective pulmonary vasodilatory effects, their effects on smooth muscle proliferation and cellular apoptosis [123, 124] may be responsible for benefit of these agents when administered chronically in patients with idiopathic PAH [125, 126]. A direct inotropic effect of sildenafil on the right ventricle has been postulated; however, the clinical relevance of this finding is uncertain [127].

Although the benefits of sildenafil and tadalafil in chronic PAH have been evaluated in prospective controlled trials, most of the acute applications for these agents have been described in case reports or small cohort studies and as such have not been approved for these indications. In the acute setting, sildenafil has been demonstrated to enhance the effects of inhaled NO and may also be useful in blunting the rebound in pulmonary pressures that occurs during weaning of inhaled NO [106, 121, 128]. The benefits of sildenafil in acute pulmonary embolism and cardiac transplantation and in patients with pulmonary hypertension being considered for pulmonary thromboendarterectomy have also been described [107, 108, 129–131]. Although pulmonary vasodilators can improve hemodynamics in patients with CTEPH [132], the merits of attempting to optimize RV function in patients with pulmonary hypertension and planned pulmonary thromboendarterectomy were recently challenged in a retrospective analysis of chronic thromboembolic pulmonary hypertension patients referred to a single center during 2005–2007 [133]. There was minimal benefit of treatment with medication on pre-PTE mean pulmonary artery pressure, but its use was associated with a significant delay in time to referral for PTE. Importantly the two groups did not differ significantly in any post-PTE outcome. Although this study did not specifically evaluate the use of sildenafil for this purpose, it suggests at the very least that planned, potentially curative surgery should not be delayed while exploring theoretic benefits of this agent on RV function. Whether it can modify surgical risk in patients with very high PVR or who have evidence of shock remains speculative [134]. Although some reports have demonstrated acute beneficial effects of sildenafil in patients with pulmonary hypertension in the context of systolic and diastolic dysfunction [135–138], and in patients undergoing valve surgery [139], the negative results of a study evaluating continuous intravenous epoprostenol for the same purpose supports the notion that a controlled trial be conducted before these agents are routinely used for this purpose [140, 141].

The activity of soluble guanylate cyclase (sGC) may also be directly influenced by sGC activators and stimulators [142]. Riociguat (sGC stimulator) has a dual mechanism of action on sGC by increasing both the sensitivity of sGC to endogenous NO and via a direct (NO independent) stimulation of sGC [143]. Unlike other agents mentioned thus far, riociguat must be up-titrated gradually over several weeks to ensure that the medication is tolerated. The efficacy of riociguat has been demonstrated in chronic pulmonary hypertension. In patients with PAH and in inoperable or persistent chronic thromboembolic disease post-endarterectomy [144, 145], riociguat improved exercise capacity (assessed by 6-min walk distance), symptoms of dyspnea, quality of life, and hemodynamics. The main relevant limitation to riociguat is twofold. First hemoptysis and pulmonary hemorrhage have been reported within the confines of the acute and long-term trials (generally less than 3% of the study cohort). Second, riociguat can cause systemic hypotension. Particularly noteworthy is the adverse interaction between this agent and the PDE_5 inhibitor class of agents and a theoretic adverse interaction between this agent and NO donors, in causing systemic hypotension [146]. The effects of endogenous/inhaled NO in combination with riociguat have not been systematically evaluated.

Endothelin Antagonists

Endothelin-1 (ET-1) is a peptide produced primarily by endothelial cells. It acts on ET-A and ET-B receptors, both of which are located on pulmonary vascular smooth muscle cells. The ET-B receptor is also located on endothelial cells. Abnormally high concentration of ET-1 in PAH is the result of increased production and decreased clearance of the peptide [147, 148]. Both circulating and pulmonary concentrations of ET-1 have been correlated with disease severity and prognosis in PAH [149].

Bosentan, ambrisentan, and macitentan are approved as treatment for patients with PAH. Both ambrisentan and bosentan have been shown to improve symptom severity, hemodynamics, and exercise capacity (quantified by improvements in the standardized 6-min walk test – 6MWT) [150]. The SERAPHIN trial (macitentan 3 mg vs 10 mg vs placebo) was the first endpoint-driven trial and demonstrated an improvement in time to clinical worsening (hospitalizations, escalation in treatments, death, or transplantation) [151]. This composite primary endpoint was primarily driven by a reduction in hospitalizations or escalation in medical treatments for PAH.

The tolerability as a class is most commonly limited by hepatotoxicity, followed by several less frequent hematologic, neurologic, cardiovascular, respiratory, and gastrointestinal adverse effects. The newer agents, ambrisentan and macitentan, have the lowest incidence of hepatotoxicity and fewer drug-drug interactions than bosentan [152]. However, interactions with agents undergoing CYP metabolism remain a potential concern for this class. The effect on cyclosporine metabolism is particularly relevant. Although effective in the chronic setting, these agents have not been utilized for acute RV failure or acute pulmonary hypertensive crisis.

In the chronic setting, medical therapies are often combined to capitalize on the different therapeutic pathways. Indeed, recent data from a randomized controlled trial suggests that upfront combination therapy (ambrisentan and tadalafil) is associated with improved outcomes compared to monotherapy with either agent [153]. In the acute setting, combination therapy (e.g., with iNO and a PDE_5 inhibitor) may also be of benefit.

Milrinone is an adenosine-3′, 5′-cyclic monophosphate (cAMP)-selective phosphodiesterase enzyme (PDE) inhibitor. When nebulized it has been shown to lead to a relative reduction in PVR compared to SVR [154–156]. Haraldsson et al. evaluated a cohort of post cardiac surgery patients and reported upon the hemodynamic effects of the combination inhaled milrinone and inhaled prostacyclins [157]. The inhalation of milrinone selectively dilated the pulmonary vasculature without systemic effects. When milrinone is combined with inhaled prostacyclin, there appears to be a potentiation and prolongation of the pulmonary vasodilatory effect [157, 158].

Prostaglandins

Prostanoids induce relaxation of vascular smooth muscle, inhibit growth of smooth muscle cells, and are powerful inhibitors of platelet aggregation [159]. Inhaled prostanoids involve an aerosol delivery system that uses a nebulizer attached to the ventilator circuit. Treatment may be limited by inefficiencies in aerosolization. Owing to the short half-life of epoprostenol, the drug must also be continuously nebulized. As a result, changes of dose delivery with alterations in ventilator volumes, FiO_2, airway pressures, and solvent evaporation may be challenging [160]. The synthetic prostanoids, treprostinil and iloprost, hold promise as inhaled vasodilators as they may only require intermitted administration. Studies of prostanoids in chronic PAH demonstrated that they were effective in improving symptoms and exercise tolerance [161, 162]. When nebulized, prostanoids can lead to similar improvements in oxygenation and pulmonary pressures as compared to inhaled NO [163–167]. Indeed, several cohort studies have failed to demonstrate a benefit of iNO over inhaled prostanoids in treating acute pulmonary hypertension [168, 169]. Similarly in critically ill patients with refractory hypoxemia, inhaled epoprostenol (n = 52) and iNO (n = 53) had similar acute effects on gas exchange. The effects on pulmonary pressures or RV function were not assessed [170]. Similar to iNO, the effects of inhaled prostanoids on gas exchange and hemodynamics may be increased with the co-administration of PDE_5 inhibitors [171].

Use of intravenous prostaglandins during OLV results in a decrease in both systemic and pulmonary pressures and either no change or a decrease in PaO_2 [172, 173]. Selective infusion of prostaglandin into the pulmonary artery of the ventilated lung in a dog model during OLV resulted in stable systemic pressure and a reduction in PVR and increase in PaO_2 [174]. However, this route of administration is not practical in routine thoracic anesthesia practice. Inhaled prostacyclin decreases PVRI and PAP with maintenance of favorable systemic pressures but does not change PaO_2 during OLV [173].

Both inhaled nitric oxide and prostaglandins have been shown to affect platelet function [175, 176]. This could theoretically contribute to perioperative bleeding during large surgeries such as lung transplantation and a consideration in regard to the risks of neuraxial analgesia. It is important to emphasize however that the clinical relevance of platelet inhibition with these inhaled agents has not been systematically evaluated. Indeed, in cardiac surgery patients, laboratory confirmation of platelet dysfunction with inhaled prostacyclin did not correlate with chest tube losses [175]. Also, in an obstetrical patient with pulmonary hypertension on intravenous prostacyclin, conversion to inhaled prostacyclin allowed for a successful labor epidural placement with no complications [177].

Until recently an efficacious oral prostanoid has remained elusive. Selexipag is an oral selective IP receptor agonist that was shown to reduce clinical events (time to clinical worsening endpoints such as hospitalization and escalation of PAH treatments) compared to placebo in patients with group I PH. Although of benefit when administered chronically, it is unlikely that this oral agent will have clinical utility in the

acute setting as it shares the same limitations as other parenteral prostanoids for the management of acute RV failure/pulmonary hypertension.

Pulmonary Vasodilators in Thoracic Surgery

Unsurprisingly, the bulk of research studying pulmonary vasodilators in thoracic surgery is in lung transplantation. Preoperatively transplant patients may be on oral, intravenous, or inhaled drugs for pulmonary hypertension. These must be continued perioperatively. Intraoperatively, inhaled pulmonary vasodilators such as nitric oxide (NO) and prostaglandins are commonly employed in attempts to decrease right ventricular afterload and optimize gas exchange. Addition of inhaled prostacyclin to inhaled NO after implantation of the first lung during bilateral sequential transplantation decreases pulmonary shunt, $PaCO_2$, and PAP while increasing PaO_2/FiO_2 with no effect on systemic hemodynamics [119]. Posttransplant, these drugs have been shown to improve the gas exchange abnormalities and increased pulmonary pressures associated with reperfusion injury [163] [114, 178]. Initial excitement over the potential ability of prophylactic NO to prevent acute graft rejection after lung transplantation [179] was tempered when a randomized trial did not show a statistically significant difference between placebo and NO for preventing reperfusion injury or changing postoperative outcome when administered 10 min after reperfusion in the operating room [116].

In non-transplant thoracic surgery, NO has been studied as a potential treatment for the gas exchange abnormalities associated with OLV. Its effects are controversial, but it would appear that it exerts its maximal benefits in patients with elevated PVRI and the poorest gas exchange before administration [117, 118, 120]. There is no evidence for the routine use of this expensive drug in otherwise normal patients undergoing routine thoracic surgery.

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Both inhaled nitric oxide and prostaglandins have been shown to affect platelet function [175, 176]. This could theoretically contribute to perioperative bleeding during large surgeries such as lung transplantation and is a concern in regard to neuraxial analgesia. The clinical relevance of platelet inhibition with these inhaled agents is unknown. Indeed, in cardiac surgery patients, laboratory confirmation of platelet dysfunction with inhaled prostacyclin did not correlate with chest tube losses [175]. Also, in an obstetrical patient with pulmonary hypertension on intravenous prostacyclin, conversion to inhaled prostacyclin allowed for a successful labor epidural placement with no complications [177].

To date there are few systematic concealed trials of pulmonary vasodilators on the acute management of intraoperative/perioperative pulmonary hypertension or RV failure. A recent systematic review of inhaled pulmonary vasodilators in cardiac surgery identified ten studies of inhaled pulmonary vasodilators (vs intravenous route or placebo) [180]. The authors concluded that while these agents seemed to be acutely better than systemic agents in improving RV function, there was no clear benefit of these agents when compared to placebo on clinical outcomes. Given the costs associated with these agents, a systematic study of their benefit to patient-relevant outcomes is needed.

Clinical Case Study

A 46-year-old woman with interstitial lung disease (ILD) presents to the pre-anesthetic clinic before an open lung biopsy.

What are the Anesthetic Considerations for This Case?

Considerations include those of ILD and the proposed case itself. In regard to the ILD, its etiology and severity (including associated connective tissue disorders and multisystem involvement), and associated right heart dysfunction should be delineated. In regard to the biopsy, the usual considerations of lung separation, analgesic options, invasive monitoring and, in this patient, the potential requirement for perioperative inhaled vasodilator therapy are present.

Besides the Usual Anesthetic History and Physical, What Would You Want to Elicit on History and Look for on Physical Exam in This Case?

On history, a careful assessment of functional status and current symptoms, personal and family history of connective tissue diseases should be undertaken.

On physical exam, vital signs including respiratory rate, potential clubbing, crackles on lung auscultation, and signs of right heart dysfunction (including increased JVP, hepatomegaly, lower extremity edema, increased P2 on heart auscultation and right ventricular heave on palpation) should be assessed.

The patient has been experiencing progressive worsening of shortness of breath for approximately 2 years. Her ability to exercise has declined markedly, to the point where she cannot climb a flight of stairs. She had a recent admission to hospital where she was started on home oxygen therapy and referred to a respirologist. An echocardiogram done at that time revealed an RVSP of 89 with mild right ventricular

dilation and hypokinesis. ECG shows sinus tachycardia at 105. The respirologist suggests a biopsy to shed light on the etiology.

Physical exam reveals a thin woman with a respiratory rate of 18 wearing oxygen via nasal prongs at 4 L/min. Her oxygen saturation is 95%, her heart rate is 95, and her blood pressure is 100/60. Airway exam is reassuring. She has coarse crackles bilaterally. JVP is normal, but P2 is increased on cardiac auscultation. There is no hepatomegaly or pedal edema.

What Can be Done to Optimize These Patients' Perioperative Course?

After communicating with the patient's respirologist, a decision is made to bring the patient to the hospital the day before the planned operation to perform a right heart catheterization and assess the patient's response to inhaled prostacyclin. A pulmonary artery catheter is inserted under local anesthesia in the intensive care unit. PAP is 75/40. Systemic blood pressure is 90/60. After institution of inhaled prostacyclin, the PAP decreases to 60/30 with no change in systemic pressure.

What is the Anesthetic Plan?

TEE is arranged to be available for the case. After an appropriate fasting interval, the patient is transferred to the operating room with inhaled prostacyclin (10 ng/kg/min) and oxygen. A baseline ABG is drawn and shows pH of 7.38, $PaCO_2$ 44, PaO_2 65, and HCO_3 28. Baseline vital signs are sinus tachycardia 103, PAP 65/37, BP 98/62, and 96% on FiO_2 40%. An epidural is placed and tested at T5/6. An epidural infusion of bupivacaine and hydromorphone is started. Preoxygenation continues without interruption of the inhaled prostacyclin, and norepinephrine is started at 0.05 mcg/kg/min. After ensuring the surgeons are in the room, induction medications are titrated to effect and include midazolam 2 mg, fentanyl 250 mcg, and ketamine 50 mg. Rocuronium 50 mg is given to facilitate endotracheal intubation. A 37F left-sided double-lumen tube is placed without difficulty, and anesthesia is maintained with sevoflurane and 100% oxygen. Inhaled prostacyclin is continued via the anesthetic circuit. Vital signs are stable with assumption of positive pressure ventilation. The patient is turned to the lateral position and surgery is started. After commencement of OLV, the patient's PAP climbs to 80/45, BP decreases to 78/40, and ST depression occurs in lead II on ECG. Oxygen saturation drops to 87% on 100%. Pre-existing right ventricular hypokinesis and dilation are seen to worsen on TEE. A temporizing bolus of phenylephrine 200 mcg is given, while the norepinephrine is titrated up to 0.1 mcg/kg/min. A bolus of 250 cc of normal saline is administered, keeping in mind the delicate balance between overloading a failing right ventricle and maintenance of adequate preload to ensure systemic cardiac output. Inhaled prostacyclin is titrated up to 30 ng/kg/min. Vital signs move back toward baseline. The surgery is completed, the patient is extubated, awake, and comfortable. Norepinephrine is titrated off in recovery, and the prostacyclin is titrated down to baseline. The patient returns back to intensive care for close observation.

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