Pulmonary Resection in the Patient with Pulmonary Hypertension

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Key Points

- Pulmonary resection in the presence of pulmonary hypertension has been associated with increased risk for perioperative morbidity and mortality; however, advances in assessment, treatment, and intraoperative management have made surgery in these patients feasible.
- Preoperative assessment of these patients requires a multidisciplinary approach and various diagnostic tests to assess severity and determine appropriate treatment. This should be optimized preoperatively.
- The anesthetic goals for these patients include optimizing preload, maintaining a low-normal heart rate, maintaining contractility, decreasing pulmonary vascular resistance, and ensuring systemic pressures are greater than pulmonary pressures.
- Intraoperative monitoring should include invasive blood pressure monitoring and potentially the use of a pulmonary artery catheter and/or transesophageal echocardiography. The use of advanced monitors such as pulmonary artery catheters or transesophageal echocardiography should be decided on a case-by-case basis.
- Understanding of the interaction between anesthetic agents and pulmonary vascular physiology is of key importance. Volatile agents may impair right ventricular function and should be used with care. Ketamine has been shown to be safe for use in pulmonary hypertension.
- Inhaled nitric oxide and prostanoids are potentially useful adjuncts in the management of pulmonary pressures intraoperatively.
- Effective pain management is of utmost importance in patients with pulmonary hypertension presenting for pulmonary resection. Epidurals are effective and may reduce pulmonary complications as well as overall mortality but require close monitoring due to their potentially significant hemodynamic effects. Paravertebral catheters are also an alternative.
- Postoperative arrhythmias, acute pulmonary hypertension, and right heart failure are potential complications post-pulmonary resection and necessitate postoperative monitoring in a step-down or critical care unit for these patients.

Abbreviations

ARDS	Acute respiratory distress syndrome
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ERA	Endothelin receptor antagonist
iNO	Inhaled nitric oxide
NYHA	New York Heart Association
OLV	One-lung ventilation
PAC	Pulmonary artery catheter
PAP or PA pressure	Pulmonary artery pressure
PCA	Patient-controlled analgesia
PDE-5	Phosphodiesterase-5
PGI_2	Prostacyclin
RHC	Right heart catheterization
RVSP	Right ventricular systolic pressure
SPAP	Systolic pulmonary artery pressure
TEE	Transesophageal echocardiography

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TTE	Transthoracic echocardiography
VATS	Video-assisted thoracoscopic surgery
WHO	World Health Organization

Introduction

Pulmonary hypertension is defined as a resting mean pulmonary artery pressure of ≥25 mmHg [1] and carries with it significant implications for the patient presenting for thoracic surgery. Pulmonary hypertension is often associated with significant end-stage lung disease and can also be associated with numerous extrapulmonary diseases. The classification of pulmonary hypertension was most recently updated in 2013 to reflect five groups of disorders that cause it [2] (Table 34.1). Presently, pulmonary hypertension is thought to have a global prevalence of 1%; however, this may increase to as high as 10% in those greater than 65 years of age [3]. Typically, for the anesthetist, there are two main types of pulmonary hypertension: pulmonary hypertension related to left-heart disease and pulmonary hypertension related to lung disease (Table 34.2). Currently, with improved diagnostic testing and therapies, it is no longer uncommon for patients with pulmonary hypertension to present to the operating room for surgery. This chapter will consider the perioperative risk profile of patients with pulmonary hypertension presenting for lung resection surgery. It will then discuss the preoperative assessment, intraoperative, and postoperative management of this population.

Perioperative Risk

The increased risk in perioperative morbidity and mortality associated with pulmonary hypertension has been well-documented in the literature. Studies in the non-cardiac surgical population have demonstrated that these patients are at increased risk for perioperative heart failure, hemodynamic instability, sepsis, and respiratory failure. Furthermore, pulmonary hypertension patients require longer durations of mechanical ventilation and longer intensive care and hospital admissions [4, 5]. Higher pulmonary-to-systemic systolic pressure ratios are also associated with higher perioperative mortality [6]. In the literature, the morbidity and mortality in pulmonary hypertension patients presenting for non-cardiac surgery have been reported to be 14–42% and 1–18%, respectively [7]. Overall, patients with pulmonary hypertension present a significant challenge in the perioperative period.

Table 34.1 World Health Organization classification of pulmonary hypertension

1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable
1.2.1 Bone morphogenetic protein receptor type II gene abnormality
1.2.2 Other genetic mutations: ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1" Persistent pulmonary hypertension of the newborn
2 Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3 Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4 Chronic thromboembolic pulmonary hypertension
5 Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

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Table 34.2 Modified classification of pulmonary hypertension for anesthesia

Left heart disease	Lung disease
Systolic dysfunction Diastolic dysfunction Mitral valvular disease: stenosis, regurgitation Congenital cardiac disease	Pulmonary vascular disease Chronic lung disease, hypoxemia, sleep apnea Thromboembolic pulmonary hypertension Miscellaneous: autoimmune, metabolic

General indications for pulmonary resection include procedures for diagnosis (e.g., open lung biopsies for tumors and pulmonary fibrosis) or treatment of malignancy, congenital abnormalities, infection, and trauma. As mentioned previously, it is not unusual for elevated pulmonary arterial pressures to coexist with lung disease. Historically, lung resection surgery has been cautioned and discouraged in patients with pulmonary hypertension [8]. In small studies and case reports examining patients undergoing pulmonary resection, the presence of pulmonary hypertension was associated with increased morbidity and mortality (by 50% and 25%, respectively, in one small study) [9]. Significant bleeding [10, 11], increases in pulmonary artery pressures postoperatively [12], and right ventricular failure [13] have all been reported. However, more recently, Wei and colleagues retrospectively examined 298 patients (19 with pulmonary hypertension) undergoing pulmonary resection for lung cancer. In this study, the presence of pulmonary hypertension was not associated with increased morbidity or mortality as compared to non-pulmonary hypertension patients [14]. Though small, this study suggests the feasibility of safely conducting lung resections in this population.

The implications of lung resection surgery on the pathophysiology of underlying pulmonary hypertension must also be considered. The loss of lung parenchyma carries with it a loss of pulmonary vasculature, which can result in increased pulmonary vascular resistance. Pneumonectomy has been shown to produce significant right ventricular dysfunction in the immediate postoperative period [15, 16], as well as up to 4 years after surgery [17]. The etiology of this dysfunction is presumed to be due to increased right ventricular afterload. Pulmonary artery systolic pressures measured by Doppler echocardiography have also been shown to be elevated after pneumonectomy [17]. The literature remains inconsistent and unclear regarding the effects of subtotal pulmonary resections (lobectomies, segmentectomies, and wedge resections) on pulmonary arterial pressures [18]. However, the majority of published studies on the subject have involved patient populations without pulmonary hypertension. Presumably, the effect of pulmonary resection on existing pulmonary hypertension (as well as existing right heart dysfunction) is likely to be more significant and warrants additional concern by the anesthesiologist.

Preoperative Assessment

The preoperative assessment of patients presenting for thoracic surgery is discussed in great detail in Chap. 2 and can be applied to the patient with known or suspected pulmonary hypertension.

History, Physical Exam, and Investigations

Patients with known or suspected pulmonary hypertension commonly present with dyspnea and fatigue. Patients may also report additional symptoms, including presyncope, syncope, angina, and symptoms of right heart failure (peripheral edema, abdominal distension, and anorexia), which may reflect disease progression and severity. Unfortunately, these symptoms are vague and nonspecific and are often attributable to more common cardiopulmonary diagnoses. Furthermore, such symptoms are common in patients presenting for thoracic surgery, in general, and make identification of undiagnosed pulmonary hypertension challenging. Additional features on history such as orthopnea or paroxysmal nocturnal dyspnea (left-sided heart disease), arthralgias or skin changes (rheumatologic or connective tissue disorder), or snoring or observed apnea (obstructive sleep apnea) may also aid in evaluation or provide a unifying diagnosis.

In patients with known pulmonary hypertension, the development of symptoms of right heart failure is a means of gauging a patient's clinical status over time. The World Health Organization (WHO) has also developed a classification of functional status of patients with pulmonary hypertension [19] based on the New York Heart Association (NYHA) system (Table 34.3), which is also useful for assessing disease severity, progression, and response to treatment. The WHO/NYHA functional status has been shown to strongly correlate with long-term survival in patients with idiopathic pulmonary hypertension [20].

Beyond history and physical examination, the assessment of the patient with suspected or confirmed pulmonary hypertension presenting for thoracic surgery should also include a

Table 34.3 World Health Organization classification of functional status of patients with pulmonary hypertension

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity

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chest X-ray and electrocardiogram (ECG). A chest X-ray not only allows for assessment of lung parenchyma and the specific lesion being operated on (e.g., tumor) but may also demonstrate features consistent with elevated pulmonary artery pressures such as prominent pulmonary arteries or right ventricular enlargement. The ECG may provide features suggestive or supportive of pulmonary hypertension including right ventricular hypertrophy or a right axis-deviation. Neither a chest X-ray nor ECG possess sufficient specificity or sensitivity to rule in or rule out pulmonary hypertension.

Transthoracic echocardiography (TTE) has rapidly become the investigation of choice for both screening and follow-up of patients with pulmonary hypertension, given its availability and noninvasiveness. TTE allows for the estimation of the right ventricular systolic pressure (RVSP), which closely approximates the systolic pulmonary artery pressure (SPAP) in the absence of pulmonary outflow obstruction. The RVSP measured by echocardiography has been shown to have moderate to strong correlation to the SPAP measured through right heart catheterization (correlation coefficient $R = 0.57–0.93$) [19]. However, in some cases, RVSP measurements done using TTE may deviate from SPAP values derived by right heart catheterization by as much as 10 mmHg in many patients, with a tendency to underestimate the true SPAP [21]. Furthermore, there is large variation in the sensitivity and specificity of TTE in the diagnosis of pulmonary hypertension, which has been shown to be 79–100% and 60–98%, respectively [22]. Additional echocardiography features include right ventricular dilatation or hypertrophy, right ventricular dysfunction, right atrial enlargement, the presence of significant tricuspid regurgitation, interventricular septal flattening, as well as the presence of pericardial effusions. The presence of these features has been associated with worse prognosis in pulmonary hypertension patients [22].

Right heart catheterization (RHC) remains the gold standard in terms of assessment and diagnosis of pulmonary hypertension. RHC allows for the measurement of pulmonary artery pressures (required for the formal diagnosis of pulmonary hypertension) as well as pulmonary vascular resistance. Additional useful information can be derived from RHC, including estimation of right heart pressures (right ventricular and right atrial pressures), pulmonary capillary wedge pressures, cardiac output, and pulmonary vasoreactivity.

In addition to the testing described above, other investigations may be necessary depending on the specific indication for pulmonary resection. Detailed discussion of these additional tests can be reviewed in Chap. 2.

Treatment and Consultations

The management and treatment of pulmonary hypertension requires a multidisciplinary approach and is a topic well beyond the scope of this chapter. However, the thoracic anesthetist should have a basic understanding of the management of pulmonary hypertension patients and the relevant perioperative implications of pulmonary hypertension treatment. All patients with significant pulmonary hypertension should ideally have consultation and ongoing follow-up with a pulmonary hypertension specialist and, if applicable, a specialist for the management of the underlying cause of their pulmonary hypertension (e.g., a cardiologist for left-sided heart disease, a rheumatologist for connective tissue disorders). Perioperative management should include consultation with these specialists to ensure proper optimization prior to presenting to the operating room.

Specific management of pulmonary hypertension is dependent on the underlying cause; however, pharmacologic management may involve the use of vasodilators, diuretics, steroids, and immune suppressants, as well as anticoagulants. Perioperative management of these pharmacologic regimens may be complex.

Pulmonary vasodilating agents, such as endothelin receptor antagonists, prostanoids, and phosphodiesterase-5 inhibitors, can be used alone or in combination in the management of pulmonary arterial hypertension (Group 1).

Endothelin receptor antagonists (ERAs) target the endothelin-1 receptor, which mediates vasoconstriction and plays a significant role in the pathogenesis of pulmonary arterial hypertension [23]. Commonly used preparations include bosentan, ambrisentan, and macitentan, all of which are administered orally. While generally well-tolerated, hepatotoxicity and the development of transaminitis are well-known adverse effects of ERAs and should be screened shortly after initiation [24]. Other less common but significant adverse effects include anemia and hypotension.

Prostanoids are prostacyclin analogues and exhibit potent vasodilating effects mediated through increasing intracellular cyclic adenosine monophosphate [25]. Presently, three prostacyclin analogues are available: epoprostenol (continuous intravenous infusion), treprostinil (continuous subcutaneous infusion), and iloprost (inhalational administration). The relatively short half-lives of these agents necessitate continuous or frequent administration. Epoprostenol's half-life is less than 5 min, and thus therapy requires continuous intravenous infusion via a portable infusion pump. The half-lives of treprostinil and iloprost are approximately 45–60 min [26]. Abrupt discontinuation of prostanoid therapy can result in life-threatening rebound of pulmonary hypertension. Additional concerns regarding prostanoids include the potential for systemic hypotension, as well as increased bleeding risk due to prostanoid-mediated inhibition of platelet aggregation [27].

Phosphodiesterase-5 (PDE-5) inhibitors were initially introduced for the management of erectile dysfunction but have found a significant role in the management of pulmo-

nary arterial hypertension. PDE-5 is predominantly found in the lungs, and its inhibition prevents the breakdown of cyclic guanosine monophosphate (cGMP) [28]. cGMP potentiates the vasodilatory effects of nitric oxide, producing pulmonary vasodilation. Oral preparations of PDE-5 inhibitors include sildenafil and tadalafil. These agents are generally well-tolerated and produce minor adverse effects such as headaches, flushing, and dyspepsia [24].

In general, these agents (especially prostanoids) are continued in the perioperative period; however, adjustment of doses and dosing may need to occur and should be managed by an experienced prescriber.

Intraoperative Management

An understanding of the pathophysiology of pulmonary hypertension and its implications for general anesthesia is of utmost importance when managing the patient with pulmonary hypertension presenting for pulmonary resection. Right ventricular failure and resulting cardiovascular collapse secondary to pulmonary hypertension present the greatest risk in the perioperative period. The right ventricle normally receives perfusing blood flow during both systole and diastole. However, elevated pulmonary arterial pressures produce increased right ventricular transmural and intracavitary pressures, which can limit ventricular perfusion during systole and result in RV ischemia [29]. Hypotension is poorly tolerated in significant pulmonary hypertension, as well as conditions impairing right ventricular filling, such as tachycardia and arrhythmias. Low systemic to pulmonary pressure ratios are associated with poorer outcomes and should be avoided intraoperatively. The pathophysiologic processes involved in right ventricular failure in the setting of increased right ventricular afterload (pulmonary hypertension) are shown in Fig. 34.1. In addition, care needs to be taken to prevent conditions which would worsen pulmonary arterial pressures, including hypoxemia, hypercarbia, hypothermia, acidosis, and elevated alveolar pressures.

The ideal anesthetic would maintain or enhance right ventricular function and systemic vascular resistance while decreasing pulmonary vascular resistance. However, in practice, this is challenging to achieve in the operating room. A summary of hemodynamic and ventilation goals is shown in Table 34.4.

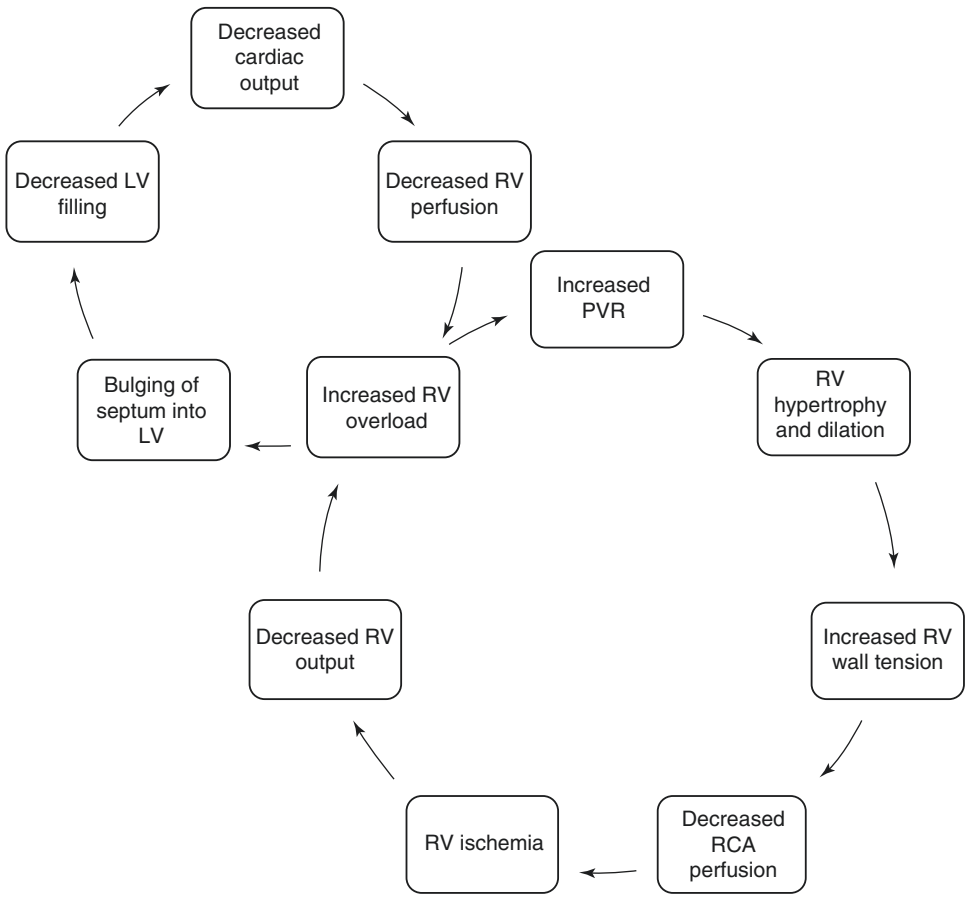

Fig. 34.1 Pathophysiologic mechanisms in right-sided heart failure. PVR pulmonary vascular resistance, RCA right coronary artery. (Reprinted from Wilcox et al. [29] with permission from Elsevier)

Table 34.4 Hemodynamic and ventilatory goals during anesthesia for pulmonary hypertension

Parameter	Goals
Hemodynamic conditions	
Preload	Avoidance of hypervolemia – precipitates RV failure Avoidance of hypovolemia – impairs stroke volume and cardiac output Hypovolemia is better tolerated
Afterload	Maintain a systemic systolic blood pressure greater than the pulmonary systolic pressure to maintain right ventricular perfusion Vasopressors may be used to achieve this
Right ventricular contractility	Avoid excessive myocardial depression (choice of anesthetic agent) Consider use of inotropes when needed
Heart rate	Normal heart rate – avoid tachycardia, which impairs right ventricular filling and cardiac output
Pulmonary vascular resistance	Avoid precipitants of increased pulmonary vascular resistance (hypoxia, hypercarbia, acidosis, hypothermia, increased sympathetic tone)
Ventilatory conditions	
Optimize oxygenation	Maintain higher FiO_2 as needed to avoid hypoxia Careful PEEP titration
CO_2	Target normocapnia to mild hypocapnia (pCO_2 30–35)
pH	Normal pH Mild alkalosis promotes pulmonary vasodilation
Airway pressure	Minimize peak inspiratory pressure as much as possible Peak inspiratory pressure <30 mmHg Avoid excessive PEEP

Premedication

The perioperative period is a stressful time for all patients, and many centers routinely provide patients with the option of an anxiolytic administered in a preoperative area. Care and attentiveness should be taken when administering sedating agents (such as benzodiazepines) to patients with pulmonary hypertension preoperatively, which is a period where continuous monitoring is not always available. Preoperative anxiolytics often have a sedating effect which can result in hypoventilation leading to hypercarbia and, in some cases, hypoxia. These two conditions can precipitate significant increases in pulmonary vascular resistance, which can be life-threatening. Sedative premedication should be used cautiously, or avoided completely, in the patient with significant pulmonary hypertension. If required, continuous hemodynamic monitoring, as well as supplemental oxygen, should be considered and readily available.

Intraoperative Monitoring

Intrathoracic surgery, including surgery for pulmonary resection, requires an increased level of intraoperative monitoring. Routine noninvasive monitors, including 5-lead ECG, pulse oximetry, capnography, temperature, and noninvasive blood pressure monitoring, are complemented by invasive blood pressure monitoring. In patients presenting for thoracic surgery, invasive blood pressure monitoring via an intra-arterial catheter is routinely done prior to induction of anesthesia at the authors' institution. This allows for continuous monitoring of systemic blood pressure during induction and maintenance of anesthesia. Of equal importance, invasive blood pressure monitoring allows regular sampling of arterial blood gases to assess oxygenation and ventilation.

Central venous access should be considered in patients with significant pulmonary hypertension, evidence of right ventricular dysfunction, or for major pulmonary resections, as it allows for infusions of vasopressors and inotropes (discussed further below). Central venous access also allows for the insertion of a pulmonary artery catheter (PAC), which in turn allows for continuous measurement of pulmonary arterial pressures and determination of cardiac output. The use of PACs for intraoperative and perioperative monitoring has been subject to significant controversy in the literature. One large observational study determined that the perioperative use of PACs in patients presenting for non-cardiac surgery was associated with an increased risk of postoperative cardiac (myocardial infarction, angina, cardiogenic shock, ventricular fibrillation/tachycardia, cardiac arrest, or complete heart block) and non-cardiac (pulmonary embolism, noncardiogenic pulmonary edema, prolonged mechanical ventilation, pneumonia, renal failure, stroke, or GI bleeding) morbidity [30]. A subsequent prospective randomized controlled study involving high-risk non-cardiac surgery patients found that the use of a PAC conferred no benefit in terms of overall mortality or cardiac and non-cardiac morbidity [31]. However, thoracic surgery patients made up only a small minority of the studied population in both studies and neither specifically assessed for pulmonary hypertension and its implications. Unfortunately, there is no large study investigating the use of PACs in thoracic (pulmonary resection or otherwise) surgery.

Given the lack of alternative means to continuously monitor pulmonary artery pressures intraoperatively, the use of PACs in patients presenting for pulmonary resection should strongly be considered in the setting of significant pulmonary hypertension and especially in patients where pulmonary artery pressures approach or exceed systemic pressures. The interpretation of PAC data can be challenging and misleading in patients with pulmonary hypertension, even for experienced clinicians [32]. Elevated and increasing pulmonary artery pressures are universally an indicator of worsening clinical status. However, decreasing pressure can indicate a desirable reduction in pulmonary artery pressures or impending right ventricular failure and subsequent cardiovascular collapse. As such, PAC data must be interpreted in

the context of other hemodynamic indices such as arterial blood pressure, cardiac output, and central venous pressures. It should also be noted that the use of a PAC is not without risk, as pulmonary hypertension is a known risk factor for PAC-associated pulmonary artery rupture, which is an exceedingly rare (incidence 0.03–0.2%) but highly fatal (mortality ~ 70%) complication [33].

Intraoperative transesophageal echocardiography (TEE) is a monitoring tool that is growing in terms of availability and utility, particularly in the setting of assessment of dynamic ventricular function (see also Chap. 30). Intraoperative TEE has been recurrently shown to enhance and influence therapeutic decision-making in the OR during surgery [34, 35]. The American Society of Anesthesiologists recommends the use of intraoperative TEE during non-cardiac surgery "when the nature of the planned surgery or the patient's known or suspected cardiovascular pathology might result in severe hemodynamic, pulmonary, or neurologic compromise" [36]. As right ventricular failure in the context of worsening pulmonary hypertension is a major concern in the intraoperative period, the utility of TEE in assessment of right ventricular function is of growing interest. The use of TEE as a monitor intraoperatively in the patient with pulmonary hypertension allows for assessment of baseline right ventricular function and the presence of significant right ventricular dysfunction, which has been shown to be an important prognostic indicator in cardiac surgery [37]. However, unlike the left ventricle, where continuous TEE monitoring of function can be reasonably performed through a single view, the complex and irregular structure of the right ventricle requires multiple views to assess changes in regional function. As such, continuous monitoring with concurrent management of the potentially failing right ventricle in the setting of worsening pulmonary hypertension may be impractical for the lone care provider. The advent of new three-dimensional TEE technology has allowed for rapid and accurate assessment of right ventricular function in a matter of minutes [38] and may eventually evolve to allow for simple, reliable, and continuous monitoring of right ventricular function in the OR.

Anesthetic Management

The pharmacology and physiologic effects of commonly used anesthetic agents make induction and maintenance of anesthesia in the patient with pulmonary hypertension challenging. The ideal anesthetic agent(s) would provide deep anesthesia while maintaining cardiac performance (specifically that of the right ventricle) and systemic vascular resistance while reducing pulmonary vascular resistance. In practice, commonly used agents generally produce impairment in cardiac contractility and reduced systemic vascular resistance while having variable or unclear effects on pulmonary vascular resistance.

Intravenous Agents

The use of intravenous agents in the anesthetic management of patients presenting to the OR is near ubiquitous. The growing number of pharmacologic agents available, as well as their varying pharmacodynamic effects, warrants closer examination, especially in the context of the deranged cardiorespiratory physiology involved in pulmonary hypertension patients.

Propofol is among the most commonly used intravenous agents for both the induction and maintenance of anesthesia. The effect of propofol on pulmonary vascular tone is unclear; however, animal studies have shown that in the setting of increased adrenergic activity, administration of propofol has a vasoconstricting effect on pulmonary vasculature [39, 40]. However, in a human model, administration of propofol in normoxic conditions had a vasodilatory effect in the pulmonary vasculature [41], raising questions regarding propofol's true effect. What is clear, however, is that propofol exhibits depressant effects on both myocardial function and systemic vascular resistance. Both effects can impair right ventricular function, either directly or by reducing coronary perfusion to the right ventricle through reduced systemic pressures. As such, caution should be exercised when using propofol in the patient with pulmonary hypertension, especially if right ventricular dysfunction is present.

Etomidate is a less commonly used intravenous induction agent with a neutral hemodynamic profile, allowing for preserved right ventricular function and perfusion. Furthermore, in vitro human pulmonary artery models have suggested some vasodilatory effects on the pulmonary vasculature [41]. While these properties would make etomidate the ideal induction agent in the patient with pulmonary hypertension, a recently published retrospective analysis looking at over 31,000 patients (ASA III–IV patients) found that the use of etomidate was associated with increased 30-day mortality and cardiovascular morbidity as compared to patients receiving propofol [42]. While the study did not specifically include patients with pulmonary hypertension or those undergoing thoracic surgery, the results do raise concerns regarding the safety of etomidate in higher-risk patients.

Ketamine is an NMDA-receptor antagonist with activity at other sites, including opioid, acetylcholine, norepinephrine, dopamine, and serotonin receptors. As such, ketamine possesses many attractive features for an intravenous agent, including its sympathomimetic effects producing increased myocardial contractility and systemic vascular resistance, as well as bronchodilator, analgesic, and antidepressant effects [43, 44]. There is much controversy surrounding the effects of ketamine on pulmonary pressures, as early studies investigating the drug's cardiovascular effects demonstrated signifi-

cant increases in both pulmonary artery pressures and pulmonary vascular resistance [45, 46]. As such, the prevailing opinion was that ketamine should be avoided in patients with pulmonary hypertension. However, these early studies did not control for hypercarbia or hypoxia, two key triggers for pulmonary vasoconstriction [47]. More recently, human and animal studies have demonstrated that the use of ketamine, when controlling for ventilation, oxygenation, and acid-base status, does not increase pulmonary vascular resistance [48], is safe when used in patients with pulmonary hypertension [49], and may produce pulmonary vasodilation [50]. Of note, at the authors' institution, ketamine is routinely used in patients with significant pulmonary hypertension and right ventricular dysfunction presenting for cardiac, thoracic, and lung transplantation procedures.

Benzodiazepines and opioids are often used in conjunction with intravenous induction agents and produce minimal hemodynamic effects beyond their attenuation of sympathetic tone [7].

Volatile Anesthetics

Modern volatile anesthetics are commonly used to maintain general anesthesia intraoperatively. While much of the literature surrounding the cardiovascular effects of volatile anesthetics (specifically desflurane, isoflurane, and sevoflurane) has focused on their impact on left ventricular function, there is some suggestion that volatile agents produce significant effects on right ventricular performance as well. Animal studies have shown that sevoflurane, isoflurane, and desflurane all produce depression of right ventricular contractility, with sevoflurane effects being quite significant [51–53]. Furthermore, sevoflurane appears to produce greater reductions in systemic vascular resistance, without altering pulmonary vascular resistance [53]. This creates an unfavorable pulmonary-to-systemic pressure ratio relative to desflurane, in which systemic vascular resistance tends to be maintained with only a small increase in pulmonary pressures [51].

Vasopressor Agents

Due to the importance of preserved systemic pressures in maintaining right ventricular perfusion, vasopressor agents are useful in the intraoperative management of patients with pulmonary hypertension. As previously mentioned, the maintenance of a high ratio of systemic pressures to pulmonary pressures is important in avoiding deterioration in hemodynamics. Commonly used vasopressor agents, including phenylephrine, norepinephrine, and vasopressin have all been shown to exert different effects on hemodynamic parameters, including systemic and pulmonary pressures.

An early animal model demonstrated that commonly used agents, including phenylephrine, norepinephrine, and epinephrine, all increased systemic and pulmonary pressures to varying degrees while largely preserving pulmonary vascular resistance [54]. Norepinephrine, in addition to its vasoconstricting effects, has β-1 receptor-mediated inotropic effects, which appear to improve right ventricular-pulmonary arterial coupling while maintaining cardiac output and right ventricular performance [55]. Animal models have also demonstrated that in doses less than 0.5 ug/kg/min, norepinephrine has minimal effects on pulmonary vascular resistance [56]. In contrast, phenylephrine has been shown to exert negative effects on right ventricular function in pulmonary hypertension patients by increasing pulmonary vascular resistance [57].

Perioperatively, in patients with pulmonary hypertension presenting for cardiac surgery, both norepinephrine and phenylephrine were shown to increase systemic and pulmonary pressures, however with distinct differences in hemodynamic parameters. Norepinephrine use resulted in a reduction of pulmonary arterial pressure to systemic blood pressure ratio without reducing cardiac index. Conversely, use of phenylephrine resulted in preservation of the pulmonary arterial pressure to systemic blood pressure ratio while reducing cardiac index [139]. These results suggest that norepinephrine is preferable to phenylephrine in the treatment of hypotension in pulmonary hypertension patients.

The effect of vasopressin on pulmonary arterial pressure has been subject to significant debate. In experimental animal models, vasopressin has been demonstrated to result in both pulmonary vasoconstriction [58] and pulmonary vasodilation [59, 60], leading to significant confusion. The absence of vasopressin receptors in human pulmonary vasculature has been widely posited, and recently, an experimental model using human radial and pulmonary arteries has demonstrated that while vasopressin exhibits a potent vasoconstricting effect in radial vessels, it had no effect on pulmonary vascular tone [61]. Subsequent to this finding, numerous publications have demonstrated consistent improvement in systemic blood pressures with minimal effect on pulmonary arterial pressures in hypotensive patients with pulmonary hypertension that are treated with vasopressin [62, 63]. These properties make vasopressin another valuable agent in the management of hypotension in pulmonary hypertension patients.

Vasodilator Agents

In addition to the use of agents to maintain systemic blood pressure intraoperatively, the use of vasodilating agents in order to decrease pulmonary vascular resistance has also garnered significant interest, particularly agents such as inhaled nitric oxide (iNO), milrinone, and prostaglandins.

iNO had garnered significant interest in the areas of acute respiratory distress syndrome (ARDS), heart and lung transplantation, and right ventricular failure, with mixed success [64–66]. Mechanistically, iNO is delivered noninvasively, or through a ventilator circuit, and is directed toward preferentially ventilated alveoli. Through its vasodilatory effects, iNO theoretically improves alveolar gas exchange and

reduces pulmonary vascular resistance without resulting in systemic hypotension – all desirable in pulmonary hypertension. Clinically, dose ranges of 10–40 ppm are typically administered [67]. In the setting of right heart failure due to pulmonary hypertension, the use of iNO has been mixed and varies from patient to patient, as well as clinical scenario [68, 69]. One study [70] has examined the use of iNO (40 ppm) in thoracic surgery patients during one-lung ventilation and demonstrated that improvements in pulmonary vascular resistance and hypoxia during one-lung ventilation were only seen in patients with preexisting pulmonary hypertension. Unfortunately, due to the significant cost, as well as the advent of other alternative pulmonary vasodilators, intraoperative use of iNO has limited usage. However, given its mechanism of action, as well as the potential benefits during one-lung ventilation, iNO should be given consideration during the management of the patient with pulmonary hypertension presenting to the operating room.

Milrinone is a phosphodiesterase-3 inhibitor with both inotropic and vasodilatory effects when administered intravenously. Due to its effect of reducing both pulmonary and systemic vascular resistances, intravenous milrinone has limited effectiveness in right heart dysfunction related solely to pulmonary hypertension and often requires the concomitant administration of a vasopressor to counter the resulting hypotension. However, milrinone has demonstrated usefulness in patients with biventricular failure in the setting of pulmonary hypertension [71]. Administration of milrinone for pulmonary vasodilation in an inhaled form has gained significant interest recently, particularly in cardiac surgery. In patients with pulmonary hypertension presenting for cardiac surgery involving cardiopulmonary bypass, administration of inhaled milrinone (5 mg) prior to bypass was associated with reductions in pulmonary arterial pressures, enhancement of cardiac output, and minimal effect on mean arterial pressures [72, 73]. Unfortunately, there were no significant improvements in terms of intraoperative or postoperative complications (including right ventricular failure) in patients receiving inhaled milrinone. In addition, the combination of inhaled milrinone and inhaled prostacyclin appears to have an additive effect on pulmonary vasodilation [74]. Presently, there are no studies investigating the use of inhaled milrinone in the thoracic surgery population; however, given the favorable hemodynamics observed in the cardiac surgery population, it presents a potentially attractive option for pulmonary resection surgeries.

As previously discussed, prostanoids have an important role in the management of pulmonary arterial hypertension and are available in intravenous and inhaled formulations that can be used intraoperatively. Animal models for one-lung ventilation have demonstrated that both aerosolized and intravenous administration of prostacyclin (PGI_2) reduce pulmonary arterial pressures [75]. While intravenous infusion of PGI_2 resulted in notable reduction in systemic vascular resistance, aerosolized PGI_2 produced selective pulmonary vasodilation. Similarly, intravenous prostaglandin E_1, a short-acting prostaglandin with pulmonary metabolism, administration during one-lung ventilation of pigs produced reductions in pulmonary vascular resistance and pulmonary arterial pressures but failed to demonstrate selective pulmonary vasodilation [76]. In the intraoperative setting, inhaled prostacyclin has been used in cardiac surgery patients with pulmonary hypertension with significant effect in terms of reducing pulmonary arterial pressures with minimal alterations in systemic blood pressure [77, 78]. Inhaled prostacyclin has also been used in the management of pulmonary hypertension during lung transplantation [79], as well as hypoxemia during one-lung ventilation for video-assisted thoracoscopic surgery in a patient without pulmonary hypertension [80]. As previously mentioned, while the use of prostanoids has been shown to significantly reduce pulmonary pressures in pulmonary hypertension patients, there is considerable uncertainty with respect to their effect on platelet function and bleeding risk, which needs to be considered in the intraoperative setting.

Analgesia

Analgesic strategies for pulmonary resection surgeries are typically determined based on the type of incision (thoracotomy vs video-assisted thoracoscopic surgery (VATS)) as well as patient-specific considerations, including decreased pulmonary reserve or a history of chronic pain or opioid use. At the authors' institution, analgesia for surgeries done using VATS are managed postoperatively with a combination of intercostal nerve blocks administered by the surgeon prior to chest closure and intravenous patient-controlled analgesia (PCA). In patients undergoing a thoracotomy without any contraindications, our practice is to provide patient-controlled epidural analgesia using a thoracic epidural placed prior to the induction of anesthesia.

Epidural analgesia carries a number of benefits, including enhanced analgesia compared to intravenous PCA [81–83]. Furthermore, it has been established that the use of epidural analgesia for major surgery, including thoracic surgery, is associated with reduced cardiovascular and pulmonary complications [84], as well as overall mortality [85]. Also of importance, the use of a thoracic epidural does not impact oxygenation during one-lung ventilation [86]. The beneficial effects on cardiorespiratory morbidity may be particularly important for high-risk patients such as those with pulmonary hypertension presenting for thoracic surgery. However, the relationship between the

use of epidural analgesia and pulmonary hypertension itself remains unclear.

The effect of thoracic epidural analgesia on left ventricular performance has been thoroughly investigated with mixed conclusions. Depending on clinical setting, the use of a thoracic epidural may enhance or reduce left ventricular ejection fraction and cardiac output [87–89]. The use of a thoracic epidural in patients with known coronary artery disease appears to enhance left ventricular function [88, 89]. The effect of thoracic epidurals on the right ventricle has also been studied, with animal models demonstrating that the use of a thoracic epidural impairs baseline right ventricular function and inhibits the homeometric augmentation of right ventricular contractility associated with increased right ventricular afterload (pulmonary hypertension) [90, 91]. However, in human patients undergoing thoracotomy for lung resection, the use of a thoracic epidural impaired baseline right ventricular contractility, but did not affect the compensatory increase in right ventricular contractility brought on by an acute increase in right ventricular afterload [92]. These negative effects on ventricular function may represent the effect of cardiac sympathectomy exerted by thoracic epidural blockade.

Overall, these findings suggest that the use of thoracic epidurals in patients with pulmonary hypertension presenting for thoracotomy should be done with care and attention, due to the potential for impairment of biventricular function. However, given that the ability of the right ventricle to increase contractility in the setting of acute increases in afterload is not abolished by epidurals, their use is not contraindicated in pulmonary hypertension patients presenting for thoracic surgery. Furthermore, due to the increased risk of postoperative complications in this population, the beneficial effects of thoracic epidural analgesia are desirable. It must be recognized, however, that these patients will require appropriate monitoring postoperatively and may require hemodynamic support in the form of inotropes and/or vasopressors when using thoracic epidural analgesia.

Paravertebral blockade is a commonly used alternative to both thoracic epidural analgesia and intravenous PCA for post-thoracic surgery pain management. Compared to thoracic epidurals, paravertebral catheters present an attractive alternative, especially given the ability to preserve the contralateral sympathetic chain and minimize hemodynamic consequences. In patients undergoing thoracotomy, paravertebral blockade has been shown to provide comparable analgesia to thoracic epidurals and reduce episodes of hypotension, nausea and vomiting, pruritus, and urinary retention [93–96, 140]. However, there is limited literature available concerning the effects of paravertebral blockade on cardiac function or their use in pulmonary hypertension patients. As such, paravertebral blockade presents a potential alternative to thoracic epidurals for post-thoracotomy pain management, with more research being needed for their use in lung resection patients with pulmonary hypertension.

Management of One-Lung Ventilation

The initiation of one-lung ventilation (OLV) for thoracic surgery presents a direct conflict with the management goals for pulmonary hypertension. Avoidance of hypoxia, hypercapnia, and elevated airway pressures is important in minimizing pulmonary vascular resistance. The early period of OLV results in acute rises in pulmonary arterial pressures due to shifting of tidal volumes (resulting in a rise in airway pressures) and pulmonary blood flow from the two lungs to a single lung [97]. This can be further exacerbated by hypoventilation and shunting, which produce undesirable hypercarbia and hypoxia, particularly in patients with preexisting pulmonary hypertension (Fig. 34.2).

General management of OLV for thoracic surgery is discussed elsewhere in this book. The same principles apply in the patient with pulmonary hypertension with a few key distinctions. Lung-protective ventilation strategies have been advocated for OLV, with tidal volumes of 4–6 mL/kg predicted body weight, the application of positive end-expiratory pressures (PEEP) of 5–10 cm H_2O, and maintaining peak inspiratory pressures of less than 30 cm H_2O being advised [97–100]. The appropriate inspired oxygen fraction (F_iO_2) is subject to debate, as higher F_iO_2 has

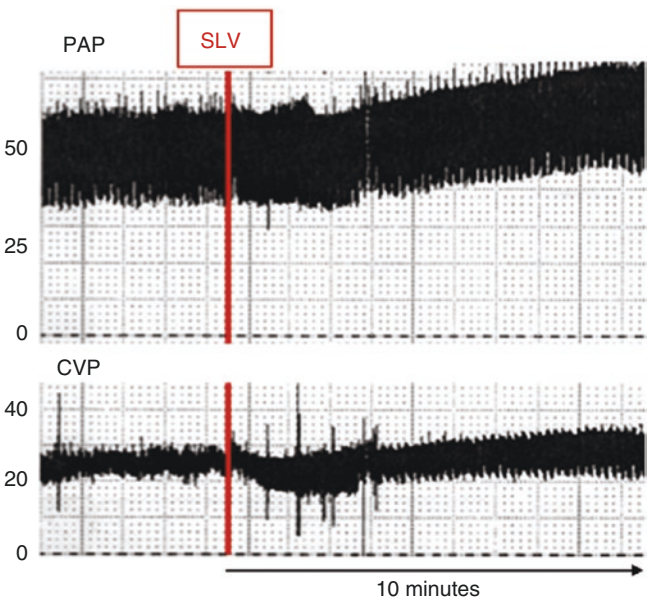

Fig. 34.2 Effect of single-lung ventilation (SLV) on pulmonary arterial pressure (PAP) and central venous pressure (CVP) in a patient with pulmonary arterial pressure. (Reprinted from McGlothlin et al. [97] with permission from Elsevier)

been shown to promote atelectasis formation and produce hypoxia [101]. This has led to the suggestion that $F_iO_2 < 1.0$ be used during the initiation of OLV [99, 100]. However, oxygen is a potent pulmonary vasodilator, especially in pulmonary hypertension patients (irrespective of underlying diagnosis) [102]. In these patients, it is advisable to maintain a higher F_iO_2 initially, with careful titration according to pulmonary pressures and arterial blood gases. Similarly, management of arterial CO_2 (P_aCO_2) is of significant importance, with mild hypocapnia ($P_aCO_2 < 30–35$ mmHg) being advocated during OLV [97], as alkalosis has been shown to produce pulmonary vasodilation [103, 104]. The use of recruitment maneuvers during the management of OLV and hypoxia during OLV is also a commonplace and, however, carries with it the risk for hemodynamic instability due to hypotension and potential for acute worsening of pulmonary hypertension. Human and animal studies have demonstrated the significant benefits of recruitment in pulmonary hypertension subjects [105, 106], with the application of 30 cm H_2O with an F_iO_2 for 1 min followed by adjustment of PEEP showing improved oxygenation and acceptable hemodynamic changes in patients with chronic thromboembolic pulmonary hypertension.

Worsening pulmonary vascular resistance and hypoxia during OLV are often difficult to avoid but require immediate attention and management. As previously discussed, iNO is a potent selective pulmonary vasodilator that has been proven to improve pulmonary hypertension and hypoxia in patients with preexisting pulmonary hypertension undergoing pulmonary resection [70]. In patients with significant pulmonary hypertension, iNO should be instituted concurrently with the initiation of OLV to limit the rise in pulmonary pressures and improve ventilation-perfusion matching.

Prostanoids have also been shown to be effective pulmonary vasodilators in pulmonary hypertension OLV models [75, 76]. Route of administration is an important distinction between prostanoids and iNO, with prostanoids being available in intravenous (epoprostenol) and inhaled (iloprost) forms. The pulmonary selectivity of iloprost allows for pulmonary vasodilation with minimal systemic hypotension and should be the route used during OLV. Importantly, in addition to pulmonary vasodilation, inhaled prostanoids have been shown to improve oxygenation during OLV as well [80, 107]. Furthermore, the combination of iNO and a prostanoid has been shown to be additive in a pulmonary hypertension animal model [108, 109]; however, this has not been studied during OLV.

In patients already stabilized on a systemically delivered pulmonary hypertension treatment (intravenous or subcutaneous), the potential for worsening systemic hypotension under anesthesia and impairment of hypoxic pulmonary vasoconstriction during OLV should be appreciated. As such, a plan for intraoperative management of these agents should be made preoperatively in conjunction with their pulmonary hypertension specialist. Fortunately, their relatively short half-lives allow for careful titration leading up to initiation of OLV. In these patients, the use of an inhaled pulmonary vasodilator initiated prior to starting OLV is recommended and allows for safe titration of their systemic agent [97] (Fig. 34.3).

Intraoperative Fluid Management

The topic of intraoperative fluid management for major surgery, including thoracic surgery, has been subject to significant debate through the years. The literature has consistently demonstrated that high intraoperative fluid balances are associated with higher rates of perioperative acute lung injury and ARDS [110–112]. Fluid overload combined with mechanical ventilation produces pulmonary endothelial damage and inflammation resulting in pulmonary edema [111, 113–115]. Furthermore, an animal model for OLV and thoracic surgery have demonstrated that compared to two-lung ventilation, OLV increases the potential for acute lung injury [116]. In addition, excessive fluid administration (> 6 mL/kg/h) intraoperatively during pulmonary resection has been shown to increase the risk for pulmonary complications such as atelectasis and pneumonia [117].

The avoidance of pulmonary complications is important for the perioperative management of patients with pulmonary hypertension, as acute lung injury, pneumonia, and atelectasis can all destabilize the already frail patient. Additionally, optimal fluid management is of paramount importance in maintaining appropriate right ventricular preload in the setting of existing right ventricular dysfunction and high right ventricular afterload. Excessive fluid administration can lead to right ventricular overdistension and eventual failure, and inadequate fluid administration can compromise cardiac output and hemodynamics [98]. Fluid management in these patients is often a fine balance.

In spite of the knowledge that excessive fluid administration in thoracic surgery patients is harmful, there are many remaining unknowns and uncertainties regarding fluid management in these patients. These include the proper type of fluid, as well as the ideal fluid balance to achieve during thoracic surgery (neutral vs negative) [118, 119]. The current recommendation for intraoperative fluid management is to adopt a goal-directed approach, with individualization and titration of the fluid administration based on specific cardiovascular measurements, which may include stroke volume, cardiac output, fluid responsiveness, or TEE-based guidance [111].

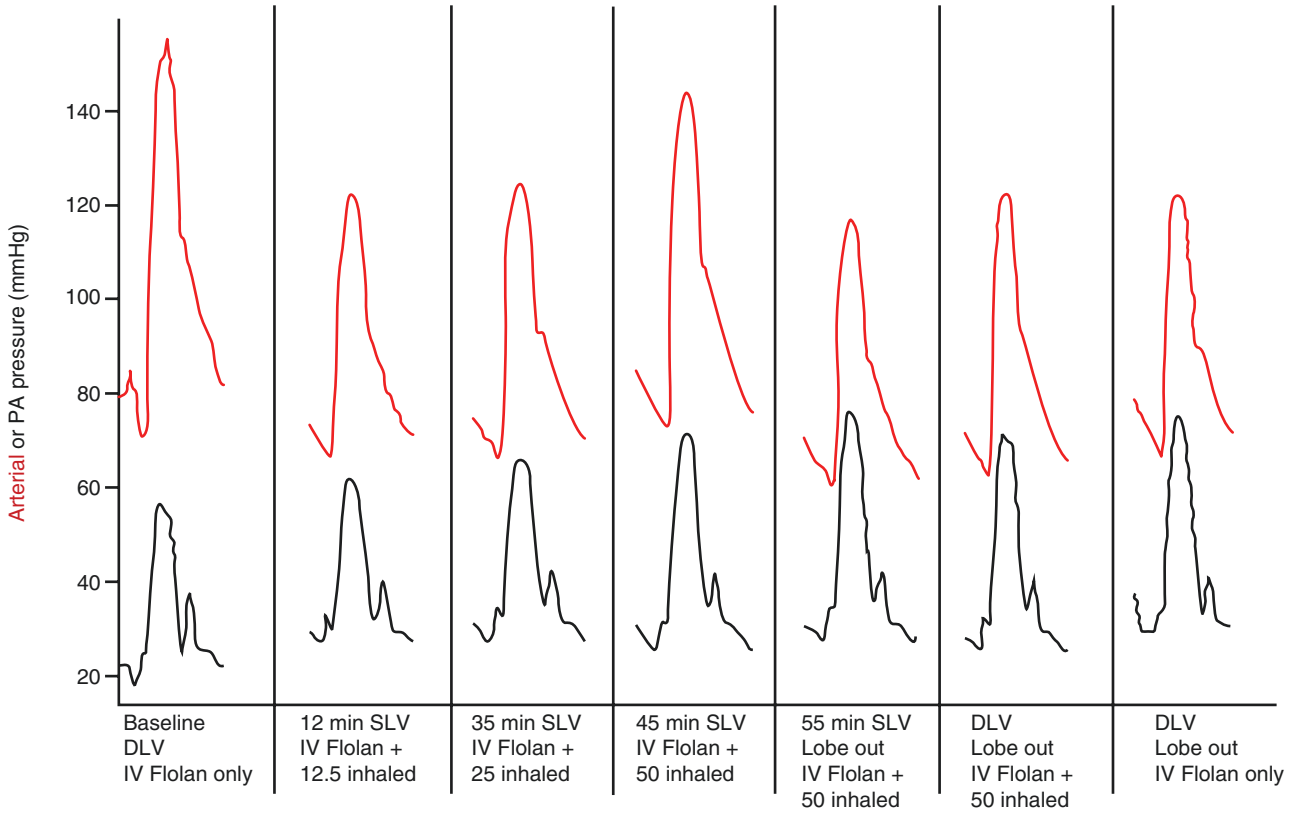

Fig. 34.3 Representative tracings of systemic and pulmonary arterial pressures during lung lobectomy in a patient with preexisting PAH. Representative simultaneous tracings of systemic arterial and pulmonary arterial (PA) pressures during lung lobectomy in a patient with preexisting PAH who was receiving intravenous (IV) Flolan (epoprostenol) preoperatively. With the transition from double-lung ventilation (DLV) to single-lung ventilation (SLV), the IV Flolan dose was decreased and inhaled Flolan initiated in order to maximize vascular dilation of the ventilated lung and potentially lessen the deleterious effects of systemic Flolan on hypoxic pulmonary vasoconstriction. Following lung resection and resumption of the preoperative Flolan dose, PA pressure remained elevated relative to baseline. (Reprinted from McGlothlin et al. [97] with permission from Elsevier)

Use of Extracorporeal Support for Pulmonary Resection (See Also Chap. 27)

There is growing use of extracorporeal life support, specifically extracorporeal membrane oxygenation (ECMO) in a variety of settings, including ARDS, cardiac failure, and transplantation. The use of extracorporeal support, such as ECMO or full cardiopulmonary bypass, during pulmonary resection surgery has been described in the literature, predominantly in cases involving large masses with significant cardiorespiratory compromise or procedures requiring tracheal or carina resection [120–123]. In patients with pulmonary hypertension, use of venoarterial ECMO allows for optimal gas exchange, as well as maintenance of cardiac output and coronary perfusion without increasing pulmonary pressures. Extracorporeal life support is presently limited to specialized centers and requires anticoagulation during its use which increases the risk for bleeding. Its use in pulmonary resection in the patient with pulmonary hypertension is presently not well-described in the literature and, however, presents an option requiring further investigation.

Postoperative Management

Postoperatively, patients presenting for pulmonary resection with significant pulmonary hypertension warrant admission to a unit with a higher-than-usual level of monitoring and care. Because of the significant cardiorespiratory compromise and the increased risk of postoperative complications, pulmonary hypertension patients require a postoperative setting capable of frequent, if not continuous, monitoring by skilled and experienced nursing care. Typically, this is an intensive care unit or a step-down unit with the ability to manage patients with invasive cardiovascular monitoring (such as invasive blood pressure monitoring, central venous pressure monitoring, or pulmonary artery catheters), patients who may require postoperative mechanical ventilation, and patients who require pharmacologic support with vasopressors, inotropes, or pulmonary vasodilators [7, 97]. It has been advocated that this should be a standard of care, irrespective of the intraoperative course [124].

In non-cardiac surgery, respiratory failure and right ventricular failure have been identified as the most common con-

tributors to early (less than 30 days) postoperative mortality among patients with pulmonary hypertension [6]. With respect to reducing the risk of pulmonary complications that may contribute to respiratory failure, a number of strategies have been shown to be of benefit, including chest physiotherapy, continuous positive airway pressure, and incentive spirometry. In upper abdominal and thoracic surgery, use of these techniques may reduce pulmonary complications by half [125–127]. Chest physiotherapy and continuous positive airway pressure may not be widely available and may pose some safety concerns in the frail or borderline patient with pulmonary hypertension. Incentive spirometry is an easy and inexpensive way of encouraging deep breathing and lung expansion [128]. As previously mentioned, excessive fluid administration can increase the risk of postoperative pulmonary and cardiac complications, and the rational fluid management strategy used intraoperatively should be continued in the postoperative period as well.

Right ventricular failure is a major cause of postoperative mortality in pulmonary hypertension patients, with one study citing it as a contributor to mortality in 50% of cases [6]. The potential causes of right ventricular failure are numerous and, in the immediate postoperative period, include pulmonary embolism, infection, bleeding/anemia, arrhythmias, and acute worsening of pulmonary hypertension. Among these causes, pulmonary embolism and infection should be protected against with appropriate intra- and postoperative prophylaxis. Ongoing bleeding and resulting anemia should be identified and addressed immediately, as hypovolemia and anemia both increase myocardial (specifically right ventricular) work and may be poorly tolerated.

Postoperative arrhythmias, specifically atrial tachyarrhythmias, are common after thoracic surgery and occur most frequently on postoperative days 2 and 3 [129]. Atrial fibrillation and flutter are both associated with right ventricular failure, clinical deterioration, and death and require immediate management [130]. In unstable patients, electrical cardioversion is the treatment of choice and should not be delayed [129, 130]. In terms of pharmacologic management of the stable patient with an atrial tachyarrhythmia, beta-blockers and calcium channel blockers should be used with caution, as their potential for reducing myocardial contractility and vasodilating effects may be poorly tolerated in pulmonary hypertension patients [97, 131]. Instead, amiodarone and/or digoxin may be considered for rhythm and/or rate control in these cases. Intravenous magnesium is another option commonly recommended in the literature for both treatment and prophylaxis of atrial arrhythmias post-thoracic surgery [129, 132], and at the authors' institution, lung resection patients are typically given 2.5–5 g of intravenous magnesium sulfate by slow infusion intraoperatively for arrhythmia prophylaxis. Care should be exercised, however, as rapid administration of magnesium can produce significant hypotension.

Worsening pulmonary hypertension is another potential cause of right ventricular failure post-lung resection and should be closely monitored for postoperatively. There are multiple mechanisms for worsening pulmonary pressures including increased right ventricular afterload following resection of a significant amount of lung parenchyma. This has been observed post-pneumonectomy [15, 16] but less so after subtotal lung resections [18]. Precipitants of pulmonary vasoconstriction, including acidosis, hypercarbia, hypoxia, hypothermia, and pain, should also be avoided in the postoperative period [133]. Patients who were previously managed on pulmonary vasodilators preoperatively should resume their pulmonary hypertension treatment as early as possible postoperatively to prevent rebound pulmonary hypertension. In patients who required pulmonary vasodilators intraoperatively, this may need to be continued postoperatively for a period of time and carefully weaned. Oral PDE-5 inhibitors have been shown to be very useful in weaning patients from iNO and preventing rebound pulmonary hypertension [134–137].

Finally, optimal pain management is important postoperatively. Inadequate pain control can exacerbate pulmonary hypertension [124, 138]. As previously discussed, thoracic epidurals, paravertebral blocks, and systemic opioids are all commonly used strategies, with thoracic epidurals demonstrating potential reduction in pulmonary complications and mortality [84, 85]. Admission to a postoperative area with higher monitoring capabilities is also important for initial pain management, as all analgesic strategies carry significant potential risk in pulmonary hypertension patients. Specifically, thoracic epidurals and paravertebral blocks may produce significant hypotension requiring vasopressors to manage, and systemic opioids can produce hypoventilation leading to hypercarbia and hypoxia that should be identified and addressed quickly. Furthermore, analgesia post-pulmonary resection should be done under the guidance of an acute pain service.

Conclusion

The patient with pulmonary hypertension has historically presented a significant challenge perioperatively, with a high risk for morbidity and mortality often precluding surgery. Improvements in diagnosis and management of pulmonary hypertension, in general as well as within the operating room, have allowed for safe management of these patients during the pulmonary resection surgery. However, significant risk remains, and the thoracic anesthetist must be knowledgeable and vigilant with respect to the assessment and management of these patients. This includes an understanding of the various etiologies of pulmonary hypertension and their pharmacologic management, as well as the intraop-

erative strategies (monitoring, pharmacology, ventilation, etc.) that are available to assist with preservation of right heart function and minimization of increases in pulmonary pressures during one-lung ventilation. Furthermore, effective postoperative analgesia is highly important in these patients. While pulmonary resection in patients with pulmonary hypertension is feasible, it should be done in a center with experienced care providers and with appropriate postoperative monitoring facilities.

Clinical Case Discussion

A 68-year-old woman is scheduled to undergo pulmonary resection for a recently diagnosed lung cancer. She initially presented with a worsening cough and shortness of breath, prompting a chest X-ray by her primary care physician. A right-sided lung lesion was seen, leading to additional investigations. A CT scan and CT-guided biopsy revealed a 3 cm × 5 cm × 3 cm right lower lobe mass, with pathology-confirmed squamous cell carcinoma.

Her past medical history includes 40 pack-year smoking history – she has quit smoking since her diagnosis, a few weeks ago. Her other past medical history includes hypertension, hypercholesterolemia, mild gastroesophageal reflux disease, and osteoarthritis of the hips and knees. She has a long-standing history of NYHA 2–3 dyspnea, preceding her recent cancer diagnosis.

She has been referred to a thoracic surgeon for management and has been offered a right lower lobectomy by video-assisted thoracoscopic surgery, possibly open.

What preoperative investigations should be arranged for this patient?

1. Pulmonary function testing:
   (a) FEV_1 70% predicted [ppoFEV_1 50%]
   (b) $FEV_1/FVC < 70\%$
   (c) DLCO 65% predicted [ppoDLCO 46%]
2. Six-minute walk test: 400 m walked, 80% predicted distance. Noted dyspnea during the testing, with desaturation events to as low as 88% on room air.
3. Arterial blood gas (on room air): pH 7.35, pCO_2 48, pO_2 70.
4. CT thorax: no significant bullous disease but evident diffuse centrilobular emphysema. The right lower lobe lesion in question is also seen.
5. Metastatic workup: no evidence of metastases.
6. ECG: sinus rhythm.
7. TTE: normal left ventricular size and function, with evidence of diastolic dysfunction. Mild right ventricular enlargement with low-normal function. There is mild tricuspid regurgitation with a right ventricular systolic pressure calculated at 55 mmHg. There are no other significant valvulopathy. Her blood pressure during the TTE was 140/92.
8. V/Q study: demonstrates preferential perfusion to the left lung (60%) relative to the right lung (40%).
9. Right heart catheterization: see below.

The investigations above reveal several key pieces of information. Pulmonary function testing shows abnormal spirometry consistent with moderate COPD. The DLCO is also abnormal, consistent with a diagnosis of COPD. The predicted postoperative values for the proposed procedure remain acceptable to proceed, however. Her 6-min walk test is suggestive of reduced cardiopulmonary reserve and may warrant further investigations to assess this. Her room air arterial blood gas is consistent with her underlying diagnosis of COPD. Her imaging and ECG are within expected parameters.

The decision to request further cardiac testing (an echocardiogram) is reasonable, given her cardiac risk factors (smoking history, hypertension, hyperlipidemia) and limited exercise ability due to dyspnea (with a limited 6-min walk test performance). Noninvasive stress testing is likely appropriate/indicated as well. Her TTE result shows clear evidence of pulmonary hypertension (elevated RVSP) with secondary signs of pulmonary hypertension (RV enlargement and impaired systolic function). Given the absence of any history or testing results suggestive of an alternative diagnosis, the underlying cause of her elevated pulmonary pressures is likely to be COPD.

The decision of whether to pursue further invasive cardiac testing, specifically a right heart catheterization, is debatable. The TTE findings are highly suggestive of pulmonary hypertension, and right heart catheterization may not provide additional information that would influence decision-making. While not as accurate as with right heart catheterization, her pulmonary-to-systemic systolic pressure ratios based on TTE remain less than 0.5, which is also reassuring. Noninvasive stress testing may be a more appropriate direction for further testing at this point, with any abnormalities observed prompting left- and right heart catheterization.

A ventilation-perfusion study was done to assess differential lung perfusion and is useful to determine tolerance of one-lung ventilation intraoperatively. The preferential perfusion of the left lung in this case is reassuring, as the risk for hypoxia and rising pulmonary pressures intraoperatively is likely lower despite the expected need to perform one-lung ventilation of the left lung. This is not an absolute predictor, however.

How do you rationalize the information provided by the investigations above? Do you proceed with the case?

This patient presents with a lung malignancy for resection. Her preoperative testing is suggestive of moderate COPD and reduced exertional tolerance and cardiopulmo-

nary reserve. Additionally, her echocardiogram shows clear evidence of pulmonary hypertension, likely related to her long-standing COPD. All of these findings are suggestive of an above-average risk for morbidity and mortality, based on the evidence in the literature concerning perioperative management of pulmonary hypertension patients [4–7].

However, recent evidence has shown that pulmonary resection in the setting of pulmonary hypertension (by TTE-based diagnosis) is not an absolute contraindication to surgery [14]. Given the presence of a single-lung lesion with no metastases, surgery presents a curative option for this patient. Additionally, the remainder of her workup would be considered acceptable for proceeding with surgery in the absence of pulmonary hypertension.

As such, proceeding with the proposed resection with caution is acceptable. A clear plan and discussion involving the patient and surgeon should be had prior to presenting to the operating room to discuss the elevated risk and the need for specialized intraoperative and postoperative monitoring. There should be a low threshold to abort the procedure should issues with pulmonary hypertension arise intraoperatively despite the adequate precautions and management.

What intraoperative monitoring should be available for this procedure?

Routine noninvasive monitors, including 5-lead ECG, pulse oximetry, capnography, temperature, and invasive and noninvasive blood pressure monitoring, are required for any pulmonary resection procedure. Invasive blood pressure monitoring is of critical importance in the patient with pulmonary hypertension, as it allows for accurate beat-to-beat blood pressure monitoring and facilitates arterial blood gas sampling for assessment of oxygenation and ventilation. Central venous access is recommended for this procedure, as management of hemodynamics with vasoactive substances will likely be required.

Pulmonary artery pressures should be monitored during this procedure, given the need to promptly address any acute rises in pulmonary pressures. The most common options for assessment of pulmonary pressures (and right heart function) are a pulmonary artery catheter or TEE. The decision of which option to employ, if not both, should be based on availability as well as potential risks and benefits as they pertain to this patient.

Typically, PACs are readily available and allow for continuous measurement of pulmonary pressures. In conjunction with invasive blood pressure monitoring, the pulmonary-to-systemic pressure ratio can be easily determined and optimally maintained. This patient has no contraindications to a PAC. However, interpretation of PAC data can be challenging. Furthermore, PACs do not provide direct monitoring of right ventricular functioning. Increases in PA pressures are undesirable but may be tolerated by a well-compensated right ventricle. Conversely, reductions in PA pressures may represent improvement in pulmonary vascular resistance or impending right ventricular failure and need to be interepreted in conjunction with other available parameters such as CVP and systemic blood pressure.

The availability of intraoperative TEE is increasing, but remains a significant barrier to its usage in non-cardiac surgery. TEE allows for monitoring of right ventricular function intraoperatively, which would be beneficial in this scenario, as preexisting right ventricular enlargement and impairment are present. Furthermore, TEE allows for assessment of global cardiac function. Potential limitations of TEE in this scenario, in addition to availability, include limited ability to assess pulmonary pressures directly, as RVSPs can be calculated, but not on a continuous basis. Furthermore, assessment of right ventricular function requires multiple TEE views, again making timely continuous monitoring difficult. Additionally, assessment of TEE views in the lateral position (as required for a thoracotomy or VATS) may be technically challenging.

Should an epidural be placed in this patient?

Given that the proposed pulmonary resection is planned as a VATS procedure, an epidural would typically not be offered to this patient. However, consideration may be given to an epidural (or paravertebral catheter) given the above-average risk for complications postoperatively associated with this patient. Epidurals provide superior analgesia compared to intravenous PCA and have been associated with reduced pulmonary complications and mortality [84, 85]. While this patient has acceptable predicted postoperative FEV_1 and DLCO, optimization of her pulmonary mechanics remains necessary given her pulmonary hypertension. The potential benefits related to an epidural need to be weighed against the potential for complications related to an epidural, as well as the potential for hypotension and possible cardiac dysfunction secondary to neuraxial blockade.

The decision to offer an epidural should also take into consideration the risks and benefits discussed above, as well as the risk for conversion to a thoracotomy (requiring a discussion with the surgeon), and patient preferences.

What strategies should be employed to prevent or manage rises in pulmonary artery pressures intraoperatively?

Rises in pulmonary artery pressures should be identified and dealt with immediately. Optimization of ventilation parameters, hemodynamics, and pharmacologic interventions should all be considered for this patient.

Transition from ventilation with two lungs to one-lung ventilation is a period associated with many potential triggers for worsening pulmonary artery pressures, specifically hypoxia and hypercarbia. For this patient, a lung-protective strategy employing higher F_iO_2 should be used to optimize ventilation of the left lung. To minimize the risk of hypoxia and avoid significant hypercarbia, the F_iO_2 should be maintained at 1.0 when initiating OLV. A tidal volume of 4–6 mL/kg

should be maintained, with the respiratory rate adjusted to target a $P_aCO_2 < 30–40$ mmHg. Normocapnia (or slight hypocapnia) is ideal; however, aggressive ventilation (higher tidal volumes or higher respiratory rates) can produce higher peak airway pressures leading to worsening pulmonary vascular resistance. The P_aCO_2 can be set to maintain a pH of greater than 7.2, provided there is no significant coexisting metabolic acidosis. The use of PEEP should be titrated carefully (0–10 cmH_2O), to maintain peak airway pressures below 30–35 cmH_2O, and may not be necessary in this patient, as obstructive lung disease tends to create intrinsic PEEP.

Maintenance of the pulmonary-to-systemic systolic pressure ratio at its baseline is also important intraoperatively, and higher ratios are associated with worse outcomes [6]. This can be achieved through augmentation of the systemic systolic pressure or by reducing pulmonary vascular resistance. Norepinephrine and vasopressin are the ideal vasopressors of choice to increase systemic vascular resistance and maintain right ventricular perfusion and cardiac output. Either agent should be started early should systemic pressure begin to drop with initiation of OLV. The use of pulmonary vasodilators should also be considered if pulmonary pressures increase significantly during the case. Consideration should be given to initiating iNO or epoprostenol IV to address this. iNO may be preferred, as its pulmonary selectivity means it can be initiated before OLV has started, and is unlikely to produce systemic vasodilation. iNO should be titrated to a maximum dose of 40 ppm before a second agent (such as epoprostenol IV) is added.

The threshold of concern for the absolute PA pressure, or pulmonary-to-systemic pressure ratio, is not well-defined in the literature but should take into account the patient's baseline ratio, in this case less than 0.5, and the right ventricular response to increased PA pressures. Continuous PA pressure monitoring using a PAC allows for the former, while TEE is more advantageous to assess the latter. For this patient, two scenarios should prompt discussion regarding aborting the case. First, a continually rising pulmonary-to-systemic ratio beyond 0.5 despite the use of systemic vasopressors and pulmonary vasodilators is highly concerning, given her preoperative baseline. Second, any PA pressure producing signs of RV dysfunction (based on TEE imaging or reduced PA pressures, rising CVP, and hypotension) that does not respond to vasopressors or pulmonary vasodilation is also a cause for alarm. At this point, two-lung ventilation should be restored (if possible), and a discussion about whether to proceed should occur.

The impact of surgical approach for the proposed pulmonary resection should also be considered. There is no evidence in the literature examining outcomes of VATS vs thoracotomy in pulmonary hypertension patients; however, both have been done successfully. A VATS approach is advantageous, since it produces less postoperative pain and, however, is more dependent on effective OLV and may be associated with longer operative time. A thoracotomy for this patient would necessitate a well-functioning epidural for postoperative pain but may allow for better surgical exposure and shorter periods of OLV. Improved surgical exposure through a thoracotomy also allows for advanced ventilation techniques (selective lobar ventilation, application of CPAP) that may be helpful for ventilation. For this patient, a discussion with the surgeon regarding surgical approach should occur preoperatively. It may be reasonable to attempt the procedure with VATS initially while having a low threshold to convert to an open thoracotomy should the surgeon believe this would expedite the surgery.

Where should this patient be admitted to postoperatively?

This patient requires admission to a unit with increased monitoring postoperatively, irrespective of intraoperative course. This should be a step-down unit at the very least; however, the need for intraoperative vasopressor or pulmonary vasodilator use should prompt admission to an intensive care unit.

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