# Pulmonary Hypertension

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## Introduction

Pulmonary hypertension (PH) is the result of a variety of disease pathomechanisms that ultimately causes an increased resting mean pulmonary artery pressure. The increased pressure, over time, exerts stress on the right ventricle and pulmonary vasculature, that is physiologically designed as a low-pressure system. Pulmonary vascular injury ensues and triggers abnormal cellular growth, inflammation and fibroproliferative changes.

Incidence and prevalence rates are difficult to establish due to significant disease heterogeneity—an epidemiologic study from the Netherlands reported an average incidence of 63.7 cases per million children per year [1]. PH-related hospital admissions have increased over time and the mortality associated with those admissions is higher compared to hospitalizations not associated with PH [2]. For the practicing anesthesia provider, children with PH will require careful assessment and management during the perioperative period because compared to all children undergoing general anesthesia, the rates of cardiac arrest during and after anesthesia and surgery are 20-fold higher in individuals diagnosed with PH [3].

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It is important to point out that adult and pediatric PH are quite different in many ways, including genetics, natural history and responsiveness to drug therapies. Also, persistent pulmonary hypertension of the newborn should be considered a separate disease.

## Definition and Diagnosis

In-utero, the pulmonary vasculature is constricted (e.g. pulmonary vascular resistance [PVR] is high) and supports only minimal flow as the majority of blood ejected into the main pulmonary artery is shunted into the systemic circulation via the ductus arteriosus. Shortly after birth, with alveolar gas expansion, the pulmonary vasculature dilates and PVR drops precipitously, reaching adult levels at 2–3 months of age. As such, PH is defined as resting mean pulmonary artery pressure equal to or exceeding 25 mmHg. Pediatric PH is currently classified using the same system that is applied to adult patients (WHO classification with five groups) [4], although experts recommend a transition to the Panama classification system (ten categories) [5], which is more specific to pediatric patients. The latter classification system was released by the pulmonary vascular research institute which also provides a more detailed definition of their preferred term, pulmonary vascular hypertensive disease (PVHD): mean pulmonary artery pressure (mPAP) > 25 mmHg and pulmonary vascu-


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lar resistance index (PVRI) > 3 Wood Units/$m^2$ for biventricular circulations; and PVRI > 3 WU/$m^2$ or transpulmonary gradient > 6 mmHg even if mPAP < 25 mmHg for univentricular circulations after palliative cavopulmonary anastomosis [5].

Echocardiography is considered the best initial non-invasive screening test and can provide a myriad of information including systolic pulmonary artery pressure (sPAP), right ventricular systolic pressure, mean pulmonary artery pressure (mPAP), end-diastolic pulmonary artery pressure, right ventricular systolic function, right ventricular strain, right ventricular volume, right ventricle-to-left ventricle diameter ratio and right atrium/ventricle dimensions [6]. In regards to adverse events in pediatric patients undergoing surgery under anesthesia, the ratio of either mean pulmonary artery pressure to mean systemic artery pressure or systolic pulmonary artery pressure to systolic systemic blood pressure can be used for risk stratification: values >0.75 are associated with a higher risk. The ratio can also be used to further define PH: <0.7 subsystemic PH; 0.7–1.0 systemic PH; >1.0 suprasystemic PH. Other risk factors for major complications include: calculated RVSP >64 mmHg, presence of syncope or dizziness, and idiopathic PAH [7]; elevated mean right atrial pressure [8]; and suprasystemic PAP, heritable PAH, decreased RV function, decreased pulmonary capacitance index, and treatment naïveness [9]; suprasystemic PH, young age, home oxygen use, encroaching of the hypertensive RV on the left heart leading to left ventricular restriction and functional impairment ("septal bowing" on echo) [10].

Right heart catheterization can confirm the diagnosis and provide additional useful information including severity, response to vasodilator therapy and exclusion of other treatable causes.

## Treatment

Treatment of pulmonary hypertension aims at reducing symptoms, improving quality of life and retarding clinical deterioration. Even though mortality has decreased with the institution of PH-targeted medical therapy, a cure cannot be achieved without definitive surgical care, namely lung transplantation. Other surgical interventions (such as atrial septostomy, Potts shunt, pulmonary artery denervation) are being continuously examined for their potential of palliation. Supportive treatment of pulmonary hypertension includes supplemental oxygen, anticoagulation, diuretics, digitalis and mineralocorticoid receptor antagonists (spironolactone, eplerenone). Calcium channel blockers are prescribed if the patient exhibits a positive response during acute vasoreactivity testing. Pulmonary artery hypertension-targeted therapy includes medications that act on three major pathways: NO/cGMP pathway (sildenafil [oral, intravenous], tadalafil [oral]), endothelin pathway (Bosentan [oral], Ambrisentan [oral]) and prostacyclin pathway (Epoprostenol [intravenous], Trepostinil [intravenous, subcutaneous, inhaled], Iloprost [intravenous, inhaled]). Other medications that are frequently employed in the critical care setting include milrinone, levosimedan and inhaled nitric oxide [11].

## Anesthetic Considerations: Perioperative Care

Prior to induction of anesthesia, a well-formulated plan should be established. During review of preoperative tests, particular attention needs to be paid to the presence of atrial or ventricular communications. If such a communication is present, air bubble precautions should be employed.

If the patient is on long-term medications that address PH, care should be taken to continue those agents in the perioperative period. Intravenous agents require special consideration: continuous infusions of prostacycline or iloprost should never be interrupted. If any problems with the pre-existing access (typically a peripherally inserted central catheter or Broviac catheter) arise through which the medications are delivered, a peripheral intravenous catheter (PIV) should be expeditiously inserted and therapy resumed as soon as possible as the half-life of some of those agents is rather short (epoporostenol = 4 min; treprostinil = 4.5 h).

The sympathetic stimulation from pre-induction PIV access or even mask induction bears the risk of an increase in PVR. Consequently, adequate anx-

iolysis and sedation can be very valuable. Routinely used agents include benzodiazepines (midazolam, 0.5–1 mg/kg by mouth, up to 20 mg) and ketamine (3–8 mg/kg by mouth). Dexmedetomidine and clonidine are other alternatives.

Hypovolemia from preoperative fasting can compromise right ventricular preload, thus, if intravenous access is available, a pre-induction fluid bolus should be considered (10–15 cc/kg).

Induction of anesthesia can be achieved via the intravenous or inhalational route. Both approaches have advantages and disadvantages. Intravenous induction requires vascular access and allows immediate intervention in case of hemodynamic instabilities or airway problems. Propofol, an otherwise frequently used induction agent, must be used with caution and preferably titrated to effect. Its significant actions on peripheral vascular resistance can jeopardize right ventricular coronary perfusion, especially in patients with right ventricular hypertrophy. Etomidate is an alternative induction agent that maintains cardiac contractility and has no significant effects on SVR and PVR [12]. The main concern with use of etomidate is its suppressive effect on adrenal cortisol production by inhibition of 11-β-hydroxylase. Ketamine is frequently used due to its ability to maintain systemic and pulmonary vascular resistance. Its use appears to be safe in children with pulmonary hypertension [8, 13, 14].

Inhalation induction is a possibility but tricky because it carries significant risks: (a) loss of the airway from obstruction or laryngospasm during induction will quickly lead to hypoxemia and hypercapnia, thus increasing pulmonary vascular resistance and possibly resulting in pulmonary hypertensive crisis or right ventricular ischemia; (b) in the uncooperative and inadequately sedated child, agitation will prolong induction and may also result in increases in pulmonary vascular resistance; (c) volatile agents are potent vasodilators and higher induction doses may result in a decrease in systemic vascular resistance, systemic hypotension and possible right ventricular ischemia.

Volatile anesthetics are associated with clinical pulmonary vasodilation and are therefore a good choice for maintenance of a general anesthetic [15, 16].

Nitrous oxide mildly depresses cardiac output and decreases heart rate and mean blood pressure but has no significant effects on PVR [17]. It can therefore be considered for induction or awake PIV placement, but the potential for hypoxia from delivery of a hypoxic gas-mixture should be kept in mind.

Dexmedetomidine can be used in multiple ways, this includes premedication, as an adjunct during general anesthesia and for peri- and post-procedural sedation. A study by Friesen et al. investigated dexmedetomidine loading in children with pulmonary hypertension. The group confirmed a significant increase in systemic vascular resistance but did not find any increases in pulmonary vascular resistance [18].

Opioids are an integral part of the anesthetic to blunt sympathetic responses to laryngoscopy, incision and other noxious stimuli. Fentanyl has been shown to have no effects on PVR [19]. Depending on the length and invasiveness of the procedure, a variety of different opioids may be employed. Care should be taken to avoid over-narcotization due to the risk of hypoventilation after extubation with subsequent hypercapnia. For this reason, remifentanil is the preferred opioid.

The anesthesiologist needs to weigh benefits and risks of both induction choices and tailor the anesthetic to each individual case. If an inhalational induction is chosen, a sufficient level of sedation will greatly aid in the induction process.

Intraoperative monitoring should include standard American Society of Anesthesiologists (ASA) monitors. Electrocardiography monitoring should be extended to include five leads in order to increase the likelihood of ischemia detection. The threshold of using invasive blood pressure monitoring should be low, although certain shorter, less invasive procedures or diagnostic exams can be performed with non-invasive blood pressure monitoring. Continuous capnography is essential in the care of these patients as it aids in ensuring normocarbia (to avoid PVR increases from hypoventilation) and can help detect sudden decrease in pulmonary blood flow.

For procedures with limited invasiveness and an uneventful anesthesia course, the child can be extubated in the operating room. Recovery often occurs in an intensive care unit setting in order to closely monitor hemodynamics, but patients with milder forms of PH undergoing diagnostic proce-

dures or smaller surgical procedures can be transported to the postanesthesia recovery unit.

Patients with PH remain at higher risk for adverse events in the postoperative period. It is important to note that almost 50% of postoperative cardiac arrests are triggered by respiratory events because the patient with PH is especially vulnerable to hypercarbia secondary to hypoventilation and/or airway obstruction resulting in rapid increases in PVR. Hence, close monitoring of the respiratory status and judicious use of respiratory depressants, such as narcotics and sedatives, is paramount. Table 48.1 summarizes pertinent aspects of anesthetic care for patients with pulmonary hypertension.

## Anesthetic Considerations: Pulmonary Hypertensive Crisis

A feared complication in patients with PH is the development of a pulmonary hypertensive crisis. Various stimuli can lead to a sudden increase in PVR with subsequent right ventricular failure. More precisely, an increase in right ventricular afterload causes an increase in end-diastolic volume and a decrease in right ventricular stroke volume and cardiac output. In the setting of ventricular interdependence, stroke volume from the left ventricle is reduced by decreased preload from reduced right ventricular stroke volume and increases in right ventricular end-diastolic vol-

**Table 48.1** Essential points summarizing care of newborns, children and adolescents with pulmonary hypertension

| Plan/preparation/adverse events | Reasoning/management |
|---|---|
| • If deep sedation without intubation is planned, have back up device for positive pressure ventilation available for immediate use<br>• In addition, all emergency drugs including muscle relaxant must be readily available | • Hypoxia and hypercapnia as a result of inadequate spontaneous ventilation lead to an increase in pulmonary vascular resistance and may cause right ventricular failure |
| • For patients receiving PAH-modifying drugs by intravenous infusion, care must be taken to continue those drugs perioperatively. A dedicated line should be used and interruptions in medication delivery should be avoided | • PAH-modifying drugs administered by the intravenous route have significant effects on the pulmonary vasculature. Interruptions in delivery can have detrimental effects |
| • Pulmonary hypertensive crisis—triggers | • Hypoxia<br>• Hypercapnia<br>• Acidosis<br>• Pain<br>• Tracheal suctioning<br>• Hypothermia<br>• Fever<br>• Interruption of prostanoid infusion<br>• Arrhythmias<br>• Pulmonary infections<br>• Pulmonary embolism<br>• Myocardial ischemia/infarct |
| • Pulmonary hypertensive crisis—treatment | • Hyperventilation<br>• $FiO_2 = 100\%$<br>• Deepen anesthetic<br>• Avoid bradycardia<br>• Sodium bicarbonate to correct acidosis<br>• Treat arrhythmias<br>• Medications:<br>– Inhaled nitric oxide<br>– Inhaled postanoid (iloprost)<br>– Intravenous prostanoid (epoprostenol)<br>– Intravenous sildenafil<br>– Inodilators (milrinone); may need to be combined with vasopressor (vasopressin, norepinephrine, epinephrine) if systemic hypotension occurs<br>• VA/VV-ECMO |

ume cause a septal shift towards the left side. Pulmonary hypertensive crises can progress into a vicious cycle (Fig. 48.1): the increased right ventricular end-diastolic volume increases wall tension which, in turn, decreases coronary perfusion. Ischemia and myocardial infarct can occur; this worsens right ventricular function and introduces a potential downward spiral [20].

Triggers for pulmonary hypertensive crises include noxious stimuli (pain from surgical incisions, laryngoscopy), hypoxemia, hypercapnia, acidemia, hypothermia, fever and interruption of prostanoid infusion [21, 22]. Avoidance or rapid recognition and treatment of those factors are the best methods to prevent the occurrence of pulmonary hypertensive crises.

If a patient with PH suffers a perioperative acute pulmonary hypertensive crisis, prompt recognition and treatment are of utmost importance as rapid decompensation towards cardiac arrest can occur. In the intubated patient, hyperventilation with an $FiO_2$ of 100% should be instituted. The anesthetic should be deepened to protect the patient from noxious stimuli that can provoke progression of the pulmonary hypertensive crisis. Inhaled nitric oxide (20–40 ppm) will decrease PVR with minimal systemic effects. If hemodynamic support is required, inodilators such as milrinone and dobutamine can reduce PVR and support cardiac contractility. Acidosis should be corrected with sodium bicarbonate [22].

Children with newly diagnosed PH that are treatment-naïve have the highest risk for developing pulmonary hypertensive crises due to their highly reactive pulmonary vasculature. In contrast, patients with longstanding, chronic PH on therapy develop progressive right ventricular hypertrophy and strain, placing them at higher risk for right ventricular ischemia secondary to coronary hypoperfusion [3].

## Outcomes

While PH is an indisputable factor that leads to an increase in morbidity and mortality during sedation and general anesthesia, it appears that specialized

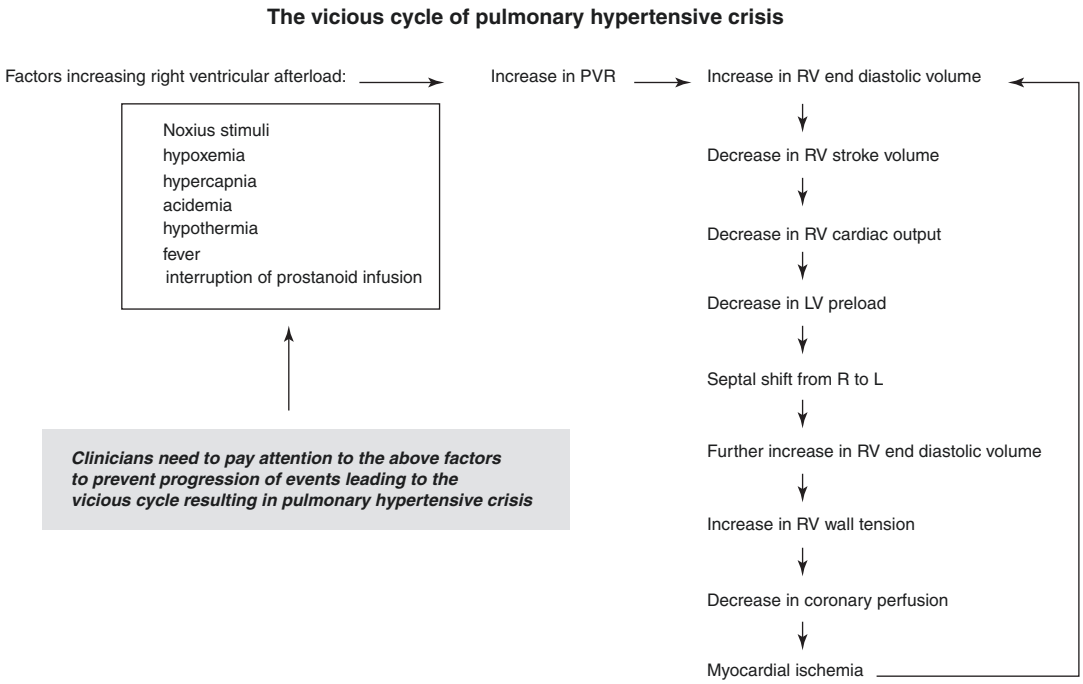


**Fig. 48.1** Modifiable factors in the perioperative period that cause an increase in pulmonary vascular resistance that may precipitate pulmonary hypertensive crisis. Increases in pulmonary vascular resistance can quickly trigger a vicious cycle as myocardial ischemia leads to further increases in right ventricular end-diastolic volume and a decrease in right ventricular cardiac output

centers with dedicated pediatric anesthesiologists familiar with this disease can limit the risks and improve outcomes. Data from the MAGIC registry documented a low adverse event rate with no periprocedural deaths during 177 cardiac catheterizations in children with PH [23].

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