

# Perianesthetic Management of Children with Pulmonary Arterial Hypertension

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## Introduction

Pulmonary arterial hypertension (PAH) is defined as the presence of a mean pulmonary artery pressure that exceeds 25 mmHg at rest or 30mmHg during exercise. PAH can be idiopathic (primary) or associated with a variety of underlying causes including congenital heart disease, chronic lung disease, chronic airway obstruction, and chronic liver disease. PAH and its anesthetic considerations have been reviewed (1-3).

PAH has been shown to add significantly to perioperative risk. Reich *et al.* (4), in a retrospective analysis, determined that pulmonary hypertension was a predictor of perioperative myocardial infarction and death in a large cohort of adult patients undergoing coronary artery bypass grafting. Ramakrishna *et al.* (5) reported a high incidence of early postoperative morbidity and a mortality rate of 7% in adults with PAH who had undergone noncardiac surgery. In a retrospective study of pediatric and adult patients with congenital heart disease undergoing noncardiac surgery, Warner *et al.* (6) found that PAH was a predictor of perioperative morbidity. A retrospective analysis of children with PAH who had undergone noncardiac surgery or cardiac catheterization (7) demonstrated incidences of major complications (cardiac arrest or pulmonary hypertensive crisis) and death that were many times greater than those reported in all children undergoing surgical procedures (8) or cardiac catheterizations (9).

## Cardiovascular Risks

Several mechanisms can be associated with hemodynamic deterioration in patients with PAH. Of critical importance among these mechanisms is a rapid increase in PVR related to pulmonary arterial vasoreactivity. Hypercarbia, hypoxia, acidosis, and noxious stimuli such as pain and airway instrumentation can trigger a rapid increase in PVR (10-13) that can lead to a pulmonary hypertensive crisis and/or right heart failure. A pulmonary hypertensive crisis is characterized by a rapid increase in PVR to the point where pulmonary artery pressure (PAP) exceeds systemic blood pressure. The resulting right heart failure leads to a decrease in pulmonary blood flow, decreased cardiac output, hypoxia, and biventricular failure (14).

Other mechanisms can also contribute to cardiac failure in patients with PAH. Right ventricular dilatation can compress the septal wall of the left ventricle, leading to inadequate filling of the left ventricle, decreased stroke volume, and decreased cardiac output. Hypovolemia can provide inadequate preload to the right ventricle, leading to decreases in stroke volume, cardiac output, and pulmonary blood flow. Systemic hypotension or a decrease in systemic vascular resistance (SVR) can cause a decrease in coronary artery blood flow, leading to biventricular ischemia. Hypoxemia related to problems with ventilation, lung disease, or decreased pulmonary blood flow can further impair ventricular function.

## Anesthetic Management

The goals of anesthetic management are to provide adequate anesthesia and analgesia for the surgical procedure, minimize stimuli for pulmonary vasoconstriction, minimize systemic cardiovascular depression, and maintain the ability to treat increases in PVR if they occur. Depending on the procedure, these goals can be met through *sedation/analgesia* or *general anesthesia*. In a review of 156 children with PAH undergoing 256 procedures, sedation vs. general anesthesia was not a contributing factor to the occurrence of complications (7). Similarly, *airway management* (natural airway, laryngeal mask airway, or endotracheal tube) was not significantly associated with complications (7). However, rapid intervention is extremely important in the treatment of rising PVR, and the anesthesiologist must maintain the ability to immediately assist or control ventilation. Furthermore, oversedation does occur during procedural sedation (15) and can be associated with hypercarbia, hypoxemia, and airway obstruction in patients managed with a natural airway and spontaneous ventilation (16). For those reasons, the use of endotracheal tubes and laryngeal mask airways is often preferred.

### **Anesthetic Drugs**

No single anesthetic agent is ideal for patients with PAH. Many anesthetics exhibit mixed hemodynamic effects, such as pulmonary vasodilatation along with depression of myocardial contractility, and may be unacceptable when used in full anesthetic dosage. We usually employ a balanced anesthetic technique, in which subanesthetic doses of several drugs are combined to provide general anesthesia. Typically, we use oral or intravenous midazolam for premedication. Induction is cautiously achieved with midazolam, fentanyl, a small dose of propofol, and/or a low concentration of sevoflurane. Anesthesia is maintained with intermittent fentanyl and isoflurane. Rocuronium or pancuronium are used for neuromuscular blockade as indicated.

The *volatile anesthetics* have been shown to have a variety of effects on the pulmonary vasculature, some of which are conflicting and incompletely understood (1,2), and can cause dose-dependent depression of cardiac contractility and reduction of SVR. Most clinical studies of the effects of volatile anesthetics on the pulmonary vasculature have been performed in the setting of one lung ventilation and are not fully applicable to the pulmonary hypertensive patient. In general, isoflurane and sevoflurane are associated with clinical pulmonary vasodilatation and are accepted components of a balanced anesthetic technique in patients with PAH.

*Nitrous oxide* was shown to have little effect on pulmonary hemodynamics in children with PAH (17); however, its effect on alveolar PO<sub>2</sub> should be kept in mind.

*Fentanyl* has minimal pulmonary and systemic hemodynamic effects (18), attenuates the pulmonary vascular response to noxious stimuli (11), and plays an important role in a balanced anesthetic in children with PAH. The bradycardia observed in association with *remifentanyl* can cause a decrease in cardiac output (19,20) that can be problematic.

*Benzodiazepines* are associated with minimal hemodynamic effects. Midazolam has become an important part of our balanced anesthetic; we use it as preanesthetic medication and/or intraoperatively. It is usually not a significant ventilatory depressant when used for presurgical sedation in children with congenital heart disease (21).

*Propofol* has not been thoroughly studied regarding direct effects on the pulmonary vasculature, but they do not appear to be great. Propofol has been used successfully in patients with PAH. However, the systemic hemodynamic effects of propofol warrant caution in its use in patients with severe PAH and/or right heart failure. A bolus of propofol administered to healthy adults (22), a sedative infusion administered to postoperative adults with coronary artery disease

(23), and an infusion to children undergoing cardiac catheterization (24) caused significant decreases in systemic blood pressure and cardiac output. The mechanisms are a marked decrease in systemic vascular resistance and a moderate decrease in cardiac contractility.

*Ketamine* is generally not used in patients with PAH because it has been associated with increases in PVR or PAP in several clinical studies. The clinical conditions under which ketamine has been studied, however, have been so variable that a consensus interpretation has been somewhat difficult. Hickey demonstrated that systemic hemodynamics of children with congenital heart disease were not significantly affected by ketamine (25). The same study found no significant effect of ketamine on PAP and PVR, even when baseline PAP and PVR were elevated; however, those subjects were intubated and receiving supplemental oxygen and mechanical ventilatory support. Significant increases in PVR and PAP were observed following ketamine bolus in three studies of children undergoing cardiac catheterization (26-28). Subjects in these studies were breathing room air through an unaided airway, raising the possibility that the changes in PVR and PAP were associated with ventilatory depression. However, two of these studies documented that  $PO_2$  and  $PCO_2$  did not change following ketamine. The important observation from these studies is that the subjects with the highest PVR and PAP at baseline generally had the most vigorous pulmonary vascular responses to ketamine (26,28). A recent unpublished study of ketamine in 10 children with PAH demonstrated minimal pulmonary vascular responses to ketamine; however, subjects were anesthetized with sevoflurane at the time (29).

*Etomidate* is known for its lack of systemic hemodynamic effects in patients with heart disease, but its pulmonary vascular effects have not been investigated adequately. A bolus of etomidate to 12 children undergoing cardiac catheterization appeared to cause elevation of PVR, but the response was highly variable (30).

### **Treatment of Pulmonary Hypertensive Crisis**

The goals of treatment are to vasodilate the pulmonary vasculature, support cardiac output, and remove stimuli associated with increases in PVR.

1. *Administer 100% oxygen.* Increasing  $PO_2$  can decrease PVR (10).
2. *Hyperventilate to induce a respiratory alkalosis.* PAP was directly related to  $PCO_2$  in mechanically ventilated children with congenital heart disease (12).
3. *Correct metabolic acidosis.* PVR is directly related to  $H^+$  concentration (31).
4. *Administer pulmonary vasodilators.* Inhaled nitric oxide (iNO) is generally the first drug of choice. Pulmonary vasodilators are discussed in detail below.
5. *Support cardiac output.* Adequate preload is important. Inotropic support is often necessary. A variety of inotropic drugs can be used. Dobutamine reduces PVR, but often dopamine is preferred in order to maintain SVR and enhance coronary perfusion.
6. *Attenuate noxious stimuli (provide analgesia).* Noxious stimuli, such as pain and tracheal suctioning, can increase PAP. These responses can be attenuated by pretreatment with fentanyl (11).

### **Pulmonary Vasodilators**

*Inhaled nitric oxide* (iNO) provides selective pulmonary vasodilatation and is the first drug of choice for intraoperative use because of its effectiveness, rapid onset, and ease of administration. Its biochemistry has been reviewed (32). iNO bypasses the damaged pulmonary vascular endothelium present in pulmonary hypertensive disorders and diffuses into the vascular

smooth muscle cell, where it activates soluble guanylate cyclase. This increases cGMP concentrations resulting in vasodilatation (3). In children with systemic or suprasystemic PAH, we administer iNO through the breathing circuit intraoperatively beginning with anesthetic induction. Postoperatively, it is continued via mask or nasal cannulae (33) until the patient is stable and weaned over time. Rebound pulmonary hypertension following weaning of iNO can occur, especially after a prolonged or severe pulmonary hypertensive episode (34,35).

*Phosphodiesterase (PDE) inhibitors* block the hydrolysis of cGMP, thus increasing the concentration of cGMP in the vascular smooth muscle cell. The PDE-5 inhibitors, sildenafil and dipyridamole, are highly effective pulmonary vasodilators with rapid onset of action and the ability to attenuate rebound hypertension following withdrawal of iNO (34,35). Sildenafil must be administered orally; if needed intraoperatively, it can be administered via a nasogastric tube. Milrinone, a PDE-3 inhibitor, is a less specific blocker of cGMP hydrolysis, but is often used perioperatively because it decreases PVR while augmenting myocardial contractility.

*Prostacyclin* analogs cause vasodilatation by increasing cAMP concentration through stimulation of adenylate cyclase and have proven to be highly effective in the treatment of PAH. They are characterized by rapid onset of action and very short half-lives. Epoprostenol, the most studied, is administered by continuous iv infusion; chronic therapy has vastly improved the five-year survival of children with idiopathic (primary) PAH (36). Many children with idiopathic PAH who are on epoprostenol therapy require anesthesia for central venous line placement or replacement; it is important that the epoprostenol infusion remain uninterrupted because of its extremely short half-life. Other analogs include treprostinil (subcutaneous), iloprost (inhaled), and beraprost (oral).

Other drugs are more suitable for chronic treatment. The *endothelin antagonist*, bosentan, does not act acutely but is a promising chronic pulmonary vasodilator. *Calcium channel blockers*, such as diltiazem, can be useful for chronic treatment of patients with reactive PAH; however, they may be detrimental to patients with nonreactive, fixed PAH because accompanying decreases in SVR and cardiac output can decrease coronary blood flow and increase right-to-left septal shift.

## Summary

PAH is associated with significant perioperative risk for major complications. It is important that anesthesiologists be aware of this increased risk, understand the pathophysiology of PAH, form an appropriate anesthetic management plan, and be prepared to treat a pulmonary hypertensive crisis.

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