Review article

Anesthetic management of children with pulmonary arterial hypertension

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Summary
Pulmonary arterial hypertension (PAH) is associated with significant perioperative risk for major complications, including pulmonary hypertensive crisis and cardiac arrest. Several mechanisms of hemodynamic deterioration, including acute increases in pulmonary vascular resistance (PVR), alterations of ventricular contractility and function and coronary hypoperfusion can contribute to morbidity. Anesthetic drugs exert a variety of effects on PVR, some of which are beneficial and some undesirable. The goals of balanced and cautious anesthetic management are to provide adequate anesthesia and analgesia for the surgical procedure while minimizing increases in PVR and depression of myocardial function. The development of specific pulmonary vasodilators has led to significant advances in medical therapy of PAH that can be incorporated in anesthetic management. It is important that anesthesiologists caring for children with PAH be aware of the increased risk, understand the pathophysiology of PAH, form an appropriate anesthetic management plan and be prepared to treat a pulmonary hypertensive crisis.

Keywords: anesthesia; cardiac; pediatric; pulmonary hypertension

Introduction
Pulmonary arterial hypertension (PAH) is defined as the presence of a mean pulmonary arterial pressure that exceeds 25 mmHg at rest or 30 mmHg during exercise in association with variable degrees of pulmonary vascular remodeling, vasoconstriction, and in situ thrombosis (1,2). In 1998 a clinical classification of PAH (Table 1) was proposed that incorporates pathophysiological mechanisms, clinical presentation, and therapeutic options and is now widely used in clinical practice (2).

Physical examination of patients with PAH may include prominent right ventricular impulse or heave, pulmonary ejection click, narrowly split second heart sound with a loud pulmonic component, systolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, and jugular venous distension. Characteristics of the chest radiograph include prominence of the main pulmonary artery, pruning of the distal pulmonary arteries and cardiomegaly. Right ventricular hypertrophy and, possibly, right atrial enlargement are noted on the
electrocardiogram. Echocardiographic findings suggestive of PAH include a tricuspid regurgitation Doppler velocity greater than 2.5 m s⁻¹ or an estimated systolic pulmonary artery pressure (PAP) that is more than 50% of systemic systolic arterial blood pressure (3). The diagnosis and severity of PAH is confirmed by right heart catheterization.

Children with pulmonary hypertension typically have an increased requirement for medical resources (3). Many receive general anesthesia for the multiple diagnostic and therapeutic procedures that are required for the assessment and management of their PAH and the underlying disease that caused it. Additionally, these patients may undergo general anesthesia for indications unrelated to pulmonary hypertension. The pathophysiology of PAH has been reviewed (4–6) as have the associated anesthetic considerations for adult patients (4,5). It is widely accepted that patients with PAH deserve special consideration because they are at increased risk from anesthesia and surgery (4,5,7,8).

### Perioperative risk

Pulmonary arterial hypertension has been shown to add significantly to perioperative risk. Experience with adult patients is more extensive than that with children. PAH was a predictor of perioperative myocardial infarction and death in a large cohort of adult patients undergoing coronary artery bypass grafting (9). Adults with PAH experienced a high incidence of early postoperative morbidity and a mortality rate of 7% associated with noncardiac surgery (10). The preoperative ratio of mean arterial pressure to mean PAP was shown to be an independent predictor of hemodynamic complications in adult cardiac surgical patients (11). In a retrospective study of pediatric and adult patients with congenital heart disease undergoing noncardiac surgery, PAH was a predictor of perioperative morbidity (12). A study of 2484 infants and children undergoing cardiopulmonary bypass for repair of congenital heart disease concluded that preoperative PAH was a significant risk factor for postoperative in-hospital death (13). Two recent retrospective analyses of children with PAH who had undergone noncardiac surgery or cardiac catheterization (7,14) demonstrated incidences of major complications (cardiac arrest or pulmonary hypertensive crisis) and death that are many times greater than those reported in all children undergoing surgical procedures (15,16) or cardiac catheterizations (17) (Table 2). The severity of baseline PAH correlated with the incidence of major complications; children with suprasystemic PAP were eight times more likely to experience a major perioperative complication than were those with subsystemic PAP (7).

### Cardiovascular risk mechanisms

Several mechanisms are associated with hemodynamic deterioration in patients with PAH. Of
critical importance among these is a rapid increase in pulmonary vascular resistance (PVR) in response to a variety of stimuli, including alveolar hypoxia, hypoxemia, hypercarbia, metabolic acidosis, and activation of the sympathetic nervous system by noxious stimuli. Both hypoxemia and alveolar hypoxia are independent and additive pulmonary vasoconstrictors (18–20), and evidence suggests that alveolar hypoxia is the more potent of these (20). PVR increases as PaO2 decreases below 60 mmHg (21). Acidosis causes pulmonary vasoconstriction, and when both acidosis and hypoxia are present, the increase in PVR is dramatically greater (21). Both respiratory and metabolic acidosis cause an increase in PVR, and changes in PaCO2 correlate with changes in PVR and PAP (22,23). Acute exacerbations of PAH have been reported following tracheal suctioning or intubation (24–26).

A rapid increase in PVR can lead to a pulmonary hypertensive crisis and/or right heart failure. A pulmonary hypertensive crisis is life-threatening and is characterized by a rapid increase in PVR to the point where PAP exceeds systemic blood pressure. Right ventricular ejection fraction decreases acutely and can rapidly progress to right ventricular failure. In the absence of a patent foramen ovale or atrial septostomy, right heart failure leads to further decreases in pulmonary blood flow, decreased cardiac output, and biventricular failure (27). In the presence of an interatrial communication, right-to-left shunting augments left atrial filling, thus supporting left ventricular output and coronary blood flow. Hypoxemia is observed in the presence of right-to-left intracardiac shunting or ventilation/perfusion mismatch from intrapulmonary shunting (28). Symptoms and physical signs accompanying a pulmonary hypertensive crisis may include syncope, dyspnea, cyanosis, pallor, bradycardia, right ventricular heave, and bronchospasm.

Other circulatory mechanisms can contribute to cardiac failure in patients with PAH. Among patients with pulmonary vascular disease, right ventricular function was impaired in 94% and left ventricular function was reduced in 20% (29). Right ventricular dilation can displace the septal wall of the left ventricle, leading to inadequate filling of the left ventricle, decreased stroke volume, and decreased cardiac output (4,26). Hypovolemia can result in 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 impaired ventilation, lung disease, or decreased pulmonary blood flow can further depress ventricular function.

**Anesthetic drugs**

The effects of volatile anesthetics on the pulmonary vasculature have been summarized in several recent reviews (4,5,30). Volatile anesthetics attenuate hypoxic pulmonary vasoconstriction, thereby decreasing ventilation-perfusion matching. In adults undergoing coronary artery bypass grafting, both isoflurane and sevoflurane were associated with increased blood flow to lung areas with a low ventilation/perfusion ratio but only sevoflurane significantly depressed PaO2 (31). Isoflurane and halothane (but not enflurane) potentiate the vasodilator response to β1 adrenoceptor activation. Isoflurane has no effect on the vasoconstriction response to α1 adrenoceptor activation whereas desflurane potentiates it. Isoflurane, halothane, enflurane, and desflurane (but not sevoflurane) inhibit endothelium-dependent relaxation by inhibiting the activity of the adenosine triphosphate-sensitive potassium

### Table 2

<table>
<thead>
<tr>
<th>Population (Ref.)</th>
<th>Procedures (n)</th>
<th>Cardiac arrest (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children (15)</td>
<td>All (1 089 200)</td>
<td>0.027</td>
<td>0.004</td>
</tr>
<tr>
<td>All children (16)</td>
<td>All except cardiac surgery (88 639)</td>
<td>0.029</td>
<td>0.016</td>
</tr>
<tr>
<td>Children with heart disease (17)</td>
<td>Cardiac catheterizations (4454)</td>
<td>0.49</td>
<td>0.08</td>
</tr>
<tr>
<td>Children with PAH (7)</td>
<td>All except cardiac surgery (256)</td>
<td>1.17</td>
<td>0.78</td>
</tr>
<tr>
<td>Children with PAH (7)</td>
<td>Cardiac catheterizations (141)</td>
<td>2.13</td>
<td>1.42</td>
</tr>
<tr>
<td>Children with PAH (14)</td>
<td>Cardiac catheterizations (70)</td>
<td>5.71</td>
<td>1.43</td>
</tr>
</tbody>
</table>

PAH, pulmonary arterial hypertension.
channels, which mediate the vasodilator effect of many endogenous mediators such as adenosine, PGI$_2$, and nitric oxide. Isoflurane, halothane and enflurane have no effect on baseline pulmonary circulation tone. In general, isoflurane and sevoflurane are associated with clinical pulmonary vasodilation and are accepted components of a balanced anesthetic technique in patients with PAH. Volatile agents can lead to dose-dependent depression of cardiac contractility and reduction of SVR which may be problematic.

**Nitrous oxide**

Nitrous oxide was shown to have little effect on pulmonary hemodynamics in infants with PAH (32); however, its effect on alveolar PO$_2$ should be kept in mind. Nitrous oxide was associated with significant elevation of PVR in adults with PAH secondary to mitral valve stenosis (33).

**Fentanyl**

Fentanyl has minimal pulmonary and systemic hemodynamic effects (34), attenuates the pulmonary vascular response to noxious stimuli (24), and serves as an important component in a balanced anesthetic in children with PAH. The bradycardia observed in association with remifentanil may cause an undesired decrease in cardiac output (35,36).

**Benzodiazepines**

Benzodiazepines are associated with minimal hemodynamic effects. Midazolam is useful for pre-anesthetic medication and as an intraoperative component of balanced anesthesia. It is usually not a significant ventilatory depressant when used for premedication in children with congenital heart disease (37) but caution is advised in PAH patients with upper airway disease.

**Etomidate**

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 caused mild elevation of PVR, but the response was highly variable and not statistically significant (38).

**Propofol**

Propofol has not been thoroughly studied regarding direct effects on the pulmonary vasculature, but such effects do not appear to be great. Propofol has been used successfully in patients with PAH. However, propofol may cause adverse systemic hemodynamic effects. A bolus of propofol administered to healthy adults (39), a sedative infusion administered to postoperative adults with coronary artery disease (40) and infusions to children undergoing cardiac catheterization (41,42) decreased SVR significantly and cardiac contractility mildly. These can adversely impact biventricular perfusion and function in patients with severe PAH and/or right heart failure. In addition, patients with cardiac shunt and fixed, elevated PVR (e.g. Eisenmenger syndrome) may experience oxygen desaturation because the decrease in SVR will augment right-to-left shunt (41).

**Thiopental**

Thiopental is reported to decrease PVR. It is, however, a less desirable choice for patients with PAH because it can cause significant myocardial depression and systemic hypotension.

**Ketamine**

Ketamine administration in patients with PAH is controversial because it has been associated with increases in PVR or PAP in some investigations. However, the clinical conditions under which ketamine has been studied have been highly variable and no consensus has been reached. Hickey observed no significant effect of ketamine on PVR and PAP, even when baseline PVR and PAP were elevated (43). However, patients in that study were intubated and receiving supplemental oxygen and mechanical ventilatory support. Significant increases in PVR and PAP were observed following ketamine administration in three studies of children undergoing cardiac catheterization (44–46). Subjects in these studies were breathing room air through a natural airway, raising the possibility that the changes in PVR and PAP were associated with
hypercarbia due to ventilatory depression. However, two of these studies documented that $P_aO_2$ and $P_aCO_2$ 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 significant adverse pulmonary vascular responses to ketamine (44,46). Two of these studies (45,46) were conducted at relatively high altitude; animal data suggested this may be a relevant factor (47). Ketamine infusion was associated with insignificant changes in PAP and PVR in children spontaneously breathing room air during cardiac catheterization (42). A recent study of ketamine in 15 children with severe PAH demonstrated minimal pulmonary vascular responses to ketamine; however, subjects were anesthetized with sevoflurane during the study (48). If ketamine does not increase PVR, such as when used in combination with a pulmonary vasodilating drug or enriched $FiO_2$, then the drug’s systemic hemodynamic effects (maintenance of blood pressure and SVR) offer several potential benefits for pediatric patients with PAH, including preservation of coronary blood flow, limitation of the right to left ventricular septal shift, and maintenance of the ratio of pulmonary to systemic blood flow.

### Anesthetic management

The goals of anesthetic management are to provide adequate anesthesia and analgesia for the surgical procedure while minimizing increases in PVR and depression of myocardial function. Depending on the procedure, these goals can be met with the administration of either sedation/analgesia or general anesthesia, each of which is associated with a high potential for adverse events. In a review of 156 children with PAH undergoing 256 procedures, the incidence of complications was not different with sedation vs general anesthesia (7). Preanesthetic medication resulted in changes in $P_aCO_2$ (>45 mmHg) and/or $SpO_2$ (<90%) more frequently in children with PAH than other forms of congenital heart disease (37). Over-sedation to depths consistent with general anesthesia occurs frequently during procedural sedation (49) and can be associated with hypercarbia, hypoxemia and airway obstruction in patients managed with a natural airway and spontaneous ventilation (50).

Despite these potential airway and ventilatory problems during sedation or anesthesia, the incidence of complications in children with PAH undergoing noncardiac surgery or cardiac catheterization was found to be independent of the method of airway management (natural airway, LMA, or tracheal tube) (7). Tracheal intubation has been reported to precipitate pulmonary hypertensive crisis and death in critically ill adult patients with severe PAH (26,51), so some anesthesiologists avoid intubation for appropriate procedures. Similarly, deep extubation or early extubation can decrease exposure to noxious airway stimulation following selected procedures. When spontaneous ventilation through the natural airway is used, endtidal $PCO_2$ should be monitored via nasal cannulae (50,52).

Pulmonary vascular resistance is affected by many other aspects of anesthesia technique such as inspired oxygen concentration, acid/base management, ventilation mode, drugs, blood products, cardiopulmonary bypass, pain management, and the stress response. Given the multiple factors involved, it is not surprising that no single anesthetic agent has been shown to be ideal for patients with PAH and that balanced anesthesia is often preferred. Published case reports indicate that many different techniques have been safely employed. Typically, oral or intravenous midazolam premedication is administered. Midazolam, fentanyl, a small dose of propofol and/or a low concentration of sevoflurane may be used for induction of anesthesia. Anesthesia may be maintained with intermittent fentanyl doses and isoflurane or sevoflurane. Some anesthesiologists include ketamine for induction and maintenance. When paralysis is required, neuromuscular blocking agents with minimal hemodynamic effects are preferable (e.g. rocuronium and vecuronium). Successful use of epidural analgesia has been reported in adult patients with PAH (53,54), but caution is advised with regional anesthesia techniques that lower SVR. Thoracic epidural anesthesia
may impair a compensatory inotropic response to acute pulmonary hypertension (55). Infiltration of local anesthetic at the surgical site can offer significant benefit by obviating the need for high doses of anesthetics or sedative drugs. High-risk cases may require close hemodynamic monitoring, including echocardiography (transthoracic or transesophageal) and placement of arterial, central venous and pulmonary artery catheters. Laboratory tests with rapid return of results can facilitate tight control of blood gases, electrolytes and acid-base balance. Preand/or postoperative management in an ICU may be necessary. Satisfactory perioperative care of patients with severe PAH requires a multidisciplinary approach with foresight in planning and good communication among medical teams.

The anesthesiologist should be prepared to treat increasing PVR throughout the surgical or catheterization procedure. An impending pulmonary hypertensive crisis must be treated aggressively. The goals of treatment are to decrease PVR, support cardiac output, and remove stimuli associated with increases in PVR (Table 3). Moderate hyperventilation with 100% oxygen, treatment of both respiratory and metabolic acidosis, and removal or attenuation of precipitating stimuli should be undertaken. Treatment with selective pulmonary vasodilators (see below) should be promptly initiated, with inhaled nitric oxide (iNO) being the usual first choice because of its rapid onset and ease of administration. Early treatment of bradycardia with atropine or another chronotropic drug is important.

If systemic hypotension persists following administration of pulmonary vasodilators, inotropic support is indicated. As isoproterenol or dobutamine can decrease SVR, many clinicians prefer dopamine, epinephrine, or norepinephrine.

Pulmonary vasodilators may be used for diagnostic and prophylactic purposes. During cardiac catheterization for evaluation of PAH, iNO is administered to test pulmonary vascular reactivity. For children with systemic or suprasystemic PAH undergoing other surgical procedures, iNO may be administered through the breathing circuit intraoperatively beginning with anesthetic induction. Postoperatively, it may be continued via mask or nasal cannulae until the patient is stable and then may be gradually weaned. Pulsed delivery of iNO through nasal cannulae reduces the total amount of iNO used and has been shown to be as effective in reducing PAP and PVR as delivery via facemask (56).

### Pulmonary vasodilators

Significant improvements in medical therapy of PAH have accompanied the ongoing development of specific pulmonary vasodilators. This has been the subject of recent reviews (6,57–59).

#### Inhaled nitric oxide

Inhaled nitric oxide provides selective pulmonary vasodilation and is the drug of choice for intraoperative use because of its effectiveness, rapid onset, and ease of administration. Its biochemistry has been reviewed (60). 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 cyclic guanosine 3',5'-monophosphate (cGMP) concentrations resulting in vasodilation (6). Rebound pulmonary hypertension following weaning of iNO can occur, especially after a prolonged or severe pulmonary hypertensive episode (61,62).

#### Phosphodiesterase inhibitors

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 are suitable for both acute and chronic use. They can attenuate rebound pulmonary hypertension following withdrawal of iNO (61,62) and can be effectively combined with other pulmonary vasodilators. 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**

Prostacyclin analogs cause vasodilation by increasing cyclic adenosine 3′,5′-monophosphate concentration through stimulation of adenylate cyclase and have proven to be highly effective in the treatment of PAH (63). They are characterized by rapid onset of action and short half-lives. Epoprostenol, the most extensively studied of these agents, is administered by continuous intravenous infusion; chronic therapy has vastly improved the 5-year survival of children with idiopathic (primary) PAH (64). Many children with idiopathic PAH who are treated with epoprostenol require anesthesia for central venous catheter placement. It is important that the epoprostenol infusion remain uninterrupted because of its extremely short half-life. The inhaled analog, iloprost, was found to be as effective as iNO for perioperative control of PVR in children with PAH and has the potential advantages of a simpler method of administration and lower toxicity (65). Other analogs include treprostinil (subcutaneous or intravenous) and beraprost (oral).

Other drugs are more suitable for chronic treatment. The endothelin antagonist, bosentan, does not act acutely but shows promise in both sole and combination chronic therapy for PAH (66). Calcium channel blockers, such as diltiazem, can be useful for chronic treatment of patients with reactive PAH. However, these agents may be detrimental to patients experiencing pulmonary hypertensive crisis and to those with nonreactive, fixed PAH because accompanying decreases in SVR and cardiac output can decrease coronary blood flow and increase right-to-left septal shift.

Caution is advised in the use of selective pulmonary vasodilators in patients with PAH secondary to downstream obstruction, such as pulmonary vein stenosis, pulmonary veno-occlusive disease, and left atrial hypertension. Although successful post-intervention treatment with selective pulmonary vasodilators has been established (67), their use prior to the relief of obstruction can be associated with acute, life-threatening pulmonary edema (68).

**Summary**

Patients with PAH are at 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.

**References**


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