Anesthesia considerations for children with pulmonary hypertension

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Children with pulmonary arterial hypertension undergoing anesthesia pose a challenge. The prevalence of morbidity and mortality in this subgroup is substantially greater than that in the general population. In this article, we attempt to describe the adverse events that occur and also identify some of the factors that may precipitate them. We also suggest mechanisms to attenuate or prevent these crises. (Pediatr Crit Care Med 2010; 11[Suppl.]:S70–S73)

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In normal healthy children, the risk associated with anesthesia is greater than in adults (1–3). The Pediatric Perioperative Cardiac Arrest Registry determined the prevalence of cardiac arrest related to anesthesia to be approximately 1.4 per 10,000 anesthetics with a 26% mortality rate (4). A follow-up study published in 2007 primarily addressed etiology but did not disclose the frequency of cardiac arrest, although the mortality rate after cardiac arrest remained at an alarmingly high 28% (5). Risk factors for cardiac arrest related to pediatric anesthesia include age <1 yr, American Society of Anesthesiologists physical status >3, and presence of comorbidities, in particular, cardiac disease (6, 7). To this risk can be added the patient with pulmonary hypertension (PHT).

There have been a few studies assessing the impact of pulmonary arterial hypertension (PAH) in children undergoing anesthesia. Carmosino et al performed a retrospective analysis of all children with PAH undergoing procedures both in the operating rooms and in the catheterization laboratory. They found the overall prevalence of cardiac arrest to be 1.17% (117 per 10,000 anesthetics) and the overall mortality to be 0.78%. The prevalence of cardiac arrest and mortality of children with PAH undergoing cardiac catheterization was higher (2.1% and 1.4%, respectively) (8). A similar risk was also demonstrated in a smaller study of children with PAH undergoing cardiac catheterization (9).

Thus, it becomes clear that PAH is a significant risk factor for anesthesia, and knowledge of the pathophysiology of the disease and the therapeutic armamentarium available to manage PAH in the perioperative period is essential for all anesthesiologists treating these patients. In particular, these patients should be managed only in centers that are familiar with this condition and have the resources available to intervene emergently if the situation requires. Close collaboration between the anesthesiologist, cardiologist, and operator is essential both before and throughout the procedure.

PAH in Children

PAH is characterized by a progressive pulmonary vasculopathy, which results in right-heart failure if untreated. Although the diagnosis is usually suspected based on clinical symptoms and signs, almost all children will require a cardiac catheterization at some stage. This is necessary to confirm the diagnosis and also to determine pulmonary vascular reactivity, which is the basis on which therapy can be determined.

Acute Pulmonary Hypertensive Crisis

A sudden rise in pulmonary vascular resistance (PVR) may precipitate an acute pulmonary hypertensive crisis. Known stimuli include hypoxemia, hypercapnia, acidemia, hypothermia, and a noxious stimulus, such as endotracheal intubation that may raise autonomic tone. The acute rise in PVR may lead to a severe increase in right ventricular (RV) afterload and an immediate increase in RV end-diastolic volume, resulting in reduced combined ventricular stroke volume and cardiac output (CO); if present, an atrial septal communication will allow right-to-left intracardiac shunting to maintain left ventricular (LV) preload and CO, although at the expense of worsening cyanosis. The increased wall tension on the RV reduces coronary perfusion, leading to ischemia and possible cardiac arrest if not treated emergently. Clinically, this sequence often becomes apparent as abrupt desaturation, systemic hypotension, sinus tachycardia, and elevated central venous pressure with new onset electrocardiographic changes, suggesting RV strain or ischemia. Bradycardia during such an event is ominous, probably reflecting more profound myocardial hypoperfusion and ischemia. An echocardiogram during an acute pulmonary hypertensive crisis may demonstrate a dilated, poorly contractile right ventricle, under-filled left ventricle, and pulmonary and/or tricuspid regurgitation. Estimated RV pressures (using the tricuspid regurgitation jet velocities) may or may not be increased, depending on the RV contractility. In children, the occurrence of syncope may be the result of an acute rise in pulmonary arterial pressure (PAP), causing a profound reduction in CO with consequent cerebral hypoperfusion. More commonly, it occurs secondary to exer-
exercise where peripheral vasodilation occurs but the child is unable to increase CO sufficiently, thereby leading to cerebral hypoperfusion (10).

**Chronic PHT**

If the PAH is secondary to vascular remodeling, this is a more insidious process. Loss of the ability to vasodilate results in a more rigid pulmonary circulation with persistently elevated PAP. Although the right ventricle is able to tolerate small increases in PAP, over time there is hypertrophy of the right ventricle, which later begins to dilate and fail resulting in a reduction in pulmonary blood flow and thus CO. Although the right ventricle is able to generate adequate CO at rest, it is unable to increase the CO during exercise. This results in dyspnea and/or chest pain upon exercise, as oxygen delivery is unable to meet both myocardial and systemic demands. If the situation continues, RV dilation leads to septal deviation and impairment of LV systolic and diastolic performance and dyspnea at rest.

**Anesthetic Management of Pediatric Patients With PAH**

The anesthetic management of the child with PAH is clearly a challenge for any anesthesiologist. It is obviously essential to review previous catheterization or echocardiographic data, if available. From a previous catheterization, data related to PAPs, RV pressure and function, mixed venous saturation, and the degree of any shunting are all valuable findings. From the echocardiographic study, the estimation of RV function as well as the presence or absence of an atrial communication is helpful when planning the anesthesiology management.

**Two Clinically Important Categories of Patients With Some Overlap**

The first group includes the child with newly diagnosed PAH. This group is likely to be at risk for a severe, acute and life-threatening pulmonary hypertensive crisis, and the primary objective is to prevent any stimuli from triggering this crisis. The younger the child, the more reactive the airway is likely to be and so the risk of crisis may be increased. In addition, Taylor et al demonstrated that children with idiopathic PAH (including familial PAH) had a greater prevalence of cardiac arrest (9).

The second group is likely to be represented by an older child with ongoing or chronic PAH, typically associated with other medical conditions. Such a child is likely to have increased PVR with a hypertrophied right ventricle. This group seems more likely to succumb to RV ischemia and arrhythmias and develop ventricular failure, rather than an acute hypertensive crisis. Although there may be some overlap, this distinction allows the anesthesiologist to plan accordingly.

The aim in both cases is to minimize stress and maintain hemodynamic conditions as close to baseline by providing adequate anesthesia and analgesia for the operative procedure (Table 1). Throughout the anesthetic, it is important to prevent or avoid any stimuli that may trigger a crisis, and to maintain hemodynamic stability such that the risk of RV ischemia is minimized. These stimuli include the stresses involved in placing the first intravenous access catheter through endotracheal intubation, mechanical ventilation if used, and emergence and extubation at the end of the procedure. Therefore, it is important that there be no interruption of any medication currently being used to control pulmonary pressures. In addition, it is important that any procedure on a patient with PAH is placed in a scheduled time slot to minimize duration of fasting to minimize the risk of dehydration. Intravenous maintenance fluids should be instituted in cases that do not allow for elective scheduling. In most cases, all oral medication should be continued. It is essential to note that if a patient is receiving a continuous infusion of prostacyclin or iloprost, the intravenous catheter containing the infusion must not be interrupted at any time because of the risk for rebound PHT; a second intravenous catheter must be placed in this circumstance for induction of anesthesia.

Before induction of anesthesia or sedation, all resuscitative equipment must be available and checked including resuscitative medicines, such as epinephrine and sodium bicarbonate; it is usually prudent to have inhaled nitric oxide immediately available in case of a pulmonary hypertensive crisis, although there is no guarantee this will reverse a crisis in all circumstances. The anticipated postprocedure care must also be considered as part of the preparation before any procedure in a patient with PAH, and in particular, the availability of a bed in an intensive care unit if deemed necessary.

**Premedication**

The premedication can be oral or intravenous, depending on the age and maturity of the child. It is essential that the premedication is adequate to preserve a calm atmosphere. Benzodiazepines have minimal effect on hemodynamic stability and so are regularly administered. Midazolam, 0.5–1 mg/kg, in particular, is tolerated very well orally and intravenously and has not been shown to cause significant hypercarbia when used as a premedicant (11). Oral ketamine, 3–7 mg/kg, as an adjunct to midazolam, consistently provides a well-premedicated child. In addition, its administration has been shown in numerous studies to have no effect on PVR, provided hypercarbia is prevented, even in patients with increased PVR (12, 13).

**Monitoring**

All monitoring should be placed before induction with particular attention paid to the use of 5-lead electrocardiogram to allow close monitoring for myocardial ischemia. Baseline saturation should be noted to allow for observation of a change in any shunting. The baseline capnograph should similarly be noted; a sudden fall in end-tidal CO2 could indicate a decrease in pulmonary blood flow. It should be remembered that the presence of any interatrial communication will allow for the possibility of a paradoxical embolus, and suitable precautions should be taken with all intravenous infusion catheters.

The decision to place invasive monitors will depend on the procedure being undertaken and the stability of the patient. If necessary, central venous access or pulmonary artery flotation catheter placement may be undertaken in the catheterization laboratory, which will also allow for baseline hemodynamic assessment before transferring the patient to the operating room.

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**Table 1. Anesthetic management of acute pulmonary hypertension**

| 1. | Administer 100% oxygen |
| 2. | Institute inotropic support |
| 3. | Initiate nitric oxide therapy |
| 4. | Administer opiate and deepen anesthesia |
| 5. | Correct metabolic and respiratory acidosis, if present |
| 6. | Treat hypothermia, if present |
Induction

In those patients with a relatively fixed PVR, it is essential to prevent any further increase in PVR, at the same time maintaining RV function and avoiding a reduction in systemic vascular resistance (SVR). Any increase in PVR will reduce pulmonary blood flow and, thus, reduce LV preload and CO. Furthermore, if the RV end-diastolic pressure increases, ventricular septal deviation leftward may further impair LV function, compounding the reduction in CO. If systemic hypotension develops, the hypertrophied right ventricle, which receives its coronary blood flow during both systole and diastole, is exquisitely sensitive to the reduction in oxygen delivery and ischemia develops rapidly. Induction of the hypovolemic patient can trigger the undesirable cascade of systemic hypotension and an assessment of the volume status of the patient should be undertaken carefully before induction as well as limiting the duration of preoperative fasting. Inotropic support and inhaled nitric oxide should be available and instituted early to prevent rapid deterioration. Hypovolemia, in particular, can result in inadequate preload to the right ventricle and, thus, a bolus of 5 mL/kg to 10 mL/kg of intravenous fluid should be given before induction.

There is no specific anesthetic technique for patients with PHT, and on each occasion, it must be tailored according to the underlying hemodynamic stability and the planned procedure. In particular, the decision to administer general anesthesia or sedation must be made carefully. Friesen et al found no significant difference in morbidity or mortality between the two methodologies in similar cohorts of patients (14). In our institution, we require close collaboration between the anesthesiologist and the cardiologist to determine the optimal approach (whether sedation or general anesthesia) is utilized. In our experience, anesthesia is provided in most cases, and when sedation is utilized, this is managed by the cardiac anesthesia team, rather than cardiology-directed nurse sedation. With this approach, in a recent review of 143 children with PAH across a 54-mo period at our institution, there were no cardiac arrests or deaths during cardiac catheterization (Mary Mullen and Lisa Bergersen, personal communication).

A balanced anesthetic technique is usually preferred, titrating doses of specific drug to provide anesthesia, analgesia, reflex attenuation, and also muscle relaxation when necessary. Intravenous induction agents may cause some degree of systemic hypotension and myocardial depression when used as the sole drug for induction. Propofol has been shown to decrease PVR both when used as a bolus and also as an infusion (15). However, its negative effect on SVR and myocardial depression makes its use in those patients with a fixed PVR a hazardous undertaking; at the same time, its ability to ablate noxious stimuli may support its cautious use in those patients with a reactive PVR. The rate of induction of anesthesia may be quite variable in patients with PHT. In patients with no intracardiac shunt and PHT, induction may be slow because of increased transit time across the pulmonary circulation and reduced LV preload. Alternatively, the induction time may be reduced in a patient with PHT and a right-to-left atrial shunt, because of rapid transit to the systemic circulation. Oklu et al compared propofol and ketamine infusions administered to children with intracardiac shunts, and concluded that only propofol increased right-to-left shunting and arterial desaturation (16). In general, if propofol is chosen to aid with the induction, it is important to administer only small incremental doses, at the same time allowing for any effect to become evident before administering subsequent doses. Ketamine maintains PVR and SVR in children undergoing anesthesia. It is generally considered safe but there may be a requirement to administer an anti-sialogogue if salivary secretions are excessive. Although etomidate is considered to have a stable hemodynamic profile in adults, it also will produce a reduction in SVR if the full induction dose is delivered (17). In children, it has been demonstrated to have minimal effects on the systemic circulation, although effects on the pulmonary circulation have not been studied (18). The routine use of opioids to attenuate the physiologic responses to various aspects of the anesthetic induction, including laryngoscopy and endotracheal intubation, should be considered. In particular, fentanyl has very little effect on pulmonary and systemic hemodynamics and is, thus, a very useful drug during induction (19). It is important during the induction process to be aware of the physiologic changes that are occurring and to act accordingly. Once the child stops ventilating spontaneously, only careful assisted ventilation must be instituted. Too great a tidal volume, too long an inspiratory phase, or too great an inspiratory pressure will all inhibit RV filling and, thus, reduce CO as well as increase PVR. Too small a tidal volume or too low a peak inspiratory pressure will reduce minute ventilation, increase atelectasis, and also increase PVR as well as increase RV workload. Thus, it is essential to observe closely all physiologic variables during this period and to ensure adequate pulmonary blood flow is maintained without signs of increased RV strain.

Maintenance

The goal here is to maintain pulmonary blood flow, at the same time preventing any additional workload for the right ventricle. Ventilation should be monitored closely, using the capnograph and the pressure-volume and flow loops, and oxygenation should be maintained at least at the child’s baseline. PVR is more directly affected by hydrogen ion concentration than hypercapnia, and so the metabolic contribution to the pH should be treated aggressively with bicarbonate as well as any respiratory component by adjustment of ventilatory parameters and ensuring adequate muscle relaxation. Maintenance of anesthesia with the volatile inhalation agents isoflurane or sevoflurane provides favorable operating conditions and depth of anesthesia to prevent hypertensive crises. The vascular smooth muscle in the pulmonary circulation is regulated largely by the action of adenosine triphosphate-sensitive potassium channels. Adenosine, prostacyclin, and inhaled nitric oxide all produce their vasodilatory effects via activation of these channels. Isoflurane (in addition to desflurane but not sevoflurane) inhibits the activity of these channels, thus reducing the vasodilatory effects to these agents. However, isoflurane potentiates the vasodilator response to β1-adrenoceptor activation and, interestingly, has no effect on baseline pulmonary tone (20, 21). In general, isoflurane is well tolerated in patients with PAH, provided systemic hypertension is prevented.

Nitrous oxide can be used although it will reduce the inspired oxygen concentration that can be delivered, and because of the increased diffusing capacity of nitrous oxide, meticulous de-airing of any intravenous infusion is essential to prevent enlargement of air bubbles, particularly if there is an intracardiac right-to-left shunt. Nitrous oxide does not have
any effect on PVR, even in the presence of PAH. It can, thus, be used safely as an adjunct agent provided its depressant effect on the myocardium is tolerated (22). Inhalation anesthetic agents can be avoided, using a total intravenous anesthetic technique. A continuous infusion of propofol is one option but the potential complications as described above must be considered. The rapidly acting synthetic opioid, remifentanil, is an ideal agent to use for relatively short procedures because of its rapid onset and offset of action, and stable hemodynamic profile.

In the event of persistent hypotension secondary to an increase in PVR, Vlahakes et al concluded that RV afterload must be reduced and systemic pressure must be maintained or increased. Although inotropic agents are required to support the right ventricle, vasoconstrictors seem to be superior to volume and inotropic agents in the setting of RV ischemia (23, 24). Phenylephrine, norepinephrine, or vasopressin should be considered in addition to normal management of acute-onset PHT.

**Immediate Post-procedure Management**

The post procedure management in a patient with PHT will depend on the procedure and anticipated complications as well as the underlying pathophysiology and, in particular, the function of the right ventricle. For example, for newly diagnosed patient with PHT undergoing diagnostic cardiac catheterization, initial post-procedure care in an intensive care unit is usually prudent to allow for continuous monitoring of PAP and RV function after extubation, and at the same time the treatment for PAH is commenced. For most procedures, this can occur within a few hours as long as the child is awake, calm, responsive, and there are no sequelae related to the procedure, such as bleeding, that still require attention. Patients who are receiving treatment for PHT and have stable clinical condition and exercise tolerance should be extubated at the end of the procedure, provided every attempt is taken to minimize any noxious stimuli during the emergence phase. Once again, these patients are often best monitored closely in the intensive care unit for the first postoperative night for signs of RV strain or an acute pulmonary hypertensive crisis.

Inotropic support may be continued during the immediate postoperative period, and adequate analgesia and antiemesis after both invasive and noninvasive procedures are essential to prevent any surge in PAP.

**REFERENCES**