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# It Is Just a Nosebleed Isn't It? Anesthetic Considerations for Unsuspected Pulmonary Hypertension

Shu Ming Wang, M.D.
University of California Irvine Medical Center, Orange, CA

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## Stem Case and Key Questions Content

A 6 year-old girl presents for emergency examination under anesthesia and control of epistaxis.

History of present illness:
The patient has uncontrolled epistaxis. *What are the common causes of epistaxis?*

Past medical history:
The patient has no significant medical history. Mom states that the patient has frequent nosebleeds that are easily stopped, but not this time. Mom also adds that the patient does not eat much, and usually is not very active because she gets tired easily. *Is it common behavior for a 6 year-old child?* Patient's mom states that they recently immigrated to the United States. She was seen by pediatrician in the clinic 2 months prior and referred for further evaluation by a heart specialist because of murmur. *Does every child with heart murmur required cardiologist consultation and evaluation? If not, who should be referred? Who should not.* The appointment is scheduled in two weeks. The rest of the medical history is unremarkable, except that the patient has missed school due of inability to clear persistent cold. *What are the common reasons for a child hard to recover from URI?*

Pre-op holding:
Patient is tearing and clinging to her mom. Blood streak over lower face, bloody tissues and bloodstained clothing noted in the OR holding. The anesthesiologist attempts to perform a physical examination, but the child traumatized by previous attempts is extremely uncooperative, and now there is more bleeding. Mom reports that patient weighs about 35 lbs. The patient had two pieces of chicken nuggets and some juice about 2 hours ago. *Should the case proceed to OR? or not? Why?* There is no IV access. *How should we proceed? Should a preoperative sedative given? If yes, what are the choices?*Decision is made premedicate the patient with IM ketamine/versed mixture. Patient struggles, vomits, and turns dusky and mom starts crying and screaming. *What are the common complications associated with premedication?* A portable pulse oxymeter is applied, it reads 76% with heart rate of 86. Anesthesiologist quickly takes the child off mom's lap, places patient on the nearby stretcher, starts ventilating the patient with 100% O2 and hurries to operating room where the nearest monitors and resuscitative equipment are available.

In operating room:
Overhead help called, first blood pressure reading is 60/24, heart rate dropping from 86 to 60. Oropharynx suctioned, mask ventilation is continued, but the patient does not show significant improvement. Intubation performed without difficulty but minimum chest movement with high positive pressure ventilation. *What are the differential diagnoses?* A second DL confirms the location of endotracheal tube through vocal cord. Heart rate is about 50, oxygen saturation is not detectable and patient color remains dusky. *What should be the next step? Intravenous line is still pending, Where should the resuscitation medication be given? ET tube vs. intraosseous?* Epinephrine 0.1 mg with 5 cc of and albuterol administered through endotracheal tube. Chest auscultation reveals bilateral rhonchi and wheezing, as well as a systolic murmur. Heart rate improved to greater 100 and oxygenation back up to 96% with $FiO_2$ of 100%. After several attempts, an intravenous line is established. Portable chest X ray performed, unremarkable. The otolaryngologist goes outside to reassure and discuss further care with mom. Decision is made to continue with the planned procedure.

Intraoperative course:
The nasal examination reveals a mass in the nasal cavity and bleeding site. Biopsy and cauterization are performed. Patient's oxygen saturation steadily improves to 100% under general anesthesia consisting of 3% sevoflurane, 50% of oxygen, and IV fentanyl 50 µg, lungs sound clear. Decision is made to extubate the patient. While she emerges from anesthesia, while still intubated, she develops hypotension, bradycardia, and hypoxia. Chest auscultation reveals rhonchi in the dependent areas. Intravenous atropine is administered, but the condition is not improving; repeated doses of intravenous epinephrine are administered and chest compression performed. *What are the common causes of agitation related cardiovascular collapse?* Patient's vital signs improve (HR 120, blood pressure 140/80 and Oxygen saturation 100%) and an arterial line is inserted for additional monitoring. After initial stabilization and sedation the patient is transferred to pediatric intensive care unit for further workup.

Intensive care course:
In the ICU the patient is overall stable, except when her endotracheal tube is suctioned, she develops hypotension, bradycardia and hypoxia. A transesophgeal echocardiogram is performed: structurally normal heart, significant right ventricular hypertrophy, estimated pulmonary artery pressure of 40/20 mmHg. *What are the common causes of pulmonary hypertension in children? What are the treatment options?* The patient is scheduled for cardiac catheterization with general anesthesia for further cardiac work-up. *How should we proceed this time around? What are the common perioperative complications associated with pulmonary hypertension?*

**Model Discussion Content**
Epistaxis (nosebleed) is a common disorder in children between 2 to 10 years of age. The most common cause of epistaxis in children is minor trauma such as nose picking.[1] Other causes are direct trauma to the nose, upper respiratory infection, nasal foreign body, vigorous nose blowing, allergic rhinitis, exposure to warm, dry air and use of nasal medications, e.g. corticosteroids. Less common causes of epistaxis in children are vascular malformations, leukemia, nasal tumor and abnormal clotting. In case of severe or recurrent epistaxis, one must look for a bleeding disorder or a nasal/nasopharyngeal tumor. Sandoval et al. [2] studied a total of

 

178 children with recurrent epistaxis and found one-third of children presenting with recurrent epistaxis have a diagnosable coagulopathy. A positive family history and prolonged PTT are useful predictive data.[2] Fortunately, most episodes of epistaxis are not serious and usually can be managed at home. Depending on the site, it is categorized into anterior and posterior nosebleed.[1] More than 90% of all nosebleeds, originated in front of the nose (anterior nosebleed) where a network of vessels converge (Kiesselbach plexus), are usually easy to control by manual compression or vestibular packing with a piece of cotton or calcium alginate. In contrast, posterior nosebleeds are less common, usually originate from an artery in the posterior part of the nose, are more complicated and typically require admission to the hospital and management by otolaryngologist. In children posterior nosebleeds are most likely caused by direct trauma, bleeding disorder or tumor.

Not every child who has a heart murmur needs cardiac consultation or receives additional cardiac workup. Literature has indicated that many healthy children have heart murmur at some point of their development.[3] Based on the etiologies of heart murmur, it is categorized into: a. Innocent heart murmur, also known as functional heart murmur, can be associated with physical activity, fever and anemia. b. Abnormal heart murmur is associated with structural abnormality of the heart (congenital heart defect) such as AV canal, ASD, VSD, PDA, PFO or heart valve stenosis or insufficiency, e.g. aortic, pulmonary, mitral or tricuspid. Other etiologies are infection and inflammation, such as endocarditis and rheumatic fever, as well as pulmonary hypertension.[3] In order to determine which child should receive cardiac consultation and workup, a thorough history and a complete physical examination are needed.[3] Characteristics of pathologic murmur include a sound level of grade 3 or louder, a diastolic murmur or an increase in intensity when the patient is standing.[4] Features of concern in infants include feeding intolerance, failure to thrive, respiratory symptoms or cyanosis. Older children complaining of chest pain, especially with exercise, syncope, exercise intolerance or family history of sudden death at young age should be referred to pediatric cardiologist.[3] The child in this case has several features such as history of failure to thrive, physical inactivity, prolonged cold symptoms and should have cardiac evaluation. Although additional cardiac workup is ideal, given the emergency nature of this procedure and the lack of pediatric cardiologist on site the case has to proceed.

It is not unusual for children to experience anxiety before surgical procedure. Thus, preoperative medication has been advocated as a treatment for anxious pediatric patients. Common preoperative sedative medications are: midazolam, ketamine, fentanyl, clonidine, and dexmedetomidine.[5] The dosages and routes of administration of preoperative sedatives are discussed below.

*a.*
*Midazolam*[5]- it is an acidic aqueous solution and highly lipid soluble at pH 7.4. The parenteral preparation has a bitter taste that is difficult to disguise. Nasal administration is very irritating and would not be helpful in a child with epistaxis. Plasma concentration correlates with clinical effect. Peak plasma concentration reaches 10-15 min following nasal application, 30-60 min after oral and around 10 min following rectal administration. Oral midazolam (0.5-0.75 mg/kg) reduces anxiety and distress at induction of anesthesia without causing delay in recovery.

*b.*
*Ketamine*[5]- NMDA receptor antagonist is available in a variety of preparations: lollipops,

lozenges or elixirs. S (+) ketamine is more potent than R(-) ketamine and is associated with less psychomimetic effects. Bioavailability ranges from 0.16 (oral) to 0.93 (intramuscularly) with nasal and rectal application in between. Generally, higher doses of ketamine provide faster onset of sedation. Intramuscular ketamine (2-5 mg/kg) works faster than intranasal and oral/rectal (6-8 mg/kg) administration. The major benefit of ketamine premedication is the additional analgesia at the expense of dose and route dependent vomiting, nystagmus, hallucinations, elevation of pulmonary vascular resistance, increased oral secretions, and neuroapoptosis in younger children.

*c.*
*Fentanyl*[5]- Commercially available oral transmucosal fentanyl preparations (lollipops) produce satisfactory anxiolysis, pain relief and sedation in a dose dependent manner. Optimal sedation is achieved after 30-45 min and doses of 10-20 µg/kg (orally) are appropriate. Pre- and postoperative nausea and vomiting are common and pruritus is mild. The benefits of intramuscular or rectal opioid administration for preoperative sedation are relatively small.

*d.*
*α2-receptor agonists*[5]- clonidine and dexmedetomidine both are taste, color, and odorless. (1) Clonidine: There are limited data available regarding the bioavailability in children. Nasal and rectal absorption appears erratic with peak plasma concentration achieved from 30 to 180 min. Oral dose of 4 µg/kg clonidine has longer onset than midazolam. It may be difficult to have a smooth induction of anesthesia; however, despite these drawbacks premedication with clonidine is superior to midazolam in emergence agitation. (2) Dexmedetomidine: it is approximately 8 times more selective for α2- than α1-receptor compared with clonidine. Similar to clonidine, oral dexmedetomidine is not satisfactory for induction of anesthesia, however intranasal (2µg/kg) dexmedetomidine is as satisfactory as p.o. midazolam (0.5 mg/kg) in providing sedation and cooperation of children undergoing surgery.

*e.*
*Melatonin*[5]-Melatonin is important in regulating the diurnal rhythm of sleep. It is available over the counter in some countries and is frequently administered to facilitate sleep. Melatonin is taste, odor, and color free so it can easily be mixed with the child's favorite drink. Oral dose ranges from 0.1- 0.5 mg/kg with approximate 1 hour to its peak sedative effect.
Unfortunately, the child in this case presentation has turned dusky and cyanotic before administration of any preoperative medication. In order to prevent situation as described in this case presentation and to facilitate management when it arises, it is best to have oxygen (wall and tank), mask and circuit as well as monitors available in the holding area prior to any intervention.

When anesthesiologists are confronted with impending cardiac arrest in a child, the key to successful resuscitation is to identify the underlying cause.[6] Majority of children develop cardiac arrest as a result of respiratory failure.[6] However, hypovolemia, cardiovascular collapse, hypoglycemia, or hypothermia can also contribute to the impending cardiac arrest in children. While sorting out the underlying causes, resuscitation medications and/or advanced airway management should be performed without delay.[6] Peripheral or central intravenous access is the best route for medication administration, but when there is no intravenous line available, an intraosseous (IO) line should be considered. In 1922 Drinker was the first to introduce IO vascular access as a method for accessing noncollapsible venous plexuses through the bone

marrow cavity to systemic circulation. Based on previous guidelines, IO access was suggested for children aged 6 years or younger, although recent studies have shown that it is safe and effective in older children and adults. In 2005, the American Heart Association recommended IO access if venous access cannot be quickly and reliably established.[6] The preferred site for intra IO access in children is in the center of the tibia, just distal to the tibial tubercle in neonate; in 6-12 month old insert 1 cm distal to tibia tuberosity, and in children > 1 year of age, insert 2 cm distal to the tibial tuberosity. IO access may be maintained at the same site for 96 hours.[6] In emergencies, such as cardiopulmonary resuscitation, if there is no established intravenous or IO line, but the airway is established with an endotracheal tube, certain medications such as epinephrine, lidocaine, atropine, naloxone and valium can be administered through endotracheal tube. Even though the child has been successfully resuscitated twice in this case scenario, the underlying etiology of her near arrest remains unclear until the results of bedside echocardiogram indicating that the child has pulmonary hypertension (PAH).

PAH is defined as the presence of a mean pulmonary artery pressure (PAP) that exceeds 25 mm Hg at rest or 30 mm Hg during exercise. Subsystemic PAH is defined as baseline pulmonary arterial pressure < 70% of systemic blood pressure, systemic PAH (70-100% of systemic blood pressure) and suprasystemic (>100% of systemic blood pressure).[7] PAH can be grouped into one of two categories depending on etiology: a. Idiopathic pulmonary hypertension (IPAH)-occasionally runs in families may be related to BMPR2 gene. However, the exact cause is not clear. b. Secondary PAH-the PAH can be associated with various conditions that can be classified into five major categories. Please refer to Strange JW et al.[8] Table 1 for the underlying pathologies. The clinical features and diagnosis of PAH routinely consists of a general history and physical examination with special focus on heart and lungs and family history.[8] Typically, the common clinical symptom of PAH is *shortness of breath* during mild physical activity.[8] In some patients the first symptom may be fainting spells, dizziness, rapid heart rate, low blood pressure, chest pain or pressure or swelling of legs and hands. Auscultation and physical examination frequently reveals loud second heart sound, systolic murmur of tricuspid regurgitation or diastolic murmur of pulmonary insufficiency, palpable 2$^{nd}$ heart sound, peripheral edema, and jugular distension.[4,8] However, these symptoms mentioned are not specific to PAH. Therefore, additional diagnostic tests i.e. chest radiography, electrocardiogram, transthoracic and/or transesophageal echocardiography and Doppler ultrasound, pulmonary function tests, ventilation/perfusion lung scan, cardiac catheterization with pulmonary angiography, CT scan, cardiac MRI, coagulation evaluation, complete blood count, and/or lung biopsy to determine the underlying cause and assess severity.[8] Once the diagnosis of PAH in a child is confirmed, there are several treatment options including the general care, pharmacological and non-pharmcological treatments.[9]

**I. General Supportive Care:**

a. *Oxygen*- Its main role is to minimize any potential hypoxic pulmonary vasoconstriction. One report on oxygen administration (>12 hr/day) in children with PAH-CHD, suggested a beneficial effect on survival but there was no beneficial effects on nocturnal oxygen administration in adult patients with PAH-CAH. In general, oxygen administration can improve level of subjective wellbeing in a subgroup of patients with PAH.

b. *Anticoagulation therapy*- the concept is based on the finding of microthrombi in the pulmonary vasculature of patients with PAH. Adult studies have shown that warfarin used to provide long-term anticoagulation to achieve INR of 2.5 -3 decreases the morbidity and mortality rates in

patients with iPAH. The use of anticoagulant therapy in children with PAH is increasing especially in conditions such as hypercoagulability, overt heart failure and when there is an indwelling central venous line. However, there are no data available on the efficacy and risk/benefit ratio of oral anticoagulation in children with PAH. Anticoagulant therapy in young children may be accompanied by age-specific problems, thus the therapy should be considered on an individual basis.

*c. Digoxin*-an oral inotropic agent is advocated in patients with right ventricular dysfunction associated with iPAH. The efficacy of digoxin in this clinical situation is somewhat controversial.

**II. Vasodilators:**
Vasodilatating agents are used to counteract the underlying pathology of PAH. In the early stage of PAH, most pulmonary vasoconstriction is believed to be reversible. Later, the changes become fixed and irreversible. An immediate response to inhaled nitric oxide or prostacyclin may serve as predictor to the ability in response to nifedipine treatment. When response to acute vasodilation is demonstrated in the catheterization lab, long-term vasodilators should be administered.

a. *Nitric Oxide*- NO is a colorless, odorless gas that is only slightly soluble in water. Inhaled NO produces selective pulmonary vasodilation and rapidly increases arterial oxygen tension without causing systemic hypotension. Although early studies of inhaled NO in the treatment of PAH used concentration of 5 to 80 ppm, it has since been realized that concentrations >20 ppm provide little additional hemodynamic benefit in most patients.

b. *Calcium channel blockers*- Uncontrolled, open-label, prospective, observational studies indicated that when patients with PAH responded to acute vasodilator testing at initiation of therapy, long-term calcium channel blocker therapy improved hemodynamic and survival in both adults and pediatric patients with IPAH.

c. *Prostanoids*- Prostacyclin is an endogenous, potent pulmonary and systemic vasodilator. In addition, it also has antimitogenic properties and antiplatelet activity. In some patients with PAH, there is a reduction of expression of prostacylcin synthetase in pulmonary endothelium and an imbalance between the thromboxane and prostacylin metabolites. The analogues used as treatment for PAH are: Epoprostenol (very short half life of 3-6 min, IV continuous, level of evidence A), Treprostinil (elimination half-life of 4-5 h, IV or S.C., or inhalation), Iloprost (biological half-life of 20-30 min, IV or inhaled), oral beraprost (half-life of 1-2 h, oral administration).

d. *Endothelin receptor blockers-* A enthothelin (ET) receptor antagonist (ERA) blocks ET receptors. ERA is found to increase exercise tolerance and time to clinical worsening. ETs are proteins that constrict blood vessels and raise blood pressure. Three types of ERAs are available:
d1. selective $ET_A$ receptor antagonists such as sitaxentan, ambrisentan, atrasentan, BQ-123, zidotentan, which affect ET receptor A.
d2. dual antagonist (bosentan, macitentan, tezosentan), which affect both $ET_A$ and $_B$ receptors.
d3. selective $ET_B$ receptor antagonists (BQ-788 and A192621) which affect $ET_B$ receptors are in

research stage and have not reached the clinical use. Sitaxentan, ambrisentan and bosentan are still undergoing clinical trials.

e. *Phosphodiesterase-5 inhibitors*-Inhibition of phosphodiesterase type 5 (PDF5) induces vasodilation through nitric oxide/cyclic guanosine monophosphate pathway, and exerts antiproliferative effects. Common PDE5 inhibitors are:
e1. Sildenafil- It is well tolerated and no significant adverse effects in adults. . Sildenafil should not be used in children due to an increased risk of death in children with PAH.
e2. Tadalafil- It is a selective PDF5 inhibitor that can be administered once daily. However, data in children are not available.

**III. Combination Therapy**
Based on above, targeted PAH therapies are generally effective and well tolerated in both children and adults. By combining therapies targeting different pathways involved in the pathophysiology of PAH, the effect may be better than in targeting just one pathway.

**IV. Future Pharmacological Treatment:**
No data are available in pediatric patients with PAH but guanylate cyclase agonists, plate-derived growth factor-receptor antagonist, prostacyclin-receptor agonists and tyrosine kinase inhibitors are been investigated in adult patients with PAH.

**V. Non-pharmacological Therapy:**
Atrial septostomy, Pott's shunt and/or lung transplantation should be considered in patients with inadequate response to maximal pharmacological therapy. The drawbacks are the effect of this procedure may be unpredictable and its mortality is substantial (5-15%).
When taking care a child with an established diagnosis of PAH, the anesthetic considerations should consist of providing adequate anesthesia and analgesia to minimize stimuli for pulmonary vasoconstriction, minimize systemic cardiovascular depression and maintain the ability to treat increased PVR, if it occurs. Based on the type of procedure/surgery the child is undergoing, sedation/analgesia, regional analgesia or general anesthesia should be provided. The airway management decision should be based on the type of procedure and the ability to easily gain access to the airway. Generally, natural airway and facemask, laryngeal mask airway or endotracheal tube can all be used safely. No single anesthetic agent is ideal for patients with PAH. Many anesthetics have mixed hemodynamic effect. Premedication should be considered if the child is anxious, proper depth of anesthesia and analgesia prior to airway intervention and/or noxious stimuli, etc. If general anesthesia is indicated, a careful titration of induction agents and balanced anesthetic technique should be employed and maintained. In addition, specific pulmonary vasodilators can be incorporated in anesthetic management. It is important that anesthesiologists caring for children with PA Hare aware of the increased perioperative cardiovascular risk, understand the underlying pathophysiology of PAH in a particular patient, formulate an appropriate anesthetic management plan and prepare to treat the potential occurrence of pulmonary hypertensive crisis. If an acute PAH crisis occurs, our goals of treatment are to dilate the pulmonary vasculature, support cardiac output and remove stimuli causing increase in PVR.[10]

a. Administer 100% oxygen- Increased $PaO_2$ can decrease PVR.
b. Hyperventilation to induce a respiratory alkalosis-PAP was directly related to $PCO_2$ thus decreases of $PCO_2$ might improve patient's condition.

c. Correct metabolic acidosis-PVR is directly related to $H^+$ concentration.
d. Administer pulmonary vasodilators- Inhaled nitric oxide (iNO) is generally the first choice followed by intravenous or inhaled prostacyclin analogs.
e. Support cardiac output- Adequate preload is important. Inotropic support is often used. Dobutamine reduces PVR but often dopamine is preferred to maintain SVR and enhance coronary perfusion.
f. Attenuate noxious stimuli- pretreatment with analgesics and anxiolytics can attenuate the hemodynamic response to noxious stimulation.

In spite of appropriate PAH treatment and careful anesthetic management, there is an increased risk of perioperative complications such as *bradycardia, supraventricular tachycardia, airway obstruction, hypotension, decreases of $SpO_2$, unplanned mechanical ventilation, PAH crisis or cardiac arrest* in children with PAH undergoing noncardiac sugery or cardiac catheterization.[7] Carmosino et al.[7] (2007) found children with suprasystemic PAH are at a significant risk of cardiac arrest and pulmonary hypertensive crisis. The investigators also found complications were not significantly associated with age, etiology of PAH, type of anesthetic technique or airway management. Thus pediatric anesthesiologist should be prepared to prevent and treat the acute PAH crisis in a child who has PAH.[10]

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