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Recognition, Stabilization, and Management of Children with Pulmonary Hypertension in the Emergency Department

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Introduction

Pulmonary hypertension (PH) is an uncommon but potentially life-threatening condition in children, and improved survival makes it more likely that acute care practitioners will encounter children with PH. This is due in part to better outcomes of extremely preterm infants who develop PH from chronic lung disease and children with congenital heart and lung defects who survive surgery but have residual PH, increased diagnosis of PH due to expanded screening indications, and better diagnostic modalities. The goal of this chapter is to provide an overview of the types of pediatric PH likely to be encountered in the acute care setting and discuss the recognition and initial management of this disease. Specific clinical cases will be presented to illustrate various pulmonary hypertensive emergencies in the five categories of PH as classified by the World Health Organization. These consist of (1) pulmonary arterial hypertension, (2) PH with left heart disease, (3) PH associated with lung diseases and/or hypoxemia, (4) PH due to chronic thrombotic and/or embolic disease, (5) and miscellaneous.

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Case 1

A 3-month-old infant presents with tachypnea and poor feeding for the last week. The mother states that the baby has decreased her formula intake to 2 ounces per feed, which takes 40 min to get in. On examination, she is noted to have a respiratory rate of 65, a heart rate of 170, a grade 3/6 harsh holosystolic murmur at the lower left sternal border, and a grade 2 diastolic rumble at the apex. She has tachypnea and retractions with mildly reduced perfusion, and the liver edge is palpated 4 cm below the right costal margin.

What is the most likely etiology of this collection of signs and symptoms?

(a) RSV bronchiolitis
(b) Large ventricular septal defect
(c) *Staphylococcus aureus* sepsis
(d) Tetralogy of Fallot
(e) Aortic insufficiency

Pulmonary artery hypertension from congenital heart disease may present several weeks to months after birth since the pulmonary vascular resistance (PVR) is high at the time of delivery due to the lungs being filled with amniotic fluid in utero. Normally, this PVR decreases dramatically after birth as the lung fluid decreases and oxygen is introduced with the first breaths. PVR then decreases to normal adult levels usually by 6 months of age as the smooth muscle in the pulmonary arterioles resorbs. When there is a large intracardiac communication present such as a ventricular septal defect (VSD), this fall in pulmonary pressure and PVR does not occur as rapidly. Thus, early in life, the infants are typically asymptomatic, and no murmur or only a very soft systolic murmur is present as not much shunting occurs through the defect. Over the next few weeks, the PVR gradually decreases, and the left to right shunting through the VSD increases. This leads to progressive pulmonary overcirculation and fluid retention, which produces the symptoms described above. The infants breathe fast to compensate for reduced lung compliance, which leads to poor feeding and post-feeding emesis. With increased flow across the VSD, the systolic murmur becomes louder, and a diastolic murmur may appear from the excess flow across the mitral valve. Fluid backs up into the liver accounting for the hepatomegaly, and there is activation of the sympathetic nervous system causing the tachycardia [1]. If the pulmonary overcirculation is severe, there is a decrease in systemic output producing the reduced peripheral perfusion, which on occasion can present as a shock-like state.

Diagnostic Clues

A chest x-ray will reveal significant cardiomegaly and diffuse pulmonary congestion. The ECG typically shows left ventricular or biventricular hypertrophy. Echocardiography is diagnostic and will show the dilated left atrium and ventricle and the large VSD (Fig. 13.1). A large PDA can present the same way; however, the murmur would be continuous and is described as “machinery” in quality.

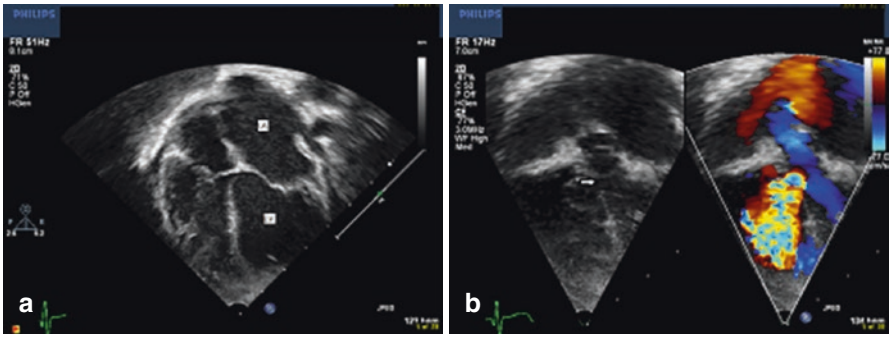

Fig. 13.1 (**a**) Apical four chamber view showing the dilated left atrium (LA) and left ventricle (LV). (**b**) Color comparison of apical five-chamber view showing a large ventricular septal defect (arrow) and the color flow from the LV to the right ventricle

Emergency Management Principles

Unlike other causes of near shock or shock in infants, large fluid boluses may be detrimental in those with large left to right shunts who are already fluid overloaded. They require a delicate balance of cautious intravenous fluid administration to maintain intravascular volume and aggressive diuresis to remove the extracellular fluid. If the echocardiogram shows any decrease in cardiac function, then low doses of intravenous inotrope administration are helpful acutely. These infants typically respond quickly to diuretics, most commonly intravenous furosemide (1 mg/kg/dose) which can be given two to three times a day and then changed to the oral form. Spironolactone is recommended to maintain electrolyte balance at a dose of 1 mg/kg/dose twice daily. Once the infant is stabilized, oral feeding can be resumed, and concentration of the formula is recommended to maximize the calories and minimize the water intake. Standard 20 cal/oz formulas can be concentrated gradually up to 24, 27, and even 30 cal/oz as long as no osmotic diarrhea occurs. In the most severe cases, the formula needs to be given through a nasal gavage tube, and if bolus feedings are not tolerated, then continuous low volumes can be delivered. As the metabolic demands are greater in pulmonary overcirculation, 140–150 kcals/kg/day may need to be given to achieve steady growth. If the infant continues to struggle despite these maneuvers, then surgical repair is indicated.

Correct answer: b-Large ventricular septal defect

Case 2

A 6-month-old is brought to the ED with 2 weeks of decreased feeding, increased post-feeding emesis, and increased work of breathing. The mother states that he had heart surgery just after birth for abnormally connected veins from the lungs. On examination, there is a well-healed median sternotomy scar with an active precordium and a right ventricular lift. The baby is afebrile but tachypneic, and there is a

loud second heart sound with no murmur. The liver edge is palpated 6 cm below the right costal margin. Oxygen saturation is 96%.

What is the most likely etiology of this collection of signs and symptoms?

(a) Pyloric stenosis
(b) Pneumonia
(c) Post-pericardiotomy syndrome
(d) Idiopathic pulmonary arterial hypertension
(e) Obstructed pulmonary venous return

A loud pulmonic component of the second heart sound is an important diagnostic clue to the presence of pulmonary hypertension, as a high diastolic pulmonary pressure will force the pulmonary valve shut with greater intensity. Pulmonary vein stenosis is an example of obstruction to blood flow returning to the left atrium and acts like obstruction in the left heart at other levels including cor triatriatum, mitral stenosis, and aortic stenosis. Isolated pulmonary vein stenosis is a rare cause of such obstruction but can occur in up to 11% of children who have undergone repair of total anomalous pulmonary venous return [2]. This leads to transmission of back pressure into the pulmonary arteries and progressive lung and hepatic congestion, poor feeding and growth, and heart failure.

It is important to auscultate the second heart sound and become familiar with the normal sound intensity so that when the sound is increased, it will be recognized and the patient evaluated for PH. The other forms of left heart obstruction should be accompanied by a heart murmur, systolic ejection in the case of aortic outflow obstruction, and a diastolic inflow murmur for cor triatriatum or mitral stenosis. Many of these lesions are amenable to surgery or catheter-based intervention; however, pulmonary vein stenosis may be due to a progressive, fibrosing, endothelial proliferation that can be resistant to such treatments.

Diagnostic Clues

A chest x-ray will reveal diffuse pulmonary venous congestion. The ECG will have large R waves in lead V1 and/or large S waves in leads V5-6 indicating right ventricular hypertrophy (Fig. 13.2). Echocardiography is important to evaluate the surgical repair, quantify the right ventricular size and function, and estimate the pulmonary pressures. Often a cardiac catheterization is required to evaluate the extent of stenosis in the pulmonary veins, and if two or more are affected, there is a poor prognosis [3].

Emergency Management Principles

Young children with left heart obstruction often present with respiratory or gastrointestinal (GI) symptoms that can mimic pneumonia, bronchiolitis, asthma, or GI

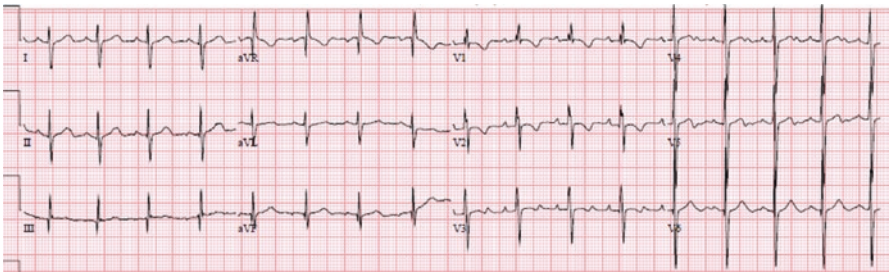

Fig. 13.2 ECG showing right axis deviation and right ventricular hypertrophy with an "rSR" in lead V1 and deep S waves in V5.6

obstruction. If they are critically ill, basic resuscitative efforts should be performed for stabilization and restoration of circulation. Those who are less sick on presentation should be given intravenous diuretics and oxygen while cardiology consultation is obtained. Fluid overload should be avoided, and evaluation for infection should be undertaken. Frank heart failure is often brought on by an acute infection in the face of previous cardiac compensation for the obstruction with myocardial hypertrophy to maintain cardiac output.

Correct answer: e-Obstructed pulmonary venous return

Case 3

A 9-month-old is brought in by ambulance after being found by her mother in bed unresponsive and blue in appearance. She performed CPR and called 911. History reveals a preterm birth at 24 weeks' gestation with a prolonged NICU stay and severe bronchopulmonary dysplasia (BPD) requiring tracheotomy and home ventilation. Home medications include diuretics, sildenafil, albuterol, and Pulmicort inhalers. Examination shows a heart rate of 135, respiratory rate of 45 (above the set ventilator rate), blood pressure of 70/30, oxygen saturation of 75%, harsh and course breath sounds throughout, and a loud second heart sound with a capillary refill of 3–4 s. An NT-proBNP is 4400 pg/mL.

What is the most likely etiology of this collection of signs and symptoms?

(a) TET (hypercyanotic) spell
(b) Ventricular tachycardia
(c) Pulmonary hypertensive crisis
(d) Tracheal tube obstruction
(e) Aspiration pneumonia

A common complication of severe BPD is pulmonary hypertension, which in the revised WHO classification of PH is class 3, "associated with lung diseases and/or hypoxemia" [4]. The presence of PH in children with BPD puts them at risk for significant morbidity and a mortality with independent risk factors for death being

severe PH at systemic or suprasystemic levels and small for gestational age status with a birth weight less than the third percentile for gestational age [5]. The presence of a patent foramen ovale or patent ductus arteriosus provides a communication for mixing of saturated and unsaturated blood, and any stimulus which acutely increases the pulmonary vascular resistance will cause more right to left shunting and desaturation. This may herald a pulmonary hypertensive crisis with progressive hypoxemia, which may escalate to decreased cardiac output, bradycardia, hypotension, and cardiac arrest.

Diagnostic Clues

An arterial blood gas will show a low-oxygen level and CO2 retention, some of which may be chronic. In a crisis, metabolic acidosis may be present as well. The chest x-ray will show the chronic lung disease of BPD (Fig. 13.3) but may also show a new pneumonia, atelectasis, or pleural effusion that has tipped the patient into a PH crisis. Other studies (ECG, echo, MRI, cardiac catheterization) may be useful after the patient has been stabilized in the ICU setting.

Emergency Management Principles

Emergency interventions include 100% oxygen delivery, sedation, suctioning to clear the airways of any mucous plugging, and transient hyperventilation. The addition of inhaled nitric oxide at a dose of 20 ppm can produce effective pulmonary vasodilation and reverse such a crisis allowing for transfer to an intensive care setting for further management [6].

Correct answer: c-Pulmonary hypertensive crisis

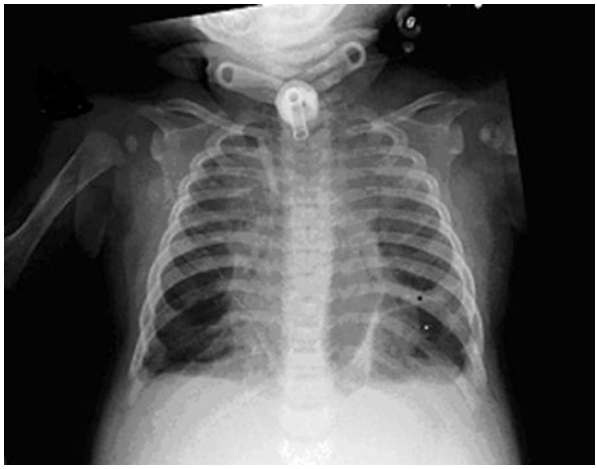

Fig. 13.3 CXR showing the tracheostomy tube, chronic lung changes of BPD, with atelectasis and hyperinflation

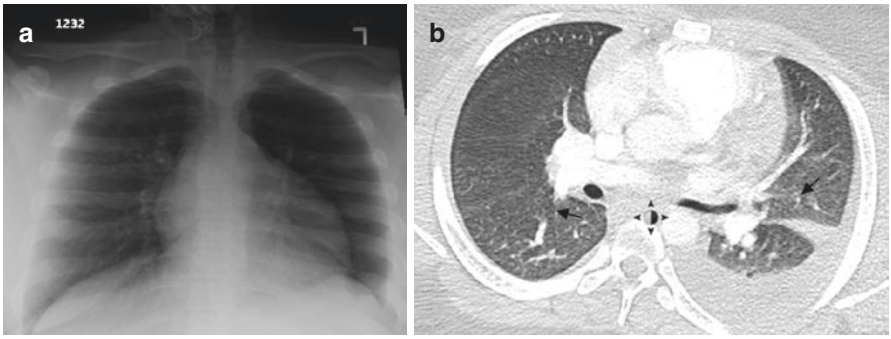

Fig. 13.4 (**a**) Chest x-ray shows small airway disease, with bilateral perihilar patchy opacities. (**b**) Axial CT with contrast of the chest showed multiple bilateral subsegmental filling defects (arrows) within the pulmonary arteries, including the right and left upper lobes. A pleural effusion is present on the left

Case 4

A 15-year-old morbidly obese female with a history of stage V lupus nephritis and hypertension presents to the emergency department with a chief complaint of fever and difficulty breathing. She began having pain in her left shoulder 1 week ago. On presentation, she complained of chest pain and "heavier than normal" breathing, preceded by 2 weeks of upper respiratory infection symptoms and a lingering dry cough. She had a T_{max} of 100.7 °F on the day of presentation. She also reports a migraine headache with vomiting 4 days ago. She is currently taking hydroxychloroquine, mycophenolate, prednisone, lisinopril, and nifedipine. On physical exam, breath sounds are clear and equal bilaterally, and respirations are non-labored. There is a regular rhythm, no murmurs or gallop is present, and the pulses are equal in all extremities with normal peripheral perfusion. The left thigh is markedly swollen compared to the right with no tenderness on palpation, but stretching of the left leg does cause pain.

Vital signs: BP 148/88, heart rate 92, respiratory rate 25, temperature 37.4 °C, and oxygen saturation 92% on room air.

Laboratory evaluation: Electrolyte panel normal, WBC 5.0×10^3/μL, hematocrit 32.5%, platelets 218×10^3/μL, PT 9.4, INR 0.89, aPTT 25.4, D-dimer 139.2, fibrinogen 610, negative viral respiratory panel, pregnancy screen negative.

Chest x-ray and chest CT with contrast (see Fig. 13.4).

What is the most likely etiology for this child's symptoms?

(a) Pulmonary embolism
(b) Pneumonia
(c) Myocardial infarction
(d) Lung abscess
(e) Anxiety

Clinical Presentation

Chronic thromboembolic pulmonary hypertension (CTEPH) is a specific subclass of pulmonary hypertension that represents the cumulative effect of acute pulmonary emboli (PE) that have not completely resolved. Each unresolved embolus eventually organizes into fibrotic material that occludes the proximal large-caliber pulmonary arteries and causes microvascular dysfunction in more distal small-caliber pulmonary arteries that remain patent [7]. Most of our understanding about the clinical presentation, therapy, and prognosis of CTEPH comes from large adult studies since there are no large studies of pediatric CTEPH to date. However, venous thromboembolism has become a more frequent diagnosis in the pediatric patient population [8]; thus, CTEPH should be an important diagnostic consideration in symptomatic children with a known hypercoagulable state, a history of thromboembolism or venous catheter placement, and/or a diagnosis of pulmonary hypertension [7, 9]. In the largest pediatric CTEPH cohort studied to date, the most common presenting symptom was exertional dyspnea and/or exercise intolerance (94%), followed by syncope or presyncope (47%), chest pain (35%), cough (29%), cyanosis (18%), edema (12%), and hemoptysis (12%) [10]. Only 35% of patients had a recognized history of a prior PE at the time of diagnosis, and up to 42% had a history or ultrasound findings consistent with a diagnosis of deep venous thrombosis. Idiopathic pulmonary arterial hypertension was the initial diagnosis in 29%. A few patients were initially diagnosed with atypical pneumonia ($n = 3$) or asthma ($n = 2$) [10].

Diagnostic Clues

It is critical to have a high index of suspicion for CTEPH in any child with risk factors for thromboembolic disease in the acute care setting. Timely initiation of definitive surgical or medical therapy can treat the underlying pathology and potentially be lifesaving. The simplest way to think about CTEPH risk is the time-honored Virchow's triad: Hypercoagulable state—endothelial injury–stasis of flow (Fig. 13.5).

A preexisting hypercoagulable state is the most commonly diagnosed risk factor for CTEPH in children. A recent study showed that over 70% of pediatric CTEPH cases necessitating pulmonary thromboendarterectomy also had an identifiable thrombophilic state such as lupus anticoagulant (30%), anticardiolipin antibody (24%), and protein C deficiency (18%) [10]. Over 30% of patients had a positive family history of thromboembolism and/or hypercoagulable state. While these numbers are not necessarily generalizable to other acute care settings, they do illustrate the importance of immediate pediatric hematology consultation to ensure the proper laboratory studies are obtained for diagnosis and that the patient receives the proper long-term follow-up upon discharge. It is also important to recognize the use

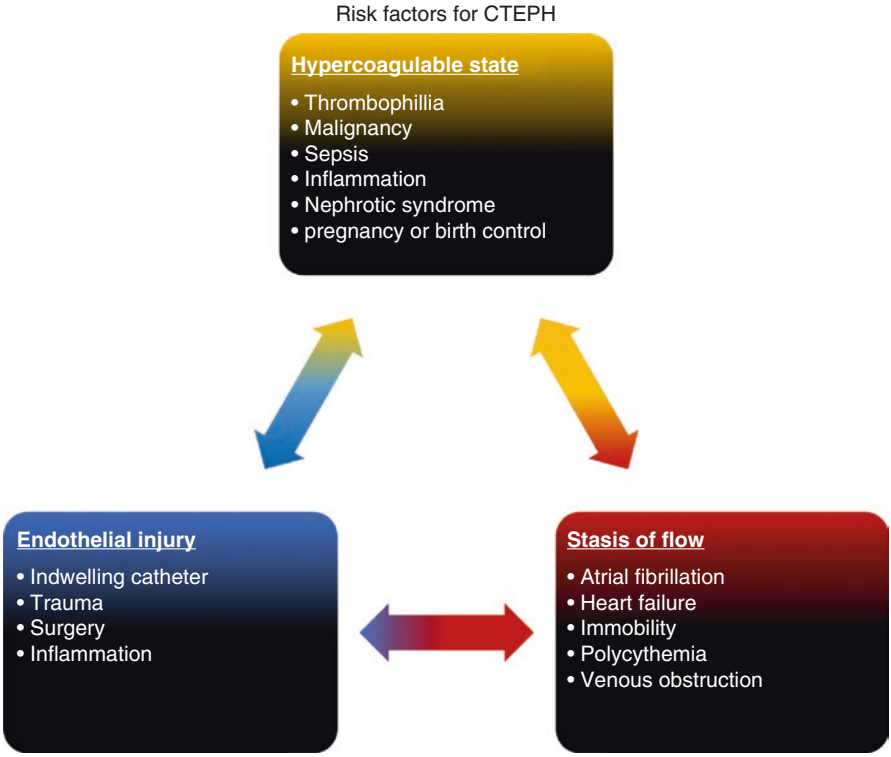

Fig. 13.5 Risk factors for chronic thromboembolic pulmonary hypertension

of oral contraceptives and pregnancy as risk factors for thrombotic disease, even in the pediatric population.

It is important to obtain a thorough history and physical exam to assess for obesity, sedentary habits, and injury-induced immobilization [10, 11] and history of cardiac disease/arrhythmias or signs/symptoms of cardiac dysfunction to assess for risk of blood flow stasis. Polycythemia, a commonly missed risk factor for venous stasis, causes increased blood viscosity and margination of platelets to the endothelial surface—further increasing the risk of thrombosis [12]. Polycythemia is common in the context of cyanotic congenital heart disease or chronic lung disease. Recent studies have cautioned against aggressive blood transfusions to achieve an arbitrary hematocrit in the absence of objective evidence of inadequate oxygen delivery [13–18]; thus, clinicians should avoid supraphysiologic hematocrit levels in the acute management of patients at risk for CTEPH.

Imaging to diagnose pulmonary thromboembolic disease and pulmonary veno-occlusive disease (PVOD) should be performed at the time of diagnosis (*class 1, Level of Evidence B*). Computed tomography pulmonary angiography (CTPA) is the most well-validated imaging modality for the diagnosis of pulmonary embolism [19, 20].

Emergency Management Principles

Once the clinician has recognized that CTEPH is the probable etiology for the child's acute presentation, stabilization and definitive surgical or medical therapy should be initiated as soon as possible and in parallel. Stabilization involves the basic ABCs of the PALS algorithm in the acute setting.

- *Airway patency*:
  - Hemoptysis:
    If severe, secure airway, isolate bleeding source (respiratory vs. GI), ventilate with high mean airway pressure to tamponade lower airway breathing, and administer appropriate blood products.
  - Loss of consciousness:
    Secure airway, determine etiology (history, examination, imaging), and treat.
  - Space-occupying tumor of the neck or mediastinum:
    Ensure anesthesia or advanced airway team available before attempting to secure airway.
- *Breathing*:
  - Infection (bacterial or viral pneumonia):
    CXR, antimicrobials, cultures, and respiratory support as needed
  - Hemoptysis-induced pneumonitis:
    See *airway*
  - Pulmonary edema:
    Deliver supplemental O_2 to maintain appropriate O_2 delivery and pulmonary vascular patency. Consider more invasive positive pressure delivery or nitric oxide in the context of persistent hypoxia.
  - Reactive airways disease/lower airway inflammation:
    Acute asthma management: Steroids
- *Circulation*:
  - Right ventricular dysfunction/cor pulmonale:
    Inotropic support for RV function and reduce RV afterload (see pulmonary vascular hypoperfusion)
  - Pulmonary vascular hypoperfusion:
    Correct hypoxia and hypercarbia, target neutral blood pH and nitric oxide, and consult cardiology for advanced PH therapy (sildenafil, bosentan, inhaled vs. IV prostacyclins).
  - Left ventricular failure:
    Echocardiogram to identify etiology (dilated, obstructive, tamponade, etc.). Treat underlying etiology (inotropes, diuresis, afterload reduction, drain effusion, etc.)
  - Sepsis:
    Antibiotics, intravascular volume expansion, and vasopressors
  - Dehydration:
    Identify source (GI loss, increased insensible loss, acute kidney injury, bleeding, etc.)
    Intravascular volume expansion

CTEPH is one of the few subclasses of pulmonary arterial hypertension that is potentially curable. Patients diagnosed with CTEPH should be rapidly transferred to a tertiary care center for consideration of surgical pulmonary thromboendarterectomy (PTE) or catheter-based removal or lysis of the acute and chronic thromboembolic material. PTE offers an effective treatment for this condition, significantly improving cardiopulmonary hemodynamics, gas exchange, functional status, and survival [7, 10]. Although there is controversy about many aspects of CTEPH management, it is generally accepted that PTE should be pursued if the patient is a candidate for the procedure.

Not all patients with CTEPH are surgical candidates, and there are emerging treatments—medical therapy and balloon pulmonary angioplasty—that have shown benefit in this patient population. In the acute setting, especially when the patient's candidacy for PTE is being evaluated, heparin is the anticoagulant of choice. Heparin can be titrated based on the individual institution's anticoagulation protocol, although a PTT range of 60–80 s is generally acceptable. Some institutions adjust heparin dose based on anti-Xa levels.

Recommendation from the American Heart Association and American Thoracic Society for management of pediatric pulmonary hypertension is to use warfarin for long-term anticoagulation. The guidelines state "Warfarin may be considered in patients with IPAH/HPAH, patients with low cardiac output, those with a long-term indwelling catheter, and those with hypercoagulable states (*Class IIb; Level of Evidence C*). Targeting the therapeutic range for an international normalized ratio (INR) between 1.5 and 2.0 is recommended for young children with PAH (*Class I; Level of Evidence C*). Anticoagulation beyond baby aspirin should not be used in young children with PAH because of concerns about harm from hemorrhagic complications (*Class III; Level of Evidence C*) [21]."

Without treatment, CTEPH can lead to progressive pulmonary vascular obstruction, right heart failure, and death. Thus, it is important for clinicians to recognize this subtype of PH.

Correct answer: a-Pulmonary embolism

Case 5

A 17-year-old boy with sickle cell disease presents to the emergency department with fatigue, tachypnea, chest pain, retractions, wheezing, hepatomegaly 3 cm below the costal margin, and pulse oximetry of 75%. He is afebrile and has a heart rate of 135, respiratory rate of 43, and BP of 110/72. Hemoglobin is 7.1 g/dL and reticulocytes 35%. Chest x-ray revealed clear lung fields and severe cardiomegaly. EKG showed biventricular hypertrophy. An echocardiogram showed mild bilateral, biventricular, and pulmonary artery dilation with an estimated right ventricular systolic pressure of 52 mmHg. Oxygen, red cell exchange transfusion, and bronchodilators were administered, and he continues to require 6 L oxygen via nasal cannula to maintain pulse oximetry >90%.

What mechanism of action best explains the presenting symptoms in this patient?

(a) Airway inflammation and bronchial smooth muscle constriction
(b) Fat emboli resulting from bone marrow infarction becoming lodged in the renal arteries
(c) Free hemoglobin scavenging endothelial nitric oxide, resulting in pulmonary vascular constriction
(d) Acute infarction of the left anterior descending coronary artery
(e) Referred pain from acute splenic infarction

Clinical Presentation

Sickle cell disease (SCD) is a monogenetic disease caused by a single point mutation in the gene for hemoglobin, resulting in a complex multimodal phenotype. Erythrocyte sickling in response to hypoxia and dehydration leads to hemolysis, highly adhesive erythrocytes, systemic inflammation, and baseline hypercoagulable state. All of these factors contribute to pulmonary vasculopathy and acute pulmonary vasoconstriction in patients with SCD.

Children with SCD most commonly present to the emergency setting with acute onset of vaso-occlusive pain requiring opiate analgesia for relief. It is important to remember that even in the case of isolated pain episodes, children with SCD can develop secondary pulmonary complications as a result of:

- Bone infarction ⇒ fat emboli ⇒ pulmonary artery embolus ⇒hypoxia
- Rib pain ⇒hypoventilation ⇒atelectasis ⇒ hypoxia and hypercarbia
- Opiate analgesia ⇒hypoventilation ⇒ hypoxia and hypercarbia

Both hypoxia and hypercarbia can predispose a child with SCD to acute chest syndrome and increased pulmonary vascular resistance in the acute setting.

Many children with SCD also present in a state of acute hemolysis, causing the release of cell-free hemoglobin in the plasma. Free hemoglobin can sequester endothelial nitric oxide, impairing the normal pulmonary artery vasoactive response [22]. Additionally, cell-free hemoglobin can also suppress arginase activity and initiate vascular inflammation through oxidant stress, all of which can further contribute to the acute impairment of normal pulmonary artery vasoactive functions [22]. This can all lead to refractory hypoxia and increase pulmonary arterial pressure.

Children presenting with acute chest syndrome are at very high risk for acute pulmonary hypertensive episodes. One study found that approximately 60% of adults presenting with severe acute chest syndrome have evidence of acute pulmonary hypertension on echocardiography, defined as a tricuspid regurgitant jet (TRJ) velocity > 2.5 m/s. Elevated TRJ velocity also positively correlated with B-type natriuretic peptide (rho = 0.54, $P < 0.01$) and cardiac troponin I (rho = 0.42, $P < 0.01$). Cor pulmonale occurred in 11 (13%) episodes [23].

Diagnogstic Clues

Mild steady-state pulmonary hypertension, with a TRV of 2.5 m/s or greater, is a major independent risk factor for death in adults with SCD [24]. It is important to remember that the relative anemia and hyperdynamic left ventricle characteristics of most individuals with SCD can lower the measured TRV. Moderate pulmonary artery pressure elevation may be poorly tolerated by patients with SCD, especially in the context of increased oxygen consumption (pain, increased work of breathing) and decreased oxygen delivery (acute on chronic anemia). These factors contribute to high risk of sudden death. Furthermore, acute pulmonary artery pressure elevation has been documented during vaso-occlusive pain crisis or exercise in patients with SCD [25]. While mild pulmonary hypertension is a risk factor for death in adults with sickle cell disease, this has not been proven in children. However, as acute PH has been reported during exercise and vaso-occlusive pain crisis in sickle cell patients [23], acute pulmonary hypertension should be suspected in any child with sickle cell disease presenting to the ED with difficulty breathing, chest pain, dyspnea on exertion, or any sign of low cardiac output.

The severity of anemia and the rate of hemolysis are risk factors for developing pulmonary hypertension in SCD [26]. Direct laboratory indicators of hemolysis include cell-free plasma hemoglobin and red blood cell microparticles, and indirect laboratory indicators include low plasma haptoglobin levels and elevated reticulocyte counts, bilirubin levels, RBC aspartate amino transferase, and lactate dehydrogenase enzymes [27]. Clinical manifestations of hemolysis—induced vascular disease in SCD—include low-oxygen saturations, pulmonary hypertension, increased systemic systolic artery pressures and pulse pressures, chronic kidney disease (proteinuria), cutaneous leg ulcerations, and stroke in children. In numerous clinical cohorts, the severity of both anemia and measured indexes of hemolytic rate is a risk factor for developing pulmonary hypertension in sickle cell patients [28–33]. Vaso-occlusive painful crisis and acute chest syndrome (ACS) are associated with higher steady-state free hemoglobin levels and high leukocyte counts [34].

Emergency Management Principles

Children with SCD who have symptoms suggestive of acute chest syndrome should be carefully managed given their unique risk for a vicious cycle of pulmonary arterial hypertension, hypoxia, and erythrocyte cycling. The following are the ABCs of emergency management:

1. *Airway patency*:
   (a) Opiate-induced loss of pharyngeal tone or preexisting obstructive sleep apnea:
      - Many patients require opiate analgesia to treat acute pain episodes.
      - Although opiate-induced hypoventilation is rare in SCD, impairment of ventilation and oxygenation can dramatically increase the risk of acute pulmonary hypertension in this population.

2. *Breathing*:
   (a) Pain-induced hypoventilation:
      - Treat pain aggressively.
      - Monitor response to opiate analgesia closely.
      - Administer supplemental oxygen to maintain $FiO_2 > 94\%$.
      - Obtain CXR if the patient requires supplemental O_2.
   (b) Opiate-induced hypoventilation:
      - Assist ventilation and administer supplemental O_2 to maintain $FiO_2 > 94\%$.
      - CXR to rule out acute chest syndrome or atelectasis.
      - Aggressively treat acute chest syndrome if suspected.
   (c) Reactive airways disease/lower airway inflammation:
      - Acute asthma management: Steroids.
      - Asthma is common in patients with SCD; wheezing in SCD can also be caused by pulmonary vascular disease or chronic lung disease.
3. *Circulation*:
   (a) Acute vaso-occlusive crises:
      - CBC, reticulocyte %, bilirubin, lactate dehydrogenase, and hemoglobin electrophoresis.
      - Simple or exchange transfusion for acute hemolysis.
      - Treat pain as needed (NSAIDs and opioids).
      - Encourage incentive spirometry while awake to reduce risk of ACS.
   (b) Acute chest syndrome:
      - CXR.
      - Treat pain as needed.
      - Supplemental O_2 to keep O_2 saturations >95%.
      - Intravenous cephalosporin and an oral macrolide antibiotic.
      - Urgent exchange transfusion in consultation with hematology, critical care, and/or apheresis subspecialists when there is rapid progression (O_2 saturation < 90% despite supplemental oxygen), respiratory distress, progressive pulmonary infiltrates on CXR, and/or decline in hemoglobin concentration despite simple transfusion
   (c) Pulmonary hypertension:
      - CXR (cardiomegaly, atelectasis, ACS)
      - EKG (right heart strain pattern)
      - Echo and cardiology consult:
        – Right heart catheterization may be useful if:
          TRJ >2.5 m/s and symptoms
          TRJ > 3.0
          No TRJ on echo to estimate pulmonary pressures
        – Consider PAH therapy for precapillary PH:
          mPAP >25 mmHg
          PAWP <15 mmHg
          PVR > 2 indexed Wood units or 160 dynes-s/cm^5
        – Outpatient evaluation when stable:
          Sleep study
          Lab evaluation: ANA, HIV, and LFTs

- Check NT-proBNP
- Supplemental O_2 for O_2 saturations <95%

Correct answer: c-Free hemoglobin scavenging endothelial nitric oxide, resulting in pulmonary vascular constriction

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