Pediatric Pulmonary Hypertension: Diagnosis And Management In The Acute Care Setting

A 10-year-old girl is brought to the pediatric emergency department after collapsing at school during her physical education class. She is well known to the emergency physicians, having been treated in the ED on multiple occasions over the past year for asthma exacerbations. Most recently, she was admitted for inpatient treatment and was discharged after 24 hours with nebulized bronchodilators.

As the paramedics transfer her to the ED staff, the patient’s mother reports that her daughter has experienced increasing shortness of breath with exercise over the past few days - even with walking up stairs at home - and, in general, has appeared to be fatigued. The patient has been using her prescribed inhaler frequently, without clear relief. The mother also mentions that on the evening prior to this event, her daughter complained of abdominal pain.

Pediatric pulmonary hypertension is a relatively rare, often rapidly progressive disease with varied etiologies that is associated with significant morbidity and mortality. In fact, until recently, virtually all patients with this condition died within a few years of diagnosis. Fortunately, fundamental advances in vascular biology over the last several decades have translated into a vast expansion of our understanding about pulmonary hypertension, and an increasing number of promising therapies have emerged to treat this condition.

Even today, however, the care of these patients remains highly specialized, often requiring referral to regional tertiary academic institutions for specialized, often requiring referral to regional tertiary academic institutions for specialized care setting.
centers with dedicated pediatric pulmonary hypertension programs. Such concentrated expertise carries many advantages but also bespeaks an inadequate permeation of knowledge about pulmonary hypertension amongst the larger healthcare community. Referrals to such centers are possible only after the diagnosis has been considered, placing the onus on local providers to correctly identify patients in need of further evaluation and care. In addition, therapies for pulmonary hypertension are generally chronic and are often associated with morbidities that are likely to manifest when patients are at home. Furthermore, the initial presentation of pulmonary hypertension in infancy or childhood often mimics other more common, less dangerous diseases, and correctly identifying these patients requires a high index of suspicion.

Emergency medicine physicians and acute care providers face a daunting challenge when knowingly or unknowingly faced with these patients. Failing to recognize the initial presentation of pulmonary hypertension can result in a life-threatening delay in the initiation of specific therapies. Furthermore, an inadequate understanding of the basic pathophysiology associated with pulmonary hypertension - and acute pulmonary hypertensive crises in particular - will retard the institution of appropriately directed therapies, even in patients already diagnosed with this condition, with potentially devastating consequences.

Because the potential consequences can be so devastating, this issue of Pediatric Emergency Medicine Practice will provide a comprehensive overview of pediatric pulmonary hypertension, with particular attention to diagnosis and acute management. An understanding of the pathophysiology of pulmonary hypertension is fundamental to the ability to recognize and treat these patients and will be reviewed in great detail.

### Abbreviations Used In This Article

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BMPR2</td>
<td>Bone Morphogenetic Protein Receptor II</td>
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<tr>
<td>ECLS</td>
<td>Extracorporeal Life Support</td>
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<td>EPCs</td>
<td>Endothelial Progenitor Cells</td>
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<td>FPAH</td>
<td>Familial Pulmonary Arterial Hypertension</td>
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<tr>
<td>IPAH</td>
<td>Idiopathic Pulmonary Arterial Hypertension</td>
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<tr>
<td>NO</td>
<td>Nitric Oxide</td>
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<tr>
<td>NOS</td>
<td>Nitric Oxide Synthase</td>
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<tr>
<td>PCPA</td>
<td>Partial Cavopulmonary Anastomosis</td>
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<td>PDEs</td>
<td>Phosphodiesterases</td>
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<td>PPHN</td>
<td>Persistent Pulmonary Hypertension of the Newborn</td>
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<td>PHTN</td>
<td>Pulmonary Hypertension</td>
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<tr>
<td>RAP</td>
<td>Right Atrial Pressure</td>
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<tr>
<td>RVSP</td>
<td>Right Ventricular Systolic Pressure</td>
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<tr>
<td>sPAP</td>
<td>Systolic Pulmonary Arterial Pressure</td>
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<tr>
<td>TCPA</td>
<td>Total Cavopulmonary Anastomosis</td>
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<tr>
<td>V/Q</td>
<td>Ventilation-Perfusion</td>
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### Critical Appraisal of the Literature

A literature review was conducted using the MEDLINE and PubMed databases. The terms hypertension and pulmonary were used. The search was limited to studies conducted between 1980 and 2007 that concerned human subjects, were written in the English language, and had an available abstract. The Cochrane Database of Systematic Reviews was searched for reviews pertinent to pulmonary hypertension. The recent evidence-based clinical practice guidelines for the diagnosis and management of pulmonary arterial hypertension from the American College of Chest Physicians were reviewed as well. The search was then further limited to studies concerning subjects from birth to 18 years of age. Older studies and pertinent basic science as well as animal-based studies referenced in the above studies were also reviewed.

The review of the literature indicated a recent surge in available therapies for pulmonary hypertension. The evidence for these newer therapies often includes randomized placebo-controlled trials. However, many of the recommendations contained within the literature, particularly for the proper diagnostic approach, are based upon uncontrolled studies or expert opinion. Additionally, far fewer data are available for pediatric patients as compared to the adult population.

### Epidemiology, Etiology, And Pathophysiology

#### Definition, Classification, Etiology And Epidemiology

Pulmonary hypertension is defined as a mean pulmonary artery pressure of greater than 25 mmHg at rest or greater than 30 mmHg during exercise. Echocardiography, rather than right heart catheterization, is increasingly used to estimate pulmonary artery pressures. Clinicians often employ a practical definition for pulmonary hypertension of a systolic pulmonary artery pressure that exceeds 50% of the systolic systemic arterial pressure, although the formal definition is used for most clinical studies.

In 2003, the Third World Symposium on Pulmonary Arterial Hypertension was convened by the World Health Organization, and a new classification system was created (Table 1). This system divided pulmonary hypertension into pulmonary arterial hypertension, pulmonary venous hypertension, pulmonary hypertension associated with hypoxemia or disordered respiratory function, pulmonary hypertension associated with thrombotic or embolic disease, and pulmonary hypertension secondary to miscellaneous diseases. This system
discarded the term “primary pulmonary hypertension” in favor of “sporadic or idiopathic pulmonary arterial hypertension” (IPAH) since it is a diagnosis of exclusion.

In neonates, the most common etiology results from a failure to undergo the normal fall in pulmonary vascular resistance at birth (persistent pulmonary hypertension of the newborn, PPHN), with an incidence of < 1 per 1000 live births. Other pulmonary abnormalities, such as congenital diaphragmatic hernia, respiratory distress syndrome, and bronchopulmonary dysplasia, may also result in neonatal pulmonary hypertension.

Beyond the neonatal period, the majority of pediatric pulmonary hypertension is due to congenital heart defects or IPAH. Congenital heart disease occurs in approximately 1% of live births.10 Without surgical palliation or repair, one-third of these patients die from pulmonary hypertension.11 In this population, risk factors for developing pulmonary hypertension include systemic to pulmonary (left-to-right) shunts, transposition of the great arteries, and pulmonary venous hypertension.8,12-14

The true incidence of IPAH is unknown, but experts believe that it has been under-diagnosed in years past.15-17 At present, the best available estimates suggest an incidence of 1-2 cases per million people.18 The disease is more common in adult women, with a reported ratio of 1.7:1, which appears to be similar to the pediatric population.7,17

Currently, the prognosis for patients with IPAH is unknown, since long-term outcomes for patients receiving newer therapies are not yet available. If untreated, however, the prognosis is dismal, with reported one-, three-, and five-year survival rates in adult patients with IPAH ranging from 68% to 77%, 40% to 56%, and 22% to 38%, respectively.19-21

Although less data are available regarding the prognosis of children with untreated IPAH, the available evidence indicates similar poor outcomes.2

Other, less common causes of pediatric pulmonary vascular disease include hypoxia-induced pulmonary vascular disease, rheumatologic disorders, sickle cell disease, portal hypertension, chronic thromboembolic disease, HIV disease, and drug-toxin induced disease.

Table 1. Clinical Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Pulmonary Arterial Hypertension (PAH)</th>
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<tr>
<td>Idiopathic (IPAH)</td>
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<td>Familial (FPAH)</td>
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<td>Related to risk factors or associated conditions (APAH)</td>
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<td>Collagen vascular disease</td>
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<td>Congenital systemic-to-pulmonary shunts</td>
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<td>Portal hypertension</td>
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<td>HIV infection</td>
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<td>Drugs and toxins</td>
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<tr>
<td>Other: thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy</td>
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<tr>
<td>Associated with venous or capillary involvement</td>
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<tr>
<td>Pulmonary veno-occlusive disease</td>
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<td>Pulmonary capillary hemangiomatosis</td>
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<td>Persistent Pulmonary Hypertension of the Newborn</td>
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<tr>
<th>Pulmonary Hypertension With Left Heart Disease</th>
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<tr>
<td>Left-sided atrial or ventricular heart disease</td>
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<td>Left-sided valvular heart disease</td>
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<tr>
<th>Pulmonary Hypertension Associated With Lung Disease And/Or Hypoxemia</th>
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<td>Chronic obstructive pulmonary disease</td>
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<td>Interstitial lung disease</td>
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<td>Sleep-disordered breathing</td>
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<tr>
<td>Alveolar hypventilation disorders</td>
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<td>Chronic exposure to high altitude</td>
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<td>Developmental abnormalities</td>
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<th>Pulmonary Hypertension Due To Chronic Thrombotic And/Or Embolic Disease</th>
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<tr>
<td>Proximal pulmonary arteries</td>
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<td>Distal pulmonary arteries</td>
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<tr>
<td>Non-thrombotic embolism (tumor, parasites, foreign material)</td>
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<tr>
<th>Miscellaneous</th>
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<tr>
<td>Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels</td>
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Pathophysiology

Pulmonary vascular resistance changes throughout gestation and after birth. Shortly after birth, the pulmonary vasculature of healthy individuals is actively maintained in a relaxed state and provides minimal resistance as blood flows through the pulmonary circulation. A complex interplay between vasoactive substances produced by pulmonary vascular endothelial cells and the surrounding smooth muscle cells regulates this process. Thus, aberrant pulmonary vascular endothelial and/or smooth muscle cell function can result in the loss of vascular relaxation and may ultimately allow resistance and pressure to rise to pathologic levels. Unchecked, this process results in progressive hypoxemia, right ventricular failure, diminished cardiac output, and ultimately death. An appreciation of the basic molecular mechanisms that regulate vascular tone in health and disease will facilitate an understanding of the various available therapies for patients presenting acutely with pulmonary hypertension. The reader is referred to the addendum on page 15 for a more complete discussion.

Pulmonary Hypertensive Crisis

Most commonly observed in susceptible patients after cardiac surgery, pulmonary hypertensive crises
are life-threatening events that involve acute eleva-
tions in pulmonary vascular resistance and pressure,
with subsequent hypoxemia, acidosis, and right
heart failure. Increasing hypoxia and acidosis com-
pounds the pulmonary vascular constriction, result-
ing in a vicious cycle. Without treatment, these
crises result in rapid cardiovascular collapse and
death.79-83

The pathophysiology of such a crisis is outlined
in Figure 1. Following an acute increase in pulmo-
nary arterial pressure, there is an acute increase in
right ventricular afterload that leads to right ventric-
ular ischemia and, ultimately, failure.84,85 The
resulting increase in right ventricular end diastolic
volume shifts the intraventricular septum to the left,
decreasing left ventricular volume and cardiac out-
put. Decreased cardiac output results in decreased
systemic perfusion and metabolic acidosis.
Increased pulmonary vascular resistance and right
ventricular failure also decrease pulmonary blood
flow, increasing dead space ventilation. Distention
of the pulmonary arteries and perivascular edema
produce large and small airway obstruction, respec-
tively, which impairs ventilation-perfusion matching
and decreases lung compliance. In fact, the decrease
in lung compliance can be so dramatic that chest
wall movement is impaired, even with manual
ventilation. The ensuing hypoxemia, hypercapnia,
and acidosis (metabolic and/or respiratory) further
increase pulmonary vascular resistance and perpet-
uate this cascade.

**Differential Diagnosis**

Patients diagnosed with new onset pulmonary
hypertension require expeditious evaluation in
order to address potential etiologies and treatment
plans. The differential diagnosis for pulmonary
hypertension follows the recent classification
scheme shown in Table 1 on page 3.

The primary challenge for the emergency physi-
cian comes in identifying the patient with pulmo-
nary hypertension rather than the disease causing it.
To this end, physicians must keep pulmonary
hypertension in the differential diagnosis for pedi-
atric patients presenting with the nonspecific find-
ings of dyspnea, fatigue, abdominal pain, abdomi-
nal fullness, weakness, palpitations, lower extremity
swelling, dizziness, syncope, or angina. An aware-
ess of the various diseases that are associated with
the development of pulmonary hypertension may
help consolidate seemingly unrelated symptoms
into a diagnosis.

**Prehospital Care**

Prehospital management of acutely symptomatic
pulmonary hypertension mandates recognition of
the process and the immediate initiation of aggres-
sive therapies. (See “Treatment” on page 8.)
Patients will likely require a period of inpatient
management, and arrangements for transport to a
facility with pediatric intensive care services should
be made promptly. The transport should be
conducted by a pediatric team with advanced life
support training.

**ED Evaluation**

**Important Historical Questions**

The initial historical questions should focus on
understanding the nature of the presenting symp-
toms. In general, symptoms related to pulmonary
hypertension are attributable to impaired oxygen
delivery and cardiac output (Table 2). Dyspnea is
the most common presenting symptom; since virtu-
ally every patient with pulmonary hypertension
eventually develops dyspnea, knowing the onset,
duration, trigger, and number of prior episodes is
important.7 Other common early symptoms that
should be investigated include fatigue, weakness,
and exercise intolerance.
Angina and chest pain, which are relatively common complaints seen in emergency departments, were reported in 40% of patients with pulmonary hypertension.7 More advanced stages of pulmonary hypertension are associated with anorexia, leg swelling, abdominal fullness, pain, and distension.86 Dyspnea at rest and syncope are particularly ominous signs.86

The age at onset of pulmonary hypertension is quite variable, and symptoms will differ depending on the age of the patient. In infants, failure to thrive, lethargy, diaphoresis (especially with feeding), and irritability may be prominent. Toddlers or children who have an atrial communication that allows a right-to-left shunt may manifest cyanosis, particularly with exercise. Hypoxia may result in hypoxic seizures or seizure-like activity at any age.

As seen in Table 1 on page 3, a host of diseases are now known to be potential causes of pulmonary hypertension. Therefore, the medical history should be evaluated for symptoms that may be related to congenital heart disease, collagen vascular disease, liver disease, HIV disease, thyroid disorders, hemoglobinopathies, and thrombotic disease. Specific questions might inquire about arthralgias, swollen extremities or joints, Raynaud’s phenomenon, and frequent illnesses. In addition, inquire about a history of snoring or obstructive sleep apnea.

Obtain a birth and neonatal history. A history of left-to-right cardiac shunts, bronchopulmonary dysplasia, or congenital diaphragmatic hernia is particularly relevant. Ask patients and their families about frequent respiratory infections or problems related to bleeding or clotting. A travel history with attention to high-altitude locations should also be elicited.

Exposures to medications or potential toxins should also be included in the history. Appetite suppressants have received significant attention as a cause of pulmonary hypertension, but other toxins (such as chemotherapeutic agents and rapeseed oil) have also been linked to pulmonary vascular disease.86,87

Finally, a careful family history is essential, especially probing for early unexplained deaths. Recent discoveries indicate that mutations in the BMPR2 gene occur in up to 50% of patients with familial pulmonary arterial hypertension (FPAH) and in as many as 25% of patients thought to have IPAH.71,72,88 The onset of pulmonary hypertension tends to occur earlier in life in each generation of family members with FPAH; this is termed genetic anticipation.89 In addition, inquire about a family history of connective tissue diseases.86

### Important Physical Findings

Signs of pulmonary hypertension can range from mild to severe. No studies are available to quantify the predictive value of any particular clinical sign in the setting of pulmonary hypertension. However, the pathophysiology of pulmonary hypertension is associated with distinct clinical findings (Table 3).

Findings on cardiac auscultation may include an accentuated pulmonary component of the second heart sound, an early systolic ejection click, a mid-systolic ejection murmur due to turbulence across the pulmonary valve, a palpable parasternal heave due to right ventricular hypertrophy, an S4 gallop, and a prominent jugular “a” wave that is consistent with elevated central venous pressures. One study reported that an accentuated second heart sound and an S4 gallop were present in over 90% and 38%

<table>
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<tr>
<th>Table 2. Symptoms Of Pulmonary Hypertension</th>
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<tr>
<td><strong>Early Symptoms</strong></td>
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<tr>
<td>Dyspnea</td>
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<td>Fatigue</td>
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<td>Exercise intolerance</td>
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<td><strong>Late Symptoms</strong></td>
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<tr>
<td>Cyanosis with exertion</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Leg swelling</td>
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<tr>
<td>Abdominal fullness/pain</td>
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<td>Anorexia</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Syncope</td>
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<tr>
<td>Dyspnea at rest</td>
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<tr>
<td><strong>Symptoms In Infants</strong></td>
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<tr>
<td>Failure to thrive</td>
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<tr>
<td>Lethargy</td>
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<tr>
<td>Diaphoresis</td>
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<td>Irritability</td>
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<th>Table 3. Physical Findings Of Pulmonary Hypertension</th>
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<tr>
<td><strong>Early Findings</strong></td>
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<tr>
<td>Accentuated pulmonary component of the second heart sound</td>
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<tr>
<td>Early ejection click</td>
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<tr>
<td>Midsystolic ejection murmur</td>
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<tr>
<td>Parasternal heave</td>
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<tr>
<td>S4 gallop</td>
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<tr>
<td>Prominent jugular “a” wave</td>
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<tr>
<td><strong>Late Findings</strong></td>
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<tr>
<td>Diastolic pulmonary regurgitation murmur</td>
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<tr>
<td>Holosystolic tricuspid regurgitation murmur</td>
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<tr>
<td>Jugular venous distention</td>
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<tr>
<td>Prominent “V” wave</td>
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<tr>
<td>S4 ventricular gallop</td>
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<tr>
<td>Pulsatile hepatomegaly</td>
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<tr>
<td>Peripheral edema</td>
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<tr>
<td>Ascites</td>
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<tr>
<td><strong>Findings Related To Various Etiologies</strong></td>
</tr>
<tr>
<td>Cyanosis</td>
</tr>
<tr>
<td>Rash</td>
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<td>Obesity</td>
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EBMedicine.net • January 2008 5 Pediatric Emergency Medicine Practice
of patients with pulmonary hypertension, respectively.\textsuperscript{7,86}

In later stages of disease, physical findings may include a diastolic pulmonary regurgitation murmur, a holosystolic tricuspid regurgitation murmur, jugular venous distention with prominent “V” waves which is indicative of tricuspid regurgitation, and a hepatojugular reflex. The findings of an S\textsubscript{3} ventricular gallop, pulsatile hepatomegaly, peripheral edema, and ascites suggest the beginning of right ventricle failure.\textsuperscript{86}

In addition, the physical examination should include inspection for stigmata of diseases consistent with pulmonary hypertension. For example, cyanosis may be seen with congenital cardiac defects due to right-to-left shunting, skin findings may suggest connective tissue disease, and obesity may cause obstructive sleep apnea.

Most importantly, patients with pulmonary hypertension who present in shock are at extreme risk for imminent cardiopulmonary collapse. Tachycardia, tachypnea, altered mental status, peripheral vasoconstriction, oliguria, and hypotension herald imminent cardiovascular collapse and death. Beyond routine resuscitation, these patients require immediate and aggressive therapy aimed at acutely decreasing pulmonary vascular resistance and supporting the failing right ventricle. (See “Treatment.”)

**Diagnostic Studies**

A summary of the diagnostic studies that should be performed in the emergency department is shown in Table 4.

**Chest Radiography**

The classic findings on chest radiography are enlargement of the main pulmonary arterial shadow and attenuation of the peripheral pulmonary vascular markings, also termed “pruning”\textsuperscript{7,86} (Figure 2). A prospective study of 187 patients reported these findings in the majority of patients with IPAH.\textsuperscript{7} An older study defined a radiographic index that was associated with pulmonary hypertension measured by right heart catheterization; a radiographic index is obtained by measuring the horizontal distances from the midline to the first divisions of the right and left pulmonary arteries and dividing the sum of these distances by the maximum transverse diameter of the thorax.\textsuperscript{90} While an index of > 0.38 was found to be abnormal, there was no correlation with disease severity.\textsuperscript{90} Right ventricular enlargement, a less common finding, may also be noted by chest radiography.

Chest radiography may also indicate processes that contribute to the symptoms of pulmonary hypertension or its etiology, such as scoliosis leading to restrictive lung disease, pulmonary congestion (suggestive of pulmonary venous disease), or effusions that may be a part of congenital heart disease or chronic thromboembolic disease. However, it should be noted that the absence of abnormalities on chest radiography does not exclude the diagnosis of pulmonary hypertension.

**ECG**

The chief finding of interest on an ECG is evidence of right ventricular hypertrophy (Figure 3). The ECG findings associated with pulmonary hypertension are right axis deviation (noted in 79\% of patients in one study), an R/S ratio of > 1 in lead V\textsubscript{1}, qR complex in V\textsubscript{1}, an rSR’ pattern in V\textsubscript{1}, a R/S
ratio < 1 in leads V₅ or V₆, or an S₁, S₂, S₃ pattern. A P wave greater than 2.5 mm in leads II, III, and aVF with a frontal P-axis of greater than 75 degrees indicates right atrial enlargement.

Findings on ECG provide important objective data as a part of the work-up for pulmonary hypertension, but studies of patients with known pulmonary hypertension have demonstrated that ECG alone lacks adequate sensitivity and specificity.

**Echocardiography**

Although cardiac catheterization is the “gold standard” for the measurement of pulmonary arterial pressure and vascular resistance, it is invasive and not readily available in most situations. Thus, echocardiography is the single best diagnostic tool for the diagnosis of pulmonary hypertension in an acute care setting.

The important data that may be obtained by echocardiography include an estimate of systolic pulmonary arterial pressure (sPAP), right and left ventricular function, and cardiac anatomy, including determinations of chamber sizes, valvular function, and intracardiac shunts. In general, the sPAP is considered equivalent to the right ventricular systolic pressure (RVSP), unless there is right ventricular outflow tract obstruction or pulmonary valve stenosis. With the use of Doppler echocardiography, RVSP is estimated by determining the velocity of flow across the tricuspid valve during systole (tricuspid [TR] jet). A modification of the Bernoulli equation is used to estimate the RVSP: RVSP = 4v² + RAP, where v is the velocity of the TR jet in meters per second, and RAP is the right atrial pressure that is either standardized or estimated by echocardiography. Multiple studies have validated estimates of sPAP determined by echocardiography using right-heart catheterization as confirmation. In the absence of a measurable TR jet, parameters related to right ventricular outflow patterns and time intervals might be assessed by Doppler echocardiography with demonstrated accuracy compared to right-heart catheterization.

The use of Doppler echocardiography is well studied. However, when used as a screen for a rare disease (such as pulmonary hypertension), its sensitivity, specificity, positive predictive value, and negative predictive value will not be perfect. In fact, as expected, studies indicate underestimates of sPAP in patients with severe pulmonary hypertension and overestimates in normal patients. However, expert consensus supports the recommendation that all patients suspected of having pulmonary hypertension undergo cardiac echocardiography in order to estimate sPAP and to evaluate for anatomic abnormalities, intracardiac shunting, and cardiac function.

**Second Tier Evaluation**

Once the diagnosis of pulmonary hypertension has been made or is strongly suspected, a number of further tests are warranted. These evaluations are better suited to an inpatient setting, outside of the emergency department. However, emergency physicians may be called upon to organize these tests and certainly would benefit their patients by preparing them for the evaluation ahead.

**Ventilation-Perfusion (V/Q) Scan**

Thromboembolic disease may present with pulmonary hypertension and can be evaluated by V/Q scan. Several studies found that V/Q scanning was both highly sensitive and specific in differentiating between idiopathic pulmonary hypertension and thromboembolic disease. Recent expert opinion guidelines state that pulmonary angiography is the study of choice for the definitive diagnosis of thromboembolic disease in the setting of a positive V/Q scan.

**CT Scan and MRI**

Contrast-enhanced CT scan and/or MRI can help identify causes of pulmonary hypertension. Thromboembolic disease may be visualized by both modalities. In addition, both imaging techniques can identify other pulmonary pathology, such as masses or vasculitis. Findings on CT scan, such as pulmonary artery size, may contribute to the
diagnosis of pulmonary hypertension, but a CT scan does not replace Doppler echocardiography. MRI can better delineate the cardiac anatomy, particularly chamber sizes and wall thickness, and MRI measurements can detect pulmonary hypertension. However, like CT, it is not clear that MRI offers any advantages for diagnosis when compared to Doppler echocardiography.

Pulmonary Function Testing And Oximetry
Studies have indicated abnormalities detected by pulmonary function testing in patients with pulmonary hypertension from multiple etiologies, including thromboembolic disease and collagen vascular disease. Nocturnal oximetry and oximetry during exercise may also provide important information, as sleep disordered breathing is a known cause of pulmonary hypertension that may be amenable to treatment.

Right Heart Catheterization
Cardiac catheterization remains the “gold standard” for the diagnosis of pulmonary hypertension. In addition to measuring pulmonary artery pressures and vascular resistance, cardiac catheterization can assess for intracardiac and extracardiac shunts; it can also measure intracardiac pressures and cardiac output. Furthermore, pulmonary vascular reactivity testing is essential in selecting appropriate therapy. Indeed, children who are responsive to acute vasodilator testing (evoked by short acting agents such as inhaled nitric oxide (NO) or iloprost and intravenous epoprostenol or adenosine), which is defined as a decrease in pulmonary artery pressure of more than 20% without a decrease in cardiac output, have been shown to have a favorable response to long-term therapy with calcium channel blockers. Conversely, calcium channel blockers may be deleterious to patients who are not responsive to vasodilator therapy, highlighting the value of this information.

Laboratory Screening
Laboratory tests are aimed at refining the differential diagnosis (Table 1 on page 3). Tests that should be considered in the emergency department are shown in Table 5. A complete blood count with smear, electrolyte panel, BUN, creatinine, coagulation studies, and a liver function panel provides a good first screen. Other studies that might be indicated are an HIV test, thyroid function studies, collagen vascular studies (such as antinuclear antibodies, rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein), urinalysis, and a toxicology screen for stimulants, especially methamphetamine.

Laboratory data are also important in order to assess oxygen delivery and cardiac output. In this regard, an arterial blood gas provides considerable data. For example, mild respiratory acidosis with evidence of chronic metabolic alkalosis indicates that the patient’s homeostatic mechanisms are compensating for the disease, whereas severe respiratory or metabolic acidosis heralds imminent cardiopulmonary collapse. Likewise, serum lactate levels increase with inadequate oxygen delivery, and central venous oxyhemoglobin saturations decrease with diminished cardiac output. Plasma B-type natriuretic peptide levels, which increase with myocardial stress, may also be helpful in distinguishing pulmonary hypertension from respiratory illnesses and may give an indication of right ventricular stress.

Treatment
The basic management of patients presenting with pulmonary hypertension follows standard emergency medicine practice, including an assessment and stabilization of the airway, control of breathing, and support of circulation. As outlined in the preceding sections, it may be challenging – yet could be lifesaving – to promptly recognize that the patient’s presenting condition is secondary to pulmonary hypertension. Attention to the history and a thoughtful analysis of the physical findings should aid in this determination.

The decision to intubate a patient must be made on an individual basis. Patients presenting with signs of shock secondary to pulmonary hypertension require intubation and mechanical ventilation.

Table 5. Laboratory Studies For Pulmonary Hypertension

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<th>Initial Screening Studies</th>
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<tr>
<td>Complete blood count with smear</td>
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<td>Electrolyte panel</td>
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<td>Ionized calcium</td>
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<td>BUN</td>
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<td>Creatinine</td>
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<td>Glucose</td>
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<th>Laboratory Studies Aimed At Identifying Etiology</th>
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<tr>
<td>Liver transaminases</td>
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<td>Erythrocyte sedimentation rate</td>
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<td>C-reactive protein</td>
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<td>Urinalysis; toxicology screen</td>
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<tr>
<th>Laboratory Results Aimed At Assessing Severity Of Acute Illness</th>
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<tr>
<td>Arterial blood gas</td>
</tr>
<tr>
<td>Mixed venous oxyhemoglobin saturation</td>
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<tr>
<td>Lactate</td>
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<tr>
<td>B-type natriuretic peptide</td>
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In this way, physicians may deliver maximal inspired oxygen concentrations, control minute ventilation in order to achieve respiratory alkalosis, sedate without fear of respiratory depression, administer muscle relaxants, and deliver inhaled NO. Keep in mind, however, that the transition from spontaneous to positive pressure breathing, particularly when combined with agents to induce anesthesia, is dangerous. Great attention to hemodynamics, the maintenance of adequate preload, and preparations for resuscitation are mandatory.

In critically ill patients, central venous and arterial access are indicated to secure the administration of all intravenous therapies, central venous pressure monitoring, determinations of central venous oxyhemoglobin saturation, continuous hemodynamic monitoring, and arterial blood gas management.

Regardless of the underlying etiology, the general treatment approach is similar and can be subdivided into four major goals: (1) prevent and acutely treat active pulmonary vasoconstriction; (2) support the failing right ventricle; (3) treat the underlying etiology; and (4) chronically promote, if possible, the regression of pulmonary vascular remodeling. The first two goals will be the primary focus in the emergency department setting. Depending on individual circumstances, treatment directed at the underlying etiology may also be crucial. Emergency physicians are first to diagnose some patients with pulmonary hypertension. Thus, starting the process of halting – or potentially reversing – the disease process will often begin with them. Treatments are summarized in Table 6.

1. Prevent And Acutely Treat Active Pulmonary Vasoconstriction

In the acute care setting, the treatment of active pulmonary vasoconstriction must be the primary focus of care for the symptomatic patient. It is well known that these patients have augmented pulmonary vasoconstriction in response to such stimuli as hypoxia, acidosis, catecholamine-mediated α₁-adrenergic stimulation associated with pain and/or agitation, and increases in intrathoracic pressure.³³,³⁰,³¹ In fact, acute increases in pulmonary vascular resistance can lead to significant cardiopulmonary compromise (i.e., a pulmonary hypertensive crisis).

Once the working diagnosis has been made, important basic therapies for the acute treatment of pulmonary hypertension must be initiated. Therapies include supplemental oxygen, analgesics, sedatives, muscle relaxants (for patients requiring mechanical ventilation), the maintenance of an alkalotic pH with the use of controlled ventilation and/or buffer, aggressive evacuation of pneumothoraces and pleural effusions, and the maintenance of the hematocrit below 55%.³²,³³ In addition, selective pulmonary vasodilator therapies are essential for the treatment of pulmonary hypertensive crises.³⁴-³⁶

The mainstay of acute pulmonary vasodilator therapy remains supplemental oxygen and moderate alkalosis, as these therapies have minimal effects on the systemic vasculature. Interestingly, the dose-dependent response of the pulmonary vasculature to these agents has not been well established. Studies in newborn lambs demonstrate dose-dependent pulmonary vasodilation in response to increasing pH from 7.30 to 7.60 and a dose-dependent response to increasing inspired oxygen concentrations from 0.21 to 0.5 with minimal effects at higher concentrations.³⁷ Several intravenous agents have been utilized to promote pulmonary vasodilation; these include tolazoline, sodium nitroprusside,

### Table 6. Therapies For Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Therapies Aimed At Acutely Decreasing Pulmonary Vascular Constriction</th>
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<tbody>
<tr>
<td>Oxygen (100% FiO₂)</td>
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<tr>
<td>Alkalization</td>
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<tr>
<td>Inhaled nitric oxide (5-80 ppm)</td>
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<tr>
<td>Inhaled prostacyclin (iloprost, ~ 2.5-5 mcg/dose)</td>
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<tr>
<td>Intravenous prostacyclin (epoprostenol, ~ 20-80 nanog/kg/min, IV infusion)</td>
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<tr>
<td>Analgesics</td>
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<td>Sedatives</td>
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<td>Muscle relaxants</td>
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<tr>
<th>Therapies Aimed At Supporting The Right Heart And Improving Cardiac Output</th>
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<tr>
<td>Intravenous PDE type III inhibitors – milrinone (0.25-1 mcg/kg/min, IV infusion)</td>
</tr>
<tr>
<td>Dopamine (3-10 mcg/kg/min, IV infusion)</td>
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<tr>
<td>Dobutamine (5-15 mcg/kg/min, IV infusion)</td>
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<tr>
<td>Creation of right-left shunt</td>
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<tr>
<td>• Atrial septostomy</td>
</tr>
<tr>
<td>• Extracardiac shunt (e.g., left pulmonary artery to descending aorta)</td>
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<tr>
<td>• Extracorporeal life support</td>
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<tr>
<th>Chronic Therapies For Pulmonary Hypertension</th>
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<tr>
<td>Endothelin receptor antagonants</td>
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<tr>
<td>• Combined ET₄ and ET₇ Bosentan</td>
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<tr>
<td>• Selective ET₄: Itaxsentan, Ambrisentan</td>
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<tr>
<td>PDE type V inhibitors: sildenafil</td>
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<tr>
<td>Prostacyclin analogues</td>
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<tr>
<td>• Oral: Beraprost sodium</td>
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<tr>
<td>• Subcutaneous: Treprostinil sodium</td>
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<tr>
<th>Novel Therapies In Development</th>
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<tbody>
<tr>
<td>• Cell-based therapy</td>
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<td>• Gene therapy</td>
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<tr>
<td>• Antioxidants: superoxide dismutase</td>
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<tr>
<td>• Statins</td>
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<tr>
<td>• Rho kinase inhibitors</td>
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<tr>
<td>• Elastase inhibitors</td>
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<td>• Platelet derived growth factor inhibitors</td>
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<tr>
<td>• Vasoactive intestinal peptide</td>
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<td>• 5-HT transport inhibitors</td>
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nitroglycerin, prostacyclin, prostaglandin E1, nifedipine, and alpha-adrenergic antagonists such as phenoxybenzamine. The efficacy of these agents is variable, at least in part due to their effects on the systemic vasculature. Systemic afterload reduction can be advantageous in the setting of left ventricular dysfunction; however, significant reductions in pulmonary arterial pressure without unacceptable systemic hypotension are often not possible. In addition, intravenous vasodilators can override intrinsic hypoxic pulmonary vasconstriction, resulting in an increase in dead space ventilation that may not be tolerated in some patients.

More recent treatment modalities, most notably inhaled NO, deliver short-acting vasodilators directly to the pulmonary vasculature via an inhalational route. When administered to the lung in its natural gaseous form, NO diffuses through the alveolar wall to reach small pulmonary arteries. It then enters vascular smooth muscle cells, initiating a cascade that results in pulmonary vasodilation via increases in cGMP. After entering the blood vessel lumen, NO is rapidly inactivated by hemoglobin which confines its effects to the pulmonary vasculature. Because of these properties, inhaled NO has several advantages over other vasodilators; these include (1) selective pulmonary vasodilation due to rapid inactivation by hemoglobin; (2) rapid onset and elimination; and (3) an improvement in ventilation-perfusion matching due to the limitation of delivery to well ventilated lung regions. Accordingly, inhaled NO (5-20 ppm) has become a mainstay of treatment for acute pulmonary hypertensive disorders and the assessment of pulmonary vascular reactivity. Although various noninvasive modalities for delivering inhaled NO are under development, the most common practice by far is delivery through an endotracheal tube. Recent studies suggest that the combination of 100% oxygen and inhaled NO (80 ppm) produces maximal pulmonary vasodilation and should be used in combination in emergency situations.

Inhaled prostacyclin has similar pulmonary selectivity, secondary to rapid inactivation by hemoglobin. Its vasodilating effects are due to increasing cAMP concentrations. Currently, studies on the use of inhaled prostacyclin for pediatric pulmonary hypertension are sparse, and comparison studies between inhaled NO and inhaled prostacyclin are lacking.

Inhibitors of phosphodiesterases (PDEs), a family of enzymes that hydrolyze the cyclic nucleotides cAMP and cGMP, are a relatively new class of agents that have potent vasodilating and inotropic effects. Milrinone is a PDE 3 inhibitor that increases cAMP concentrations. Animal and human data demonstrate pulmonary vasodilation in response to milrinone that can be in excess of its systemic effects if the pulmonary vasculature is constricted.

Sildenafil, a PDE 5 inhibitor that increases cGMP concentrations, also has potent pulmonary vasodilating effects. The oral formulation is currently being investigated for chronic pulmonary hypertensive therapy, and recent short-term studies demonstrate beneficial effects in children with advanced pulmonary vascular disease. The intravenous formulation is currently being investigated for acute pediatric pulmonary hypertensive disorders.

Increasing data implicate alterations in ET-1 in the pathophysiology of pulmonary hypertension, and suggest that ET receptor antagonism may be a useful therapeutic strategy. In fact, bosentan, an oral combined ETA and ETB receptor antagonist, has demonstrated efficacy as a chronic therapy for advanced pulmonary vascular disease. There have been no large studies on the use of ET receptor antagonists for acute pulmonary hypertensive disorders to date. The use of selective ET receptor antagonism is under investigation.

Patients with pulmonary arterial hypertension have histological evidence of in situ pulmonary vascular thrombosis which can cause or contribute to increased pulmonary arterial pressure and resistance. Although several adult studies have demonstrated efficacy for anticoagulation therapy, pediatric studies are lacking. Warfarin is currently the treatment of choice in adult patients and in large pediatric centers with significant experience with pediatric pulmonary arterial hypertension. Low molecular weight heparin is another alternative, aspirin does not have demonstrated efficacy.

2. Support The Failing Right Ventricle

A significant component of the pathophysiology of both acute and chronic pulmonary hypertension is the development of right ventricular dysfunction; this often requires pharmacologic support. Maintenance of adequate preload is necessary to optimize cardiac output in patients with pulmonary hypertension. Continuous central venous pressure monitoring may be helpful to guide volume therapy, keeping in mind that patients with a poorly compliant right ventricle or increased right ventricular afterload may require elevated central venous pressures to maintain an adequate cardiac output. Frequent clinical assessment of liver size can be helpful, particularly in infants.

Despite adequate preload, cardiac output may be compromised secondary to elevated right ventricular afterload and/or biventricular myocardial dysfunction, necessitating the use of inotropic agents. These agents increase stroke volume at a given preload and afterload by stimulating β1 adrenergic receptors. However, some of these agents also
stimulate $\beta_2$ or $\alpha_1$ adrenergic receptors, which are found on the smooth muscle cells of both the pulmonary and systemic arteries. Agents that stimulate $\beta_2$ adrenergic receptors decrease both pulmonary and systemic vascular resistance and improve right and left ventricular function. Agents that stimulate $\alpha_1$ adrenergic receptors may increase both systemic and pulmonary vascular resistance. Therefore, a rational approach to using inotropic agents in the setting of pulmonary hypertension is to utilize agents with beta selectivity and minimal $\alpha_1$ adrenergic stimulation, such as low dose dopamine (3-10 mcg/kg/min, continuous intravenous infusion) or dobutamine (5-15 mcg/kg/min, continuous intravenous infusion). Although animal studies have shown that high doses of dopamine increase pulmonary vascular resistance, human studies have shown increased cardiac output with minimal effects on pulmonary vascular resistance, making dopamine a relatively safe choice. Milrinone (0.5-1 mcg/kg/min, continuous intravenous infusion) is also a useful therapy for patients with pulmonary hypertension and myocardial dysfunction, given its vasodilatory and inotropic properties.

In patients with refractory pulmonary hypertension, short-term extracorporeal life support (ECLS) has been used successfully. However, its use should be limited to support those patients in which the underlying pulmonary vascular disease is deemed reversible.

3. Treat The Underlying Etiology

Whenever possible, treatment of the underlying disorder must coincide with symptomatic treatment for pulmonary hypertension if attenuation and/or reversal of the disease are to be successful. For example, in neonates, this may involve correction of underlying metabolic disturbances, antibiotics for infectious etiologies, and exchange transfusions for polycythemia. For patients with congenital heart disease, repair of the underlying defect after determining that the pulmonary vascular disease is reversible (see below) is mandatory. For hypoxia-induced disease, tonsillectomy and adenoidectomy may be required for sleep apnea, and a descent to sea level may be needed for high-altitude-related disease. Lastly, for rheumatologic disease, immunosuppression may be required.

4. Chronically Promote, If Possible, The Regression Of Pulmonary Vascular Remodeling

The mainstay of chronic therapy has been aimed at decreasing pulmonary vascular resistance, thereby assisting right ventricular function and perhaps attenuating the progression of vascular remodeling by decreasing the pressure to which the vasculature is exposed. In this regard, the continuous infusion of prostacyclin (epoprostenol) has been the most successful therapy to date. Several studies in humans with advanced pulmonary vascular disease demonstrated improved five-year survival and improved exercise tolerance. Interestingly, even those patients without an initial vasodilating response to the infusion show significant long-term benefit, suggesting that effects beyond vasodilation (such as anti-platelet effects, cAMP-mediated inhibition of smooth muscle cell growth, or other unknown mechanisms) may be responsible for the treatment effect. Despite the impressive results, several factors limit its utilization, including the need for chronic intravascular access with the associated infectious and thrombotic risks and many other untoward effects, including headache, flushing, and acute cardiopulmonary compromise with disruption of the infusion.

With the increasing appreciation for the role of ET-1 in the pathophysiology of pulmonary vascular disease, ET receptor antagonists have been developed as a potential treatment modality. To date, bosentan, a combined ETA and ETB receptor antagonist, is the most widely studied agent, and it is approved for the treatment of pulmonary hypertension. Recent studies in adults with primary pulmonary hypertension demonstrate similar improvements in survival and exercise tolerance as those demonstrated with epoprostenol. The use of ET receptor antagonists for pediatric pulmonary hypertensive disorders is currently under investigation. Deficiencies in the NO-cGMP cascade in pulmonary vascular disease are well documented. In addition, the vasodilating effects, anti-platelet effects, and anti-proliferative effects of augmenting this cascade are well appreciated. Therefore, new chronic therapies that augment NO-cGMP signaling, which include chronic inhaled NO delivered by nasal cannula and sildenafil, are currently under investigation. In fact, the short-term benefit of sildenafil in children with advanced pulmonary hypertension has recently been reported.

Data indicate that several of these new oral therapies, such as bosentan and sildenafil, may offer additional benefit by virtue of their ability to inhibit vascular smooth muscle growth and fibrosis. A number of other treatment strategies, including combination drug therapies, are currently under investigation.

Special Circumstances

Acute Withdrawal Of Prostacyclin

The continuous infusion of prostacyclin (epoprostenol) has been the most successful therapy to date for the chronic treatment of pulmonary hypertension. However, patients receiving this
therapy may suffer significant dyspnea with brief interruptions of the infusion and, in fact, may die.201 In children, infusions are normally given through a permanent indwelling central line by a portable infusion pump. Any patient receiving continuous prostacyclin who presents to an urgent care setting with symptoms that may be attributable to pulmonary hypertension must have the entire system interrogated immediately. Indeed, making the assumption that the infusion is not functioning would be prudent. Possibilities for malfunction include incorrect drug formulation, inoperative pump, and central line malfunction. Resumption of the infusion is the best therapy, but otherwise aggressive therapies, as outlined previously, to acutely decrease pulmonary vasoconstriction and support the right ventricle are necessary.

**Neonatal Sepsis**

Newborns presenting to the emergency department with septic shock are far more common than presentations of pulmonary hypertension. However, elevated pulmonary arterial pressures and vascular resistance can complicate neonatal septic shock. Normally, pulmonary vascular resistance and pressure decrease dramatically after birth, reaching adult levels by six weeks of age. However, sepsis, acidosis, and/or hypoxia can impair this transition, maintaining high pulmonary arterial pressures and vascular resistance, which can lead to right ventricular failure (Figure 1 on page 4).

In fact, recent clinical practice guidelines for neonates with septic shock, put forth by a task force of the American College of Critical Care Medicine, include therapies aimed at altering pulmonary vascular resistance and supporting the right ventricle in their recommendations for stepwise management.202 These therapies include systemic alkalization, inhaled NO, type III phosphodiesterase inhibitors, and ECLS.

**Congenital Heart Disease – Single Ventricle Physiology**

The most common treatment for neonates born with single ventricular congenital heart disease is staged surgical palliation, which is achieved through a series of operations. The first stage is aimed at ensuring adequate systemic blood flow and securing pulmonary blood flow through the creation of a systemic to pulmonary shunt. The second and third stage, which are partial cavopulmonary anastomosis (PCPA) and total cavopulmonary anastomosis (TCPA) respectively, transition to a circulation wherein the single ventricle provides systemic blood flow and passive venous return provides pulmonary blood flow. Importantly, the absence of a dedicated subpulmonary ventricle requires the single ventricle to supply the total kinetic energy for pulmonary and systemic blood flow, making patients extremely susceptible to elevations in pulmonary vascular resistance. Even levels that do not meet the definition of pulmonary hypertension may greatly disrupt the circulation in these later stages.

For this reason, pulmonary vasoconstriction must be considered as a potential problem when patients with single ventricle congenital heart disease present to the emergency department. Even with mild elevations in pulmonary vascular resistance, these patients may become hypoxic and cyanotic. Without treatment, their cardiac output may decrease due to inadequate preload from impaired pulmonary venous return. Treatment aimed at

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**Key Points**

- Pediatric pulmonary hypertension is a rare, often rapidly progressive disease, with varied etiologies and significant associated mortality.

- Failing to recognize the initial presentation of pulmonary hypertension can result in a life-threatening delay in the initiation of specific therapy.

- In neonates, the most common cause of pulmonary hypertension results from a failure to undergo the normal fall in pulmonary vascular resistance at birth.

- Beyond the neonatal period, the majority of pediatric pulmonary hypertension is due to congenital heart disease or idiopathic pulmonary hypertension.

- Symptoms of pulmonary hypertension are generally attributable to impaired cardiac output and oxygen delivery.

- A pulmonary hypertensive crisis represents a period of acutely increased pulmonary vascular constriction that can result in right ventricular failure and complete cardiopulmonary collapse.

- Acute treatment of pulmonary hypertension combines routine emergency medicine practices with specific therapies aimed at decreasing pulmonary arterial pressure and supporting the right ventricle.
Clinical Pathway For The Acute Management Of Pediatric Pulmonary Hypertension

Pediatric patient presenting with symptoms suggestive of, or consistent with, PHTN (Table 2 on page 5).

Evaluate and stabilize consistent with Pediatric Advanced Life Support (PALS) guidelines.

**Known history of PHTN?**

- **YES**
  - Receiving PHTN therapy?
    - **YES**
      - Therapy interrupted?
        - **YES**
          - Restart therapy (Class II)
        - **NO**
          - Improved?
            - **YES**
              - Consider period of inpatient monitoring. Consult with physician managing PHTN prior to discharge (Indeterminate).
            - **NO**
              - Improved?
                - **YES**
                  - Consider period of inpatient monitoring. Consult with physician managing PHTN prior to discharge (Indeterminate).
                - **NO**
                  - Prompt referral to or consultation with specialty center for further diagnostic studies and treatment. (Class II)

- **NO**
  - Signs of PHTN (Table 3 on page 5)
    - **YES**
      - Perform initial diagnostic and laboratory studies (Table 4 and 5 on pages 6 and 8): CXR, ECG (Class III) and echocardiography (Class II).
    - **NO**
      - Studies suggest PHTN?
        - **YES**
          - Continue therapy
          - **YES**
            - Improved?
              - **YES**
                - Consider period of inpatient monitoring. Consult with physician managing PHTN prior to discharge (Indeterminate).
              - **NO**
                - Prompt referral to or consultation with specialty center for further diagnostic studies and treatment. (Class II)
        - **NO**
          - Consider other diagnoses

**Serious and unresolved PHTN?**

- **YES**
  - **Consider obtaining central venous and arterial access.** (Class III)
  - **Initiate initial diagnostic and laboratory studies** (Table 4 and 5 on pages 6 and 8): CXR, ECG (Class III) and echocardiography. (Class II)
  - **Initiate therapies for PHTN** (Table 6 on page 9):
    - Acutely decrease PVR
      - Oxygen – FiO2 100% (Class I)
      - Alkalization – pH > 7.4 (Class II)
      - Inhaled nitric oxide (5-80 ppm) (Class II) or
      - Inhaled prostacyclin (2.5-5 mcg/dose) (Class II) or
      - Intravenous prostacyclin (20-80 nanograms/kg/min) (Class I)
    - Support the right heart
      - Dopamine 5-15 mcg/kg/min (Class III) and/or
      - Dobutamine 5-15 mcg/kg/min (Class III)
    - Supportive measures
      - Analgesics, sedatives, muscle relaxants (Class III)

  - **NO**
    - **YES**
      - Therapy interrupted?
        - **YES**
          - Restart therapy (Class II)
        - **NO**
          - Improved?
            - **YES**
              - Consider period of inpatient monitoring. Consult with physician managing PHTN prior to discharge (Indeterminate).
            - **NO**
              - Prompt referral to or consultation with specialty center for further diagnostic studies and treatment. (Class II)

The evidence for recommendations is graded using the following scale. For complete definitions, see back page. **Class I:** Definitely recommended. Definitive, excellent evidence provides support. **Class II:** Acceptable and useful. Good evidence provides support. **Class III:** May be acceptable, possibly useful. Fair-to-good evidence provides support. **Indeterminate:** Continuing area of research.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Acute Lung Injury

The pathophysiology of acute lung injury involves damage to both the alveolar epithelium and pulmonary vascular endothelium. Vascular endothelial injury accounts for key features of acute lung injury, including intravascular thrombosis and capillary permeability that increases alveolar fluid. In fact, pulmonary vascular injury, in the setting of acute lung injury, can lead to pulmonary arterial hypertension that results in increased intrapulmonary shunting, hypoxia, pulmonary edema, and right ventricular dysfunction. In children with acute lung injury, persistently elevated pulmonary arterial pressures have been associated with worse outcomes. Vasodilators have been utilized in the management of these patients. However, intravenous vasodilators that dilate both the systemic and pulmonary vasculature have significant problems; these include systemic hypotension, right ventricular ischemia, increased intrapulmonary shunting (i.e., increased V/Q mismatch), and increased hypoxemia. Consequently, selective pulmonary vasodilation with inhaled NO has been utilized, as it improves V/Q matching and oxygenation without untoward systemic effects. Unfortunately, improvements in oxygenation associated with inhaled NO have been utilized, as it improves V/Q matching and oxygenation without untoward systemic effects. Unfortunately, improvements in oxygenation associated with inhaled NO are transient, and large randomized trials have failed to demonstrate an improvement in mortality with its use. Therefore, the routine use of inhaled NO in patients with acute lung injury cannot be justified; however, it may be indicated in individual patients, particularly those with acute hemodynamic compromise and refractory hypoxemia due to elevated pulmonary arterial pressures. Clearly, physicians caring for pediatric patients with acute lung injury must include an awareness of the pulmonary vascular aberrations associated with the disease in their management considerations.

Controversies/Cutting Edge

In 1997, endothelial progenitor cells (EPCs) were first isolated from human blood, and autologous EPCs were shown to incorporate into vessels during angiogenesis in animal models. Subsequently, therapeutic administration of EPCs was shown to ameliorate injury in animal models with improved efficacy when EPCs were transduced with eNOS. Recently, Wang and colleagues performed a prospective, randomized trial to assess the safety and efficacy of adding autologous EPCs infusions to conventional therapy in 31 patients with idiopathic pulmonary hypertension, with encouraging results. Specifically, treated patients demonstrated improved hemodynamics and exercise capacity and did not have increased adverse events during the study period. Together, these studies suggest that cell based therapy may become an important part of treatment for patients with pulmonary hypertension.

In the setting of pulmonary hypertension secondary to congenital heart defects, an atrial communication can be beneficial in that it allows the failing right ventricle to decompress when right atrial pressure rises. The existence of an atrial level communication decreases the risk of right ventricular failure and maintains left sided cardiac output. The resulting right-to-left shunt is generally well tolerated, particularly if high hemoglobin concentrations are maintained. As right ventricular function improves, right-to-left shunting decreases and oxygenation improves. Thus, atrial septostomy as a part of management for chronic pulmonary hypertension on the physical examination.

Risk Management Pitfalls For Pediatric Pulmonary Hypotension

1. Failure to consider pulmonary hypertension in the differential diagnosis.
2. Failure to recognize a pulmonary hypertensive crisis.
3. Failure to add therapies to resuscitative efforts that are aimed at decreasing pulmonary vascular constriction and supporting the right ventricle.
4. Assuming that previous diagnoses are correct.
5. Failure to appreciate signs of pulmonary hypertension on the physical examination.
6. Failure to appreciate signs of pulmonary hypertension on diagnostic studies.
7. Failure to link pulmonary hypertension to other systemic illnesses.
8. Failure to obtain a thorough family history and past medical history.
9. Losing patients to follow-up.
Pulmonary hypertension has been advocated. However, atrial septostomy in the setting of an acute exacerbation of chronic pulmonary hypertension may lead to unacceptable hypoxemia due to excess right-to-left atrial shunting. In addition to atrial septostomy, other palliative shunts, such as a shunt from the left pulmonary artery to descending aorta, are currently under investigation.

In addition, novel therapeutic agents targeting various cascades that are now known to contribute to pulmonary vascular disease under different conditions are at various levels of development. These include antioxidants, statins, rho kinase inhibitors, elastase inhibitors, platelet-derived growth factor inhibitors, vasoactive intestinal peptide, and 5-HT transport inhibitors.

Finally, heart/lung, single lung, or bilateral lung transplantation has been successful in pediatric patients with terminal pulmonary hypertension. The International Society for Heart and Lung Transplantation reported a survival of approximately 50% at five years in pediatric patients. Consensus is lacking as to the best type of transplant.

**Disposition**

In general, patients presenting with acute symptoms secondary to pulmonary hypertension warrant admission to an inpatient setting. Patients with any degree of instability should be transferred to a pediatric intensive care unit, if possible. Newly diagnosed patients almost certainly require admission, whereas patients with a known diagnosis may be managed with extended observation in the emergency department if the trigger for their acute presentation is well understood and adequately treated (e.g., interruption of prostacyclin infusion). In such patients, consultation with the physician managing their chronic treatment would be prudent.

**Case Conclusion**

This patient was suffering from arterial pulmonary hypertension, and her previous presentations to the ED were incorrectly diagnosed as reactive airway disease. In the ED, she had significant dyspnea that improved somewhat with 100% oxygen delivered by facemask. CXR revealed clear lung fields with pruned distal pulmonary vessels and dilated central pulmonary arteries. ECG revealed right ventricular hypertrophy. Echocardiography revealed supra-systemic systolic pulmonary artery pressures. She was intubated, and mechanical ventilation was adjusted to achieve respiratory alkalosis. She was maintained on an inspired oxygen concentration of 100% and started on 20 ppm of inhaled nitric oxide and intermittent inhaled prostacyclin. The child was then transferred to the pediatric intensive care unit. A pulmonary hypertension specialist was consulted and the patient was scheduled for a diagnostic right heart catheterization. Genetic testing and family history subsequently confirmed a diagnosis of familial arterial pulmonary hypertension. The patient improved and was eventually discharged home on intravenous prostacyclin and bosentan.

**Summary**

Every day of practice, emergency physicians face continuous challenges. A neonate, infant, or child presenting with symptomatic pulmonary hypertension—a rare but deadly condition that may masquerade as a common benign condition and that requires immediate and specific therapy—combines multiple challenges together into a perfect storm ripe with potential disaster. An awareness of this disease entity, its various presentations, and effective first-line therapy is the single best resource for emergency physicians finding themselves in this unenviable situation.

Fortunately, over the past decade, an expanded understanding of the vascular endothelium, vascular smooth muscle cells, and the role of their interactions in the pathophysiology of pulmonary vascular disease have resulted in new effective treatments, with additional potential therapies evolving rapidly. In addition, accumulated experience and focused research have uncovered a multitude of disease processes that contribute directly or indirectly to the development of pulmonary hypertension. Physicians caring for children must remain abreast of these illnesses, the pathophysiology of pulmonary hypertension, and the available treatment options in order to translate these advances into improved outcomes for patients.

**Addendum**

**Pathophysiology**

Pulmonary vascular resistance changes throughout gestation and after birth. The resistance of the pulmonary circulation at any one time is related to several factors and can be estimated by applying the resistance equation and the Poiseuille-Hagen relationship. The resistance equation (the hydraulic equivalent of Ohm’s law) states that the resistance to flow between two points along a tube equals the decrease in pressure between the two points divided by the flow. For the pulmonary vascular bed, where \( R_p = \) pulmonary vascular resistance and \( Q_p = \) pulmonary blood flow, the decrease in mean pressure is from the pulmonary artery (Ppa) to the pulmonary vein (Ppv) or left atrium, where \( la = \) mean left atrial pressure:

\[
R_p = \frac{(P_{pa} - P_{pv} \text{ or } la \text{ [mean]})}{Q_p}
\]

Therefore, the calculated pulmonary vascular resistance increases when pulmonary arterial pressure increases or when pulmonary blood flow decreases.
Other factors that affect pulmonary vascular resistance can be defined by applying a modification of the Poiseuille-Hagen relationship which describes the resistance (R) to flow of a Newtonian fluid through a system of round, straight glass tubes of constant cross sectional area:

\[ R_p = \frac{8l\eta}{\pi r^4} \]

Where \( l \) = length of the system of vessels, \( v \) = vessel number, \( r \) = the internal radius of the system of vessels, and \( \eta \) = the viscosity of the fluid. According to this relationship, increasing the viscosity of blood perfusing the lungs or decreasing the radius or cross-sectional area \((\pi r^4)\) of the pulmonary vascular bed increases pulmonary vascular resistance.

A schematic of some of the vasoactive factors produced by the pulmonary vascular endothelium is shown in **Figure 4** on page 16. These substances, such as nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin are capable of producing vascular relaxation and/or constriction, modulating the propensity of the blood to clot and inducing and/or inhibiting smooth muscle cell migration and replication. NO is a labile humoral factor produced by nitric oxide synthase (NOS) from \( \lambda \)-arginine in the vascular endothelial cell. NO diffuses into the smooth muscle cell and produces vascular relaxation by increasing concentrations of guanosine 3’5’-monophosphate (cGMP) via the activation of soluble guanylate cyclase. NO is released in response to a variety of factors including shear stress (flow) and the binding of certain endothelium-dependent vasodilators (such as acetylcholine, ATP, and bradykinin) to receptors on the endothelial cell. Basal NO release is an important mediator of both resting pulmonary and systemic vascular tone in the fetus, newborn, and adult, as well as a mediator of the normal fall in pulmonary vascular resistance that occurs immediately after birth. In addition, aberrant NO-cGMP signaling is integral to the pathophysiology of pulmonary hypertension.

ET-1 is a 21 amino acid polypeptide also produced by vascular endothelial cells. The vasoactive properties of ET-1 are complex and studies have shown varying hemodynamic effects on different vascular beds. Its most striking property is its sustained hypertensive action. In fact, ET-1 is the most potent vasoconstricting agent discovered, with a potency 10 times that of angiotensin II.

The hemodynamic effects of ET-1 are mediated by at least two distinctive receptor populations: ETA and ETB. The ETA receptors are located on endothelial cells and smooth muscle cells and may mediate both vasodilation and vasoconstriction, respectively. Individual endothelins occur in low levels in the plasma, generally below their vasoactive thresholds. This suggests that they are primarily effective at the local site of release. Even at these levels, they may potentiate the effects of other vasoconstrictors, such as norepinephrine and serotonin. The role of endogenous ET-1 in the regulation of normal vascular tone is unclear at present. Nevertheless, alterations in ET-1 have been implicated in the pathophysiology of pulmonary hypertensive disorders.

The breakdown of phospholipids within vascular endothelial cells results in the production of the important byproducts of arachidonic acid, including prostacyclin (PGI2) and thromboxane (TXA2). PGI2 activates adenylate cyclase, resulting in increased cAMP production and subsequent vasodilation, whereas TXA2 results in vasoconstriction via phospholipase C signaling. Other prostaglandins and leukotrienes also have potent vasoactive properties. Evidence in patients with congenital heart disease and pulmonary hypertension indicates that an imbalance between TXA2 and PGI2 that favors TXA2-mediated vasoconstriction contributes to the development of pulmonary vascular disease in these patients.

Increasing evidence suggests that endothelial injury and the resulting alteration in the balance of
these and other vasoactive substances has a significant role in the development of pulmonary hypertension and increased vascular reactivity. Support for this hypothesis is strengthened by observations that endothelial injury precedes pulmonary hypertension and its associated vascular remodeling in several animal models of pulmonary hypertension. In humans, endothelial dysfunction, including histological abnormalities of the endothelium, impairment of endothelium-dependent pulmonary vasodilation, and increased plasma ET-1 concentrations, have been described in children with congenital heart defects and pulmonary hypertension before the development of significant vascular remodeling. In addition, neonates with PPHN and adults with advanced pulmonary vascular disease have evidence of endothelial dysfunction, as manifested by impaired endothelium-dependent pulmonary vasodilation, increased plasma ET-1 concentrations, and decreased prostacyclin production. The mechanism of injury to the vascular endothelium is unclear, but it is likely multi-factorial and dependent in part upon the etiology of the pulmonary hypertension. For example, in children with congenital heart disease and increased pulmonary blood flow, the initiating endothelial injury is likely mediated by increased shear stress. However, once pulmonary arterial pressure is elevated, shear stress-mediated endothelial injury appears to promote the progression of the disease, independent of the underlying etiology. Finally, a genetic disposition appears to be important in some subtypes of pulmonary vascular disease and remains an area of active research. For example, up to 50% of patients with familial pulmonary hypertension have mutations resulting in the loss of function of bone morphogenetic protein receptor II (BMPR2).

Following an initial endothelial injury, smooth muscle proliferation and progressive structural remodeling occurs. The progression of anatomic changes is best characterized in congenital heart disease. However, regardless of the etiology, advanced disease is characterized by medial hypertrophy, intimal hyperplasia, angiomatoid formation, in situ thrombi, and eventual vascular obliteration. Untreated, these structural changes progress to the point of becoming functionally "fixed," or irreversible. An important goal of therapy is to halt this progression and reverse the early vascular remodeling, when possible.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


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**CME Questions**

1. **Pulmonary hypertension is defined as:**
   a. A systolic pulmonary artery pressure of 25 mmHg at rest or greater than 30 mmHg during exercise
   b. A mean pulmonary artery pressure of 25 mmHg at rest or greater than 30 mmHg during exercise
   c. Right ventricular hypertrophy with signs of impaired cardiac output and oxygen delivery
d. An acute increase in pulmonary arterial pressure, resulting in right ventricular failure and cardiopulmonary collapse

2. The most common cause of pulmonary hypertension in neonates is:
   a. Congenital heart disease
   b. Connective tissue disease
   c. Persistent pulmonary hypertension of the newborn
   d. Familial pulmonary hypertension

3. **Nitric oxide is:**
   a. An anesthetic agent
   b. A gas produced by vascular endothelial cells that results in smooth muscle cell relaxation through cGMP signaling
   c. A potent vasoconstricting factor produced by vascular endothelial cells
d. Increased in patients with pulmonary hypertension

4. When treating a pulmonary hypertensive crisis, the most important goals are:
   a. To decrease pulmonary arterial pressure and support right ventricular function
   b. To reverse pulmonary vascular remodeling
   c. To increase systemic oxygen saturation
   d. To maintain systemic blood pressure

5. Which disease is associated with pulmonary hypertension?
   a. HIV
   b. Asthma
   c. Cerebral palsy
   d. Hypertension

6. A key physical finding in patients with pulmonary hypertension is:
   a. Difficulty palpating the liver edge
   b. A loud second heart sound
   c. Bounding pulses
   d. Carotid bruit

7. The key findings on ECG are:
   a. S-T segment changes consistent with ischemia
   b. Evidence of right ventricular hypertrophy
   c. Heart block
   d. Atrial flutter or fibrillation

8. Estimates of pulmonary artery pressure are made with echocardiography by:
   a. Measuring the main pulmonary artery diameter
   b. Right ventricular wall thickness
   c. Tricuspid regurgitation jet velocity
   d. Pulmonary valve regurgitation jet velocity

9. Children with pulmonary hypertension may be considered for therapy with calcium channel blockers if:
   a. They do not have systemic hypotension
   b. They do not have known allergies to calcium channel blockers
   c. They demonstrate an acute decrease in pulmonary vascular resistance without decreased cardiac output in response to vasodilator testing during right heart catheterization
   d. They fail other therapies

10. Which of the following laboratory studies aid in the assessment of cardiac output?
    a. Complete blood count
    b. Coagulation studies
    c. Central venous oxyhemoglobin saturation
    d. C-reactive protein

11. The best first-line therapy for decreasing pulmonary arterial pressure is:
    a. Prostacyclin
    b. Endothelin receptor antagonism
    c. Inhaled nitric oxide
    d. Oxygen

12. The drug(s) of choice for supporting the right ventricle in the setting of pulmonary hypertension is/are:
    a. Epinephrine
    b. Norepinephrine
    c. Vasopressin
    d. Dopamine and/or dobutamine

13. The acute withdrawal of intravenous prostacyclin may be associated with:
    a. A pulmonary hypertensive crisis
    b. Infection
    c. The ability to restart at a lower dose after a “drug holiday”
    d. Depression

14. Pulmonary hypertension may complicate neonatal sepsis because:
    a. HIV disease is a common cause of neonatal sepsis
    b. Septic neonates often have hypothyroidism
    c. Sepsis, acidosis, and/or hypoxia may impair the fall in pulmonary vascular resistance that occurs over the first few weeks of life
    d. Congenital heart disease is a common cause of sepsis in neonates

15. Which patient with congenital heart disease may be most affected by an increase in pulmonary arterial pressure and vascular resistance?
    a. A neonate with unrepaired hypoplastic left heart syndrome (HLHS)
    b. An infant with an unrepaired ventricular septal defect (VSD)
    c. A child with an unrepaired atrial septal defect (ASD)
    d. An infant with a partial cavopulmonary anastomosis (PCPA)

16. Pediatric patients presenting to an acute care setting with pulmonary hypertension should:
    a. Be immediately transferred to a pediatric facility
    b. Have pulmonary vasodilator therapy initiated immediately
    c. Undergo right-heart catheterization immediately
    d. Be referred to a tertiary center with a dedicated pediatric pulmonary hypertension program