

Persevering against **pediatric pulmonary arterial hypertension**

Despite recent therapeutic advances, prognosis is still poor for children with this incurable disease.

By Michelle T. Ogawa, MSN, RN, CPNP

PULMONARY ARTERIAL HYPERTENSION (PAH) is a disease primarily of the small distal pulmonary arteries that narrow and constrict, leading to increased pulmonary vascular resistance. Over time, the right ventricle may thicken and grow weak, causing right-sided heart failure.

Over the past decade, PAH treatment options have improved, extending patients' lives and improving their quality of life. However, when supportive pharmacologic therapies can no longer maintain adequate heart function, transplantation must be considered. This article discusses PAH pathophysiology, clinical presentation and diagnosis, drug therapies, and other interventions.

Defining PAH

Normally, mean pulmonary artery pressure (mPAP) is 11 to 20 mm Hg. A patient may be diagnosed with PAH if mPAP exceeds 25 mm Hg at rest or 30 mm Hg with exercise. In severe cases,

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LEARNING OBJECTIVES

1. Summarize the pathophysiology of pulmonary arterial hypertension (PAH).
2. List common assessment findings for a child with PAH.
3. Discuss management of PAH in children, including drug therapy.
4. Describe special considerations for children with PAH.



Pulmonary artery hemodynamics

Pulmonary arterial pressure depends on blood flow (the amount of blood traveling through the pulmonary arteries) and the resistance of blood flow through this system. This equation sums up the relationship:

$$\text{Pressure} = \text{flow} \times \text{resistance}$$

Increased pressure can result from any of the following:

- high-volume flow with normal resistance
- normal blood flow with increased resistance
- increased flow and resistance.

it may rise to systemic (aortic) or suprasystemic levels.

Ordinarily, the right ventricle works against a consistently low PAP that decreases to near-adult levels by ages 6 to 8 weeks. In PAH, it must work harder to maintain cardiac output and thus becomes hypertrophied. This, in turn, causes dilation and poor functioning, which ultimately lead to right-sided heart failure.

PAH may occur with or without elevated pulmonary vascular resistance (PVR). While the terms pulmonary hypertension (PH) and pulmonary vascular disease are often used interchangeably, they're not the same thing.

- PH simply refers to elevated PAP, which may or may not imply abnormal pulmonary vascular tone.
- Pulmonary vascular disease usually is defined as an abnormal anatomic narrowing of the pulmonary vasculature (from remodeling or thickening of the vascular wall or inherent structural abnormalities).

Simply put, PH may occur with or without elevated PVR, whereas pulmonary vascular disease by definition implies elevated PVR. In the context of this article, PAH represents the disease process that results from elevated PAP, or pulmonary vascular disease. (See *Pulmonary artery hemodynamics*.)

Pathophysiology

Decreased production of nitric oxide (NO) and prostacyclin and overexpression of endothelin-1 are the ma-

inor factors associated with pulmonary artery vasoconstriction in PAH. NO and prostacyclin are endogenous pulmonary vasodilators; endothelin-1 mediates pulmonary vasoconstriction. These three factors cause abnormal vascular tone, pulmonary vascular wall remodeling, and prothrombotic tendencies.

In all PAH forms, vascular remodeling of distal pulmonary arteries results from smooth-muscle cell proliferation. In severe PAH, a layer of myofibroblasts and extracellular matrix also develops between the endothelium and internal elastic lamina, further thickening and narrowing pulmonary arterial walls. In some cases, proliferation of disorganized endothelial cells creates lesions. What causes these lesions isn't fully understood but may include genetic predisposition, hypoxia, shear stress, inflammation, or such environmental triggers as drugs or toxins.

Inflammatory responses also may be involved in PAH pathophysiology. In some patients with PAH associated with systemic lupus erythematosus, immunosuppressive therapy has improved hemodynamics. Procoagulant activity and fibrinolytic function in pulmonary endothelial cells also may be dysfunctional in PAH, causing thrombogenesis. Shear stress or another insult to the pulmonary vascular wall may trigger thrombogenesis as well.

Causes of PAH

Various conditions have been linked to PAH, although in some cases the cause isn't known.

Besides idiopathic PAH and familial PAH, many of the diseases associated with PH occur with equal frequency in the adult and pediatric populations. Diseases and disorders commonly associated with PAH in children include congenital heart defects associated with systemic-to-pulmonary shunts and certain pulmonary diseases.

Congenital heart defects

PAH associated with congenital heart defects (CHD-PAH) accounts for a large percentage of children with PAH. If the defect is repaired by age 2, PAH rarely develops. If left unrepaired, increased blood flow may lead to shear stress and may mediate structural changes that increase PVR. Over time, increased blood flow may cause the vascular walls to thicken, resulting in pulmonary vascular disease. CHD-PAH is the most common cause of severe illness and premature death in patients with congenital heart defects.

Assessment and diagnosis

Children with PAH commonly present with initial complaints of decreased exercise tolerance, dyspnea with exertion, increased fatigue, or syncope. Because these symptoms are vague, the disease often goes undiagnosed or is misdiagnosed as another condition, such as asthma.

A history of one or more syncopal episodes (PH crises) is the most ominous finding for severe PAH. A PH crisis occurs when PVR increases rapidly to the point where PAP exceeds systemic pressure. When this happens, pulmonary blood flow decreases, causing reductions in pulmonary venous return and cardiac output. In many cases, PH crises are the defining events that lead clinicians to conduct a more aggressive evaluation.

Physical examination may reveal a prominent pulmonic component of the second heart sound, a systolic regurgitant murmur secondary to tricuspid regurgitation, or both.

When assessing a child in heart failure caused by severe PAH, you may note jugular venous distention, hepatomegaly, or peripheral edema.

Evaluation and work-up

Expect the patient to undergo an extensive battery of tests, including ECG, chest X-ray, and pulmonary function tests. Additional studies include extensive serum laboratory tests (such as electrolyte and thyroid panels), liver function tests, extensive coagulopathic studies, levels of lipoprotein A and brain natriuretic peptide (a marker for heart failure), rheumatologic panel, and tests for acquired diseases linked to PAH (such as HIV infection and hepatitis A, B, and C). Because obstructive sleep apnea may be associated with PAH, a sleep study is recommended for patients with a history of snoring, sleep apnea, obesity, or chronic fatigue.

Cardiac catheterization is considered the gold standard for diagnosis and risk stratification. Angiography can help determine the severity of pulmonary vascular disease. During this study, an acute vasodilator challenge is done—usually with NO (with or without 100% oxygen) but in some cases with I.V. prostacyclin or adenosine. In the past, an mPAP decrease of at least 20% with unchanged or increased cardiac output was deemed a positive vasodilator response. But more recent definitions of vasoreactivity include an mPAP reduction of more than 10% and an mPAP decrease to below 40 mm Hg with normal cardiac output, as this predicts those patients most likely to respond well to therapy.

Once the work-up is complete, the patient's functional class is determined by assigning the New York Heart Association (NYHA) classification. Appropriate treatment is based on both the patient's NYHA functional class and diagnostic data.

Management

Ideally, an underlying defect or dis-

ease associated with PAH should be addressed before PAH therapy begins. For example, a congenital heart defect should be repaired surgically, when possible. Patients with rheumatologic diseases, such as juvenile rheumatoid arthritis, may have clinical signs of PAH when their primary disease is exacerbated. When possible, rheumatologic therapies are used to stabilize the child before PAH drug therapy begins or a change in PAH therapy is considered. However, drug therapy may start sooner if the rheumatologic process isn't likely to stabilize or reverse for some time and the child needs increased support.

Drug therapy

In the last 10 years, pharmacologic options have grown, extending the lives of patients with PAH and prolonging their time to transplant. Although some safety and short-term efficacy studies for PAH therapies have been conducted in children, much of the data derive from adult studies. (See *Drug therapy for PAH*.)

Calcium channel blockers

One of the first therapies used for idiopathic PAH, calcium channel blockers decrease PVR by dilating pulmonary arteries. These oral agents may be considered for patients who respond positively to a vasodilator challenge during cardiac catheterization.

Endothelin-receptor antagonists

Endothelin-receptor antagonists (ERAs) block endothelin-1 from binding to the receptor, preventing pulmonary vasoconstriction. Two types of endothelin receptors exist—type A (ET_A) and type B (ET_B). The ET_A receptor causes vasoconstriction when activated, whereas the ET_B receptor mediates both vasoconstriction and vasodilation. Until June 2007, bosentan was the only ERA approved for PAH treatment. This drug blocks both ET_A and ET_B receptors; eliminated by hepatic metabolism, it can cause

temporary liver enzyme elevations and requires frequent monitoring. The recently approved ambrisentan selectively blocks ET_A receptors and is associated with decreased incidence and severity of liver enzyme abnormalities.

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors include sildenafil, a potent pulmonary selective vasodilator originally used to treat erectile dysfunction (marketed as Viagra). Like other PDE-5 inhibitors, it blocks the breakdown of cyclic guanylate monophosphate, prolonging the effects of NO. A large double-blind randomized placebo study is currently in progress to determine its safety and efficacy in pediatric patients.

Prostanoids

Prostanoids provide exogenous prostacyclin analogues to replace endogenous prostacyclin deficiency in PAH. Most clinicians reserve these drugs for patients with moderately severe to severe pulmonary hypertension.

Epoprostenol, the first drug approved for PAH, has a half-life of only about 6 minutes and must be given I.V. on a continuous basis. It's also unstable at room temperature for more than 8 hours. The patient needs a permanent central-line catheter to ensure its delivery and must carry a specially designed medication pump with ice packs that must be replaced at least every 4 to 8 hours. Family members require extensive training in mixing the drug, managing the medication pump, and changing central-line dressings at home.

Treprostinil is given subcutaneously or I.V. on a continuous basis. It has a much longer half-life (approximately 4 hours) than epoprostenol and is stable at room temperature for 48 hours. Although subcutaneous delivery eliminates the risks associated with a permanent central line, more than 85% of pa-

Drug therapy for PAH

Drugs used to treat pulmonary arterial hypertension (PAH) fall into the four categories below. Except where indicated, the drugs are approved for use in adults. None of these drugs is approved for children.

Drug class and agent	Efficacy	Nursing considerations
Calcium channel blockers (CCBs) <ul style="list-style-type: none"> amlodipine diltiazem nifedipine 	<ul style="list-style-type: none"> 2005 study by Sitbon et al found that adult responders to vasodilator challenge on CCBs achieved near-normal hemodynamics at 1 year. In 1999 study by Barst et al, 31 pediatric responders on CCBs had better survival rates than 43 nonresponders. Half of responders required I.V. prostacyclin after 2 to 126 months. 	<ul style="list-style-type: none"> Monitor patient's heart rate, blood pressure, and oxygen (O₂) saturation when giving initial dose. Drug may cause systemic vasodilation.
Endothelin-receptor antagonists <ul style="list-style-type: none"> ambrisentan bosentan 	<ul style="list-style-type: none"> 2003 study of 19 pediatric patients by Barst et al found that bosentan was safe and produced improved hemodynamics. 2005 study of 68 pediatric patients by Rosenzweig et al found functional and hemodynamic improvements in patients receiving bosentan ± prostanoids. 	<ul style="list-style-type: none"> Check alanine aminotransferase and aspartate aminotransferase levels before initiating therapy; then monitor levels monthly. Teratogenic; for adolescent females, recommend initial pregnancy test before initiating therapy; monthly testing should be done thereafter. Counseling on pregnancy risks and birth control is strongly recommended.
Phosphodiesterase-5 (PDE-5) inhibitors <ul style="list-style-type: none"> sildenafil tadalafil* vardeafil* 	<ul style="list-style-type: none"> 2005 study of 14 pediatric patients by Humpl et al found that oral sildenafil produced functional and symptomatic improvement. 	<ul style="list-style-type: none"> Initial dosage may be half of maintenance dosage. Monitor heart rate, blood pressure, and O₂ saturation before administration and 1 hour after. Monitor for possible adverse effects: flushing, headache, dizziness, nausea, and leg pain. Be aware that transient impairment of color discrimination may occur.
Prostanoids <ul style="list-style-type: none"> epoprostenol treprostinil iloprost 	<ul style="list-style-type: none"> 1999 study of 20 patients with pulmonary hypertension (PH) and congenital heart disease by Rosenzweig et al found long-term epoprostenol therapy improved hemodynamics. 2004 study of 77 pediatric patients by Yung et al found significantly improved survival with long-term epoprostenol therapy at 1 and 3 years. 2007 study of 39 pediatric patients by Lammers et al found that epoprostenol ± oral therapy improved functional class during first year and exercise tolerance at about 1 year after treatment. 2007 study of 13 patients by Ivy et al found that drug caused no change in 6-minute walk distance, pediatric patients who switched to I.V. treprostinil from I.V. epoprostenol experienced fewer adverse effects, and treprostinil carried greater risk of line infection than epoprostenol. 2002 study by Olschewski et al found drug effective in adults with severe PH after 1 year of treatment. 2005 study by Optiz et al found drug effective as monotherapy in 42% of sample adult patients after 1 year of treatment. Only 5 of 76 adults who had been effectively treated with iloprost alone were alive at 5-year follow-up; other 71 patients required combination therapy. 	<ul style="list-style-type: none"> I.V. prostanoid therapy must be initiated with frequent hemodynamic monitoring in catheterization lab or intensive care unit. Dosing may be based on clinical changes; monitor hemodynamic status and stay alert for adverse effects (flushing, headache, dizziness, nausea, and jaw pain). Instruct patient and caregivers in central line dressing care and at-home drug management. <p>I.V. and subcutaneous therapy:</p> <ul style="list-style-type: none"> Same as for epoprostenol <p>Subcutaneous therapy:</p> <ul style="list-style-type: none"> Manage injection site pain. Monitor patient's tolerance closely and implement appropriate interventions for pain as needed. Therapy may be initiated either in hospital or outpatient setting. Monitor heart rate, blood pressure, and O₂ saturation during first dose. Monitor for adverse effects (flushing, headache, dizziness, nausea, and jaw pain). Emphasize importance of medication compliance, as dosing schedule is demanding.

*Currently in clinical trials for use in PAH

tients receiving this drug experience site pain and need pain management interventions ranging from local anesthetic gel to narcotics. In pediatric patients, the drug usually is given I.V. rather than subcutaneously. Because treprostinil is safer and more convenient than epoprostenol, some patients receiving epoprostenol have been switched to treprostinil.

Epoprostenol or treprostinil administration by a central line poses the risk of infection or bacteremia. A 2007 retrospective study found higher bacteremia rates for adults and children on treprostinil than those on epoprostenol. Such factors as a slower pump rate with treprostinil, preparation and storage differences, and facility-specific differences in catheter care may account for the discrepancy.

Iloprost, delivered by metered inhaler, is the newest addition to PAH therapeutic options. However, it must be given six to nine times daily, so compliance may be difficult—especially for children attending school. Nonetheless, iloprost is a useful option for patients with severe PAH caused by an unrepaired ventricular septal defect, as central line placement can increase the risk of thromboembolic stroke.

Other prostanoid therapies currently under study include oral and inhaled treprostinil.

Nitric oxide therapy

Inhaled NO, a potent and highly selective pulmonary vasodilator, replaces lack of endogenous NO production associated with PAH. It's given routinely in intensive-care settings for acute PAH exacerbation or perioperative PAH after cardiac surgery. In infants, the drug reduces the severity of PH crises. Safety and efficacy of chronic inhaled NO haven't been studied, although a few patients have been managed on outpatient therapy.

Oxygen therapy

Supplemental oxygen helps main-

tain adequate oxygen saturation through vasodilation, which helps prevent PAH from worsening. It may be used periodically for patients who experience marked desaturation with physical activity, those having episodes of severe upper respiratory infections, patients with obstructive sleep apnea, or those traveling by airplane (especially for an extended period) or who travel or live at high altitudes (above 6,000 ft). Patients who have severe PAH with chronic oxygen desaturation need continuous supplemental oxygen even at rest.

Anticoagulant therapy

Warfarin commonly is prescribed at a dosage that obtains an international normalized ratio of 1.5 to 2.5. Although no formal studies have examined warfarin efficacy in PAH patients, uncontrolled studies found longer survival in adults receiving warfarin compared to those not receiving anticoagulants. For younger and highly active children with mild to moderate disease severity, risks and benefits must be weighed to ensure optimal but safe anticoagulant management.

Other drug therapies

Diuretics, such as furosemide, help decrease preload and reduce the work of the right side of the heart; they may be used in patients with signs and symptoms of right-sided heart failure. Digoxin also may be used in patients with heart failure, although no formal studies have been done in children.

Challenges in therapeutic management

Ironically, the increased number of therapeutic options for PAH presents a challenge for clinicians. Most pediatric patients in NYHA functional classes I and II and with mild to moderate PAH can be treated fairly easily with oral drugs. At the other extreme, patients with severe PAH (systemic or suprasystemic

pressures) and in NYHA class IV are almost uniformly started on I.V. or subcutaneous prostanoid therapy (unless contraindications exist). However, a child with moderate to moderately severe PAH who's in NYHA class III poses a predicament for clinicians, who must decide how and when more aggressive I.V. therapy should be started.

Recent studies have compared the efficacy of monotherapy and combination therapy. Further pediatric studies are needed to provide better direction. With limited scientific basis, some clinicians have combined oral and I.V. therapy, depending on disease severity.

Organ transplantation

When the most aggressive PAH treatment options fail, double lung or heart-lung transplantation is the only treatment alternative. Unfortunately, complications such as organ rejection and bronchiolitis obliterans are hard to manage and have a high mortality rate in both adult and pediatric recipients. The average survival rate 5 years after transplantation is 50%.

Other management considerations

Although large PH treatment centers for pediatric patients are limited, patients should be referred to these centers whenever possible—if only for initial evaluation. Initiating appropriate and aggressive therapy early may help slow or prevent further disease progression. The expertise and experience of clinicians at these centers, in addition to extensive support staff, are essential aspects of care that may influence the prognosis of some patients.

Anesthesia considerations

Pediatric patients with PAH should be evaluated and provided with sedation or anesthesia only under the care of anesthesiologists trained in cardiac and cardiopulmonary diseases. Those with suprasystemic

Many children with PAH can lead relatively normal daily lives at home and at school.

PAH are at increased risk for major perioperative complications, including PH crisis and cardiac arrest.

Nursing care for PAH patients

Nurses can play a valuable role by providing continuity of care, close monitoring, and extensive education for patients and their families.

Physical activity

Many children with PAH can lead relatively normal daily lives. Encourage them to get regular aerobic exercise, self-limit their activity, and rest as they feel necessary. They should avoid weight-bearing exercises, which can increase the risk of a PH crisis.

Birth control

For girls beginning menses, discuss birth control options with the patient and family. PAH patients who become pregnant are significantly at risk for death. Also, warfarin, bosentan, and ambrisentan are teratogens that could harm the fetus. Some experts recommend prescribing progesterone-only contraceptives because those containing estrogen may increase the thrombus risk.

Vaccinations

Inform parents that their child should receive all childhood vacci-

nations. Also recommend pneumococcal vaccinations and annual influenza vaccinations.

Family stressors

Like all progressive diseases, PAH can take a devastating emotional toll on all family members. The daily responsibilities associated with I.V. drug therapy may cause constant anxiety and stress. PAH therapies and follow-up tests can be extremely costly, adding financial concerns. Refer the family to appropriate resources to help them cope with stressors.

Therapeutic gains, but still no cure

In the last decade, medical science has made therapeutic inroads against PAH, developing drugs that target major pathways of the disease. However, understanding of the disease process and its management is still limited. To improve survival for children with PAH, further scientific and clinical studies are needed—with the ultimate goal of finding a cure. ★

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For a complete list of selected references, visit www.americannursetoday.com.

To learn more about PAH classification, diagnostic tests, and associated conditions, scroll down. This information is not included in the CE hours.

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1. Which of the following is a physiologic factor associated with pulmonary artery constriction that occurs in pulmonary arterial hypertension (PAH)?

- a. Decreased nitric oxide production
- b. Increased prostacyclin production
- c. Decreased endothelin-1 levels
- d. Increased endothelin-3 levels

2. Which is a true statement about the pathophysiology of PAH?

- a. An inflammatory response may cause an increased bleeding risk.
- b. Endothelin-1 mediates pulmonary vasodilation.
- c. Several factors, including shear stress, may cause thrombogenesis.
- d. Ventricular remodeling of the proximal pulmonary arteries occurs.

3. A possible physical assessment finding in children with PAH is a:

- a. prominent pulmonic component of the first heart sound.
- b. prominent aortic component of the second heard sound.
- c. systolic regurgitant murmur secondary to tricuspid regurgitation.
- d. diastolic regurgitant murmur secondary to bicuspid regurgitation.

4. Which test is considered the gold standard for PAH diagnosis and risk stratification?

- a. Echocardiography
- b. Angiography
- c. Cardiac catheterization
- d. Electrocardiography

5. Which statement about signs and symptoms of PAH is true?

- a. Vague symptoms in the early stages of PAH make diagnosis difficult.
- b. A history of one or more syncopal episodes is not a concern.
- c. Characteristic signs and symptoms make it easy to diagnose PAH.
- d. Patients typically have decreased jugular venous pressure.

6. If your patient with PAH is receiving an endothelin-receptor antagonist, you should keep in mind that:

- a. bosentan blocks only ET_A receptors.
- b. bosentan and ambrisentan block both ET_A and ET_B receptors.
- c. liver enzyme levels should be checked every 6 months.
- d. females should undergo pregnancy testing before starting therapy.

7. If your patient with PAH is receiving a prostanoid, keep in mind that:

- a. these drugs are used for patients with mild PAH.
- b. patients who switched from I.V. epoprostenol to I.V. treprostinil had more adverse effects.
- c. a patient receiving epoprostenol will need teaching about peripheral I.V. care.
- d. the patient will need frequent hemodynamic monitoring when starting the first I.V. dose.

8. Which statement about treprostinil is true?

- a. It is stable at room temperature for 24 hours.
- b. It has a longer half-life than epoprostenol.
- c. It is usually given subcutaneously rather than I.V.
- d. It is less convenient than epoprostenol.

9. Which international normalized ratio (INR) range is commonly used to adjust warfarin dosage?

- a. 0.5 to 1.0
- b. 1.0 to 2.0
- c. 1.5 to 2.5
- d. 2.5 to 2.75

10. A child in NYHA functional class II with moderate PAH is usually treated with:

- a. subcutaneous prostanoid therapy.
- b. oral drugs.
- c. combination oral and I.V. therapy.
- d. I.V. drugs.

11. Which statement about double lung or heart-lung transplantation in patients with PAH is true?

- a. The procedure is performed only when the most aggressive treatment options have failed.
- b. Surgical complications are typical but easy to manage.
- c. The average survival rate is 70% at 5 years post-transplantation.
- d. Outcomes are similar to those of other solid organ transplantation.

12. Which of the following statements about physical activity in children with PAH is true?

- a. Children should rest at least 15 minutes every 4 hours.
- b. Children should get regular aerobic exercise.
- c. Children should perform weight-bearing exercises daily.
- d. The child's daily activity is likely to be significantly restricted.

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Evaluation form

1. In each blank, rate the extent to which you achieved each objective of this study module, from 1 (low/poor) to 5 (high/excellent).

- (1.) Summarize the pathophysiology of PAH. _____
- (2.) List common assessment findings for a child with PAH. _____
- (3.) Discuss management of PAH in children, including drug therapy. _____

(4.) Describe special considerations for children with PAH. _____

Also rate the following from 1 to 5.

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Classifying pulmonary hypertension

In 2003, the World Pulmonary Hypertension Symposium revised the clinical classifications of pulmonary hypertension as shown below.

- A. Pulmonary arterial hypertension (PAH)
 - 1. Idiopathic PAH
 - 2. Familial PAH
 - 3. Associated with:
 - a. Collagen vascular disease
 - b. Congenital systemic-to-pulmonary shunts
 - c. Portal hypertension
 - d. Human immunodeficiency virus infection
 - e. Drugs and toxins
 - f. Other: thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
 - 4. Associated with significant venous or capillary involvement
 - a. Pulmonary veno-occlusive disease
 - b. Pulmonary capillary hemangiomatosis
 - 5. Persistent pulmonary hypertension of the newborn
- B. Pulmonary hypertension with left-sided heart disease
 - 1. Left-sided atrial or ventricular heart disease
 - 2. Left-sided valvular heart disease
- C. Pulmonary hypertension associated with lung diseases and/or hypoxemia
 - 1. Chronic obstructive pulmonary disease
 - 2. Interstitial lung disease
 - 3. Sleep-disordered breathing
 - 4. Alveolar hypoventilation disorders
 - 5. Chronic exposure to high altitude
 - 6. Developmental abnormalities
- D. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
 - 1. Thromboembolic obstruction of proximal pulmonary arteries
 - 2. Thromboembolic obstruction of distal pulmonary arteries
 - 3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
- E. Miscellaneous
 - 1. Sarcoidosis
 - 2. Histiocytosis X
 - 3. Lymphangiomatosis
 - 4. Compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Source: Simonneau G, Galie N, Rubin L, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2004;43(12):55-125.

Conditions associated with PAH in children

The following conditions are associated with pulmonary arterial hypertension (PAH) in children:

- congenital heart defects associated with systemic-to-pulmonary shunts (aortopulmonary window, atrial septal defect, partial or complete atrioventricular septal defect, partial or total anomalous pulmonary venous return, patent ductus arteriosus, single ventricle with unobstructed pulmonary blood flow, truncus arteriosus, and ventricular septal defect)
- pulmonary diseases (bronchopulmonary dysplasia, congenital diaphragmatic hernia, hyaline membrane disease, interstitial lung disease, obstructive sleep apnea, pulmonary hypoplasia, and chronic exposure to high altitudes)
- persistent pulmonary hypertension of the newborn
- pulmonary veno-occlusive disease
- rheumatologic diseases (systemic lupus erythematosus and juvenile rheumatoid arthritis)
- coagulopathic disorders
- collagen vascular disease
- connective tissue disease
- portal hypertension
- thyroid disease.

Sources: Galie N. Classification of patients with congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension: current status and future directions. In: Beghetti M, ed. *Pulmonary Arterial Hypertension Related to Congenital Heart Disease*. Munich, Germany: Elsevier GmbH; 2006:15.
Simonneau G, Galie N, Rubin L, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2004;43(12):55-125.

Diagnosing PAH

A complete initial work-up for pulmonary arterial hypertension (PAH) includes the tests below.

Diagnostic test	Purpose	Typical findings in PAH
12-lead electrocardiography	To identify heart rhythm and cardiac morphologic changes	<ul style="list-style-type: none"> • Right ventricular (RV) hypertrophy • Prolonged QRS wave in leads V₁, V₂, and V₃
Chest X-ray	To determine heart size and detect lung abnormalities	<ul style="list-style-type: none"> • Cardiomegaly • Increased central pulmonary artery size • Pulmonary disease
Echocardiography	To estimate RV pressure, size, and function	<ul style="list-style-type: none"> • Increased RV systolic pressure • Reduced RV function • Tricuspid regurgitation • RV hypertrophy • Ventricular septal bowing
Cardiopulmonary exercise test	To evaluate exercise capacity	<ul style="list-style-type: none"> • Decreased maximal rate of oxygen consumption
Pulmonary function tests	To measure functional lung capacity and perfusion capability	<ul style="list-style-type: none"> • Restrictive or constrictive pulmonary disease • Decreased lung diffusing capacity for carbon monoxide
6-minute walk test	To measure exercise capacity (distance walked and vital signs)	<ul style="list-style-type: none"> • Increased dyspnea score with exercise • Possible reduced walking distance
Computed tomography (CT) angiography	To visualize the cardiopulmonary and hepatic vascular systems	<ul style="list-style-type: none"> • Pulmonary disease (such as interstitial lung disease) • Exclusion of congenital vascular defects and hepatic disease
Abdominal ultrasound (if not examined by CT)	To detect hepatic abnormalities	<ul style="list-style-type: none"> • Exclusion of arteriovenous malformation, portal hypertension, and persistent ductus venosus
Cardiac magnetic resonance imaging	To evaluate RV function and detect scarring	<ul style="list-style-type: none"> • Reduced RV function with severe PAH • Delayed enhancement of RV, indicating RV scarring
Ventilation/perfusion scan	To detect pulmonary emboli (PE)	<ul style="list-style-type: none"> • In PE, unequal perfusion to affected lobe
Cardiac catheterization	To measure right-sided heart pressures, pulmonary artery pressure (PAP), oxygenation, and cardiac output	<ul style="list-style-type: none"> • Increased right atrial pressure • Decreased RV diastolic function • Decreased cardiac output • Mean PAP above 25 mm Hg

Classifying heart failure

The New York Heart Association (NYHA) classification system places adult and pediatric patients in one of four categories based on limitations during physical activity. Many children even with severe pulmonary arterial hypertension may fall into functional class II.

NYHA functional class	Functional capacity
I	No symptoms or limitations of ordinary physical activity
II	Mild symptoms and slight limitations of physical activity
III	Symptoms occurring with ordinary activity; marked physical activity limitation; comfortable only at rest
IV	Unable to complete any physical activity without discomfort