Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg during physical activity. Pulmonary arterial hypertension is classified into subgroups, including idiopathic, heritable, and pulmonary arterial hypertension associated with other conditions. A detailed history, thorough physical examination, and most importantly, a high index of suspicion are essential to diagnosis. Evaluation includes echocardiography and exclusion of other causes of symptoms. Targeted laboratory testing can help identify the subgroup of pulmonary arterial hypertension. Right heart catheterization is required to confirm the diagnosis. Standard treatment options include oral anticoagulation, diuretics, oxygen supplementation, and for a small percentage of patients, calcium channel blockers. Newer treatments include prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Combination therapy has been shown to improve pulmonary arterial pressure, but more research is needed. Interventional procedures for patients with pulmonary arterial hypertension include balloon atrial septostomy and lung transplantation. (Am Fam Physician. 2010;82(4):370-377. Copyright © 2010 American Academy of Family Physicians.)

Clinical Features
The early phases of PAH may be asymptomatic. Patients usually present with dyspnea exacerbated by exertion, fatigue, chest pain, and palpitations. The diagnosis of PAH is often delayed because many other conditions can cause similar symptoms. The differential diagnosis includes congestive heart failure, coronary artery disease, pulmonary embolism, and chronic obstructive pulmonary disease. Advanced PAH may present as clinically evident right-sided heart failure, dizziness, syncope, edema, or cyanosis.

If PAH is incidentally discovered, the physician should attempt to find or exclude possible modifiable causes. Confirmation by right heart catheterization should be considered before beginning an extensive search for an underlying cause, starting therapy, or providing prognostic advice.

Diagnosis
A detailed history, thorough physical examination, and most importantly, a high index of suspicion are essential to diagnosing PAH. A French study reported an average delay of 27 months from the onset of symptoms to diagnosis. PAH should be considered in any patient with dyspnea who shows no or minimal signs of specific heart or lung disease. Suspicion should be especially high in patients who also have conditions associated with PAH, such as sickle cell anemia, HIV, and systemic sclerosis. The American College of Cardiology Foundation and the American Heart Association offer screening guidelines for patients with known risk factors for PAH (Table 2).
Physical examination of a patient with PAH may reveal a right parasternal lift, accentuated pulmonary second heart sound, pansystolic murmur (tricuspid regurgitation), third heart sound, and a diastolic murmur (pulmonary valve insufficiency). Edema may present as jugular vein distension, hepatomegaly, peripheral edema, or ascites.6

DIAGNOSTIC TESTING

Diagnostic testing options for PAH are listed in Table 3.6 Electrocardiography (ECG) may show right ventricular hypertrophy and right axis deviation, but ECG has inadequate sensitivity and specificity to reliably detect PAH.7 One study showed that a combination of P- and T-wave indicators may provide an effective means of assessing treatment response in patients with PAH.8

Chest radiography is abnormal in 90 percent of patients at diagnosis and usually shows right ventricular enlargement, a prominent central pulmonary artery, or peripheral hypovascularity7 (Figure 1). A normal chest radiograph does not rule out the diagnosis.7

Studies have shown a correlation in pulmonary arterial systolic pressure measurement between transthoracic echocardiography and right heart catheterization.9-11 Echocardiography has been used to identify PAH in patients with associated conditions.12-14 Measuring parameters such as septal systolic strain and strain rate may allow for earlier detection of PAH.15 Increased tricuspid regurgitation, and right ventricular and atrial enlargement are echocardiographic signs of PAH.7

PAH must be distinguished from other causes of pulmonary hypertension. Pulmonary function tests and arterial blood gas measurements help identify underlying lung disease. Patients may have mild to moderate reduction of lung volumes on these tests, but the partial arterial oxygen tension (PaO2) is normal or only slightly decreased and the partial arterial carbon dioxide tension (PaCO2) is usually decreased from hyperventilation.7 High-resolution computed tomography can assist in the evaluation of thromboembolic disease, emphysema, or interstitial lung disease. Although cardiac magnetic resonance imaging (MRI) is not currently used as a routine assessment tool, continued improvement in MRI acquisition and spatial resolution may lead to improved understanding of PAH pathophysiology, and aid in diagnosis and prognosis. Cardiac MRI may replace more invasive diagnostic tests.16

Evidence of associated conditions may identify the type of PAH. Routine chemistry panels, complete blood count, and thyroid function tests should be obtained. Antinuclear antibody (ANA), anti-Scl-70, anticentro-
mever, and ribonucleoprotein antibody levels are recommended to evaluate for connective tissue disease. About one third of patients with idiopathic PAH have low ANA titers (less than 1:80). If the ANA levels are elevated or if clinical features suggestive of connective tissue disease are present, rheumatologic consultation is recommended. All patients should be tested for HIV. Liver ultrasonography is a reliable test to exclude cirrhosis or portal hypertension.

**CONFIRMATORY AND PROGNOSTIC TESTING**

Right heart catheterization is required to confirm the diagnosis of PAH and to evaluate the severity of hemodynamic dysfunction. This should be performed at an institution with considerable experience with PAH, specifically with vasoreactivity testing because of potential procedural complications. Vasoreactivity testing is also needed to identify patients who may benefit from treatment with calcium channel blockers. Patients with a mean pulmonary arterial pressure decrease of more than 10 mm Hg to below 40 mm Hg and with an unchanged or increased cardiac output when challenged are considered vasoreactive. Lung biopsy is not recommended because it has considerable risks and a very low likelihood of altering the diagnosis or treatment.

The best test to classify the severity of PAH and estimate prognosis is the six-minute walk test. This simple test measures the distance walked in six minutes. It is predictive of survival in idiopathic PAH. Research is ongoing to better assess prognosis for patients with all subtypes of PAH.

**Treatment**

Because of the complexity of treatment, patients should be followed regularly at an institution that specializes in PAH. Family physicians should be aware of PAH treatments and their potential adverse effects. Figure 2 presents an algorithm for the treatment of PAH.

### Table 2. Risk Factors for PAH and Screening Recommendations

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Further assessment</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMPR2 gene mutation</strong></td>
<td>Echocardiography yearly</td>
<td>Early detection of PAH; 20 percent chance of developing PAH</td>
</tr>
<tr>
<td><strong>Congenital heart disease with shunt</strong></td>
<td>RHC if echocardiography demonstrates evidence of PAH*</td>
<td>High probability of PAH developing in unrepaired shunt (Eisenmenger syndrome)</td>
</tr>
<tr>
<td><strong>First-degree relative with BMPR2 gene mutation or within pedigree of two or more patients with a diagnosis of PAH</strong></td>
<td>Genetic counseling and recommendation for BMPR2 genotyping; proceed as above if positive</td>
<td>Autosomal dominant transmission</td>
</tr>
<tr>
<td><strong>HIV infection</strong></td>
<td>Echocardiography if symptoms or signs suggestive of PAH RHC if echocardiography demonstrates evidence of PAH*</td>
<td>0.5 percent prevalence of PAH</td>
</tr>
<tr>
<td><strong>Portal hypertension</strong></td>
<td>Echocardiography if OLT considered</td>
<td>4 percent prevalence of PAH in candidates for OLT; PAH is predictive of poor OLT outcome</td>
</tr>
<tr>
<td><strong>Previous use of appetite suppressant (fenfluramine)</strong></td>
<td>Echocardiography only if patient is symptomatic</td>
<td>Incidence of PAH is approximately 0.005 percent if agent is used longer than three months</td>
</tr>
<tr>
<td><strong>Recent acute pulmonary embolism</strong></td>
<td>Ventilation-perfusion scintigraphy three months after event if symptomatic; pulmonary angiography if positive</td>
<td>3 percent risk of chronic thromboembolic PH; negative ventilation-perfusion scan excludes chronic thromboembolism</td>
</tr>
<tr>
<td><strong>Sickle cell disease</strong></td>
<td>Echocardiography yearly</td>
<td>Increased mortality if PH is present; early detection of PH; 30 percent develop PH; about 10 percent develop PAH</td>
</tr>
<tr>
<td><strong>Systemic sclerosis</strong></td>
<td>Echocardiography yearly</td>
<td>About 8 percent (by RHC) to 27 percent (by echocardiography) prevalence of PAH in systemic sclerosis</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; OLT = orthotopic liver transplantation; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.

*—Elevated right ventricular systolic pressure or right heart chamber enlargement.
†—Not available in the United States.

STANDARD TREATMENTS

A number of established treatment options for PAH continue to be useful. Two retrospective analyses have reported favorable results with the oral anticoagulant warfarin (Coumadin). Although there is no expert consensus, an International Normalized Ratio of 1.5 to 2.5 is recommended. Patients with right-sided heart failure may benefit symptomatically from diuretics, although no randomized controlled trials have been performed to demonstrate improvement in symptoms or outcomes with diuretic use.

Table 3. Diagnostic Testing Options for PAH

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Other noninvasive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticentromere antibody levels (if clinically indicated)</td>
<td>Cardiac magnetic resonance imaging (if clinically indicated)</td>
</tr>
<tr>
<td>Antinuclear antibody levels (if clinically indicated)</td>
<td>Chest radiography</td>
</tr>
<tr>
<td>Anti-Scl-70 antibody levels (if clinically indicated)</td>
<td>Computed tomography of chest (if clinically indicated)</td>
</tr>
<tr>
<td>Arterial blood gas measurement</td>
<td>Echocardiography (bubble study optional)</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>Complete chemistry panel</td>
<td>Liver ultrasonography</td>
</tr>
<tr>
<td>Human immunodeficiency virus test</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>Ribonucleoprotein antibody levels (if clinically indicated)</td>
<td>Procedures</td>
</tr>
<tr>
<td>Sickle cell screening (if clinically indicated)</td>
<td>Right heart catheterization with vasoreactivity testing</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone levels</td>
<td>Six-minute walk test (to assess severity of PAH)</td>
</tr>
</tbody>
</table>

PAH = pulmonary arterial hypertension.

Information from reference 6.

Figure 1. Chest radiography shows bilateral hilar enlargement, which is a typical finding in patients with pulmonary arterial hypertension, as well as cardiomegaly.

Figure 2. Algorithm for the treatment of PAH. (ERAs = endothelin receptor antagonists; IV = intravenous; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5.)

Table 4. New Medications for PAH

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Dosing</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin analogues</td>
<td>Epoprostenol</td>
<td>Commonly started in hospital at 2 ng per kg per minute by continuous intravenous infusion; typical dosing is around 15 ng per kg per minute; titration based on symptoms and adverse effects</td>
<td>Flushing, headache, skeletal pain, diarrhea&lt;br&gt;Local infections (related to central venous catheter system)&lt;br&gt;Abrupt interruption of treatment can lead to worsening of PAH&lt;br&gt;Cough (from inhaled formulation), flushing, headaches, insomnia, vomiting</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhaled: 2.5 to 5.0 mcg taken six to nine times per day, but not more than once every two hours, via adaptive aerosol device&lt;br&gt;Intravenous infusion: maintenance dosage of 2 to 4 ng per kg per minute&lt;br&gt;Oral: 50 to 300 mcg twice per day</td>
<td>Similar to epoprostenol, including facial flushing, headache, jaw pain, nausea, diarrhea&lt;br&gt;Infusion site pain occurs in 85 percent of patients; can lead to discontinuation of treatment in 8 percent of patients when administered via continuous transcatheter system&lt;br&gt;Increased risk of gram-negative bacteremia</td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Maintenance dosage typically around 15 ng per kg per minute via continuous subcutaneous or intravenous infusion</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Ambrisentan</td>
<td>5 to 10 mg orally once per day</td>
<td>Generally well tolerated&lt;br&gt;Adverse effects generally unrelated to dose&lt;br&gt;Peripheral edema mostly in patients older than 65 years&lt;br&gt;Hepatic transaminase elevations occur at lower rate than with bosentan&lt;br&gt;Dose-dependent reversible elevations of hepatic transaminase levels in 10 percent of patients&lt;br&gt;Anemia and edema can occur</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>125 mg orally twice per day</td>
<td>Dose-dependent reversible elevations of hepatic transaminase levels in 10 percent of patients&lt;br&gt;Anemia and edema can occur</td>
</tr>
<tr>
<td></td>
<td>Sitaxsentan†</td>
<td>Dosages of 100 to 300 mg orally once per day are being studied</td>
<td>Appears similar to other medications in the class</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td>Sildenafil</td>
<td>20 mg orally three times per day (FDA-approved for PAH treatment)</td>
<td>Headache, dyspepsia, flushing</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>2.5 to 40 mg orally once per day (40 mg was needed for statistically significant effects)</td>
<td>Headache, flushing, myalgias</td>
</tr>
</tbody>
</table>

FDA = U.S. Food and Drug Administration; NA = not applicable; PAH = pulmonary arterial hypertension.

†—Currently not approved by the FDA.
Information from references 6, and 21 through 38.

Most patients with PAH have only mild arterial hypoxia at rest. Although symptomatic improvement has been reported with oxygen supplementation, this has not been confirmed in controlled studies. An oxygen saturation greater than 90 percent at all times is recommended. Inotropic agents, such as digoxin, have been considered for treatment, but no data are available on the effects of long-term treatment.

Less than 10 percent of patients with idiopathic PAH have a clinically significant reduction of pulmonary arterial pressure with calcium channel blocker therapy. NEWER TREATMENTS

More recent medications for PAH include prostacyclin analogues, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 inhibitors (Table 4). Prostacyclin is a potent vasodilator that maintains low vascular tone, has antiproliferative properties, and prevents platelet aggregation. The prostacyclin analogues currently approved in the United States are epoprostenol (Flolan), iloprost (Ventavis), and treprostinil (Remodulin).

Endothelin is a potent vasoconstrictor and stimulator of vascular smooth muscle cell proliferation and...
Phosphodiesterase type 5 inhibitors increase the intracellular concentration of cyclic guanosine monophosphate, increase nitric oxide (which induces relaxation of blood vessels), and create antiproliferative effects on vascular smooth muscle cells. Sildenafil (Revatio) and tadalafil (Adcirca) are two phosphodiesterase type 5 inhibitors currently approved for PAH treatment.

Because multiple pathophysiological mechanisms may be involved in PAH, combination therapy may be considered. The addition of sildenafil to epoprostenol monotherapy has been shown to safely improve pulmonary arterial pressure. More research is needed in this area. More research is also needed to determine whether patients with different types of PAH should have different treatment strategies.
INTERVENTIONAL PROCEDURES

Severe PAH may benefit from an interatrial defect by allowing right-to-left shunting and increasing systemic output. Balloon atrial septostomy has been evaluated only in small studies and the benefit is uncertain. Mortality rates for this procedure range from 5 to 15 percent. 7

At this time, balloon atrial septostomy is recommended only for patients in advanced functional classes III and IV (Table 5 43) to relieve symptoms before lung transplantation or as a sole treatment modality when no other options are available. 6

Lung transplantation has been evaluated only in prospective uncontrolled series because formal randomized controlled trials are considered unethical in the absence of alternative treatment options. The three- and five-year survival rates after transplantation are 55 and 45 percent, respectively. 6 Lung and heart-lung transplantation are indicated in patients in advanced functional classes III and IV who are refractory to available medical treatments. 6 Compared with other lung transplant recipients, patients with PAH have a poorer postoperative course and a higher mortality rate. 42 The unpredictability of the waiting list period and the donor organ shortage complicate the decision-making process.

Prognosis, Preventive Care, and Pregnancy

There is no cure for PAH, and the overall prognosis is poor. The course of PAH is progressive and irreversible, with an approximate mortality rate of 15 percent within one year, despite modern therapy. 43 Lifestyle changes and appropriate therapy can relieve symptoms and potentially slow disease progression.

Patients with PAH should receive the pneumococcal vaccine and annual influenza immunization. Smoking cessation is recommended. A healthy lifestyle, including physical activity as tolerated and a nutritious diet, is also advised.

The mortality rate for pregnant women with PAH approaches 30 percent. 44-46 Contraception is strongly recommended in women of childbearing age with PAH, 44,45 particularly mechanical contraception (intrauterine device) or surgical sterilization. 47

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Author disclosure: Nothing to disclose.

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Pulmonary Arterial Hypertension


