Annals of Internal Medicine®

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Pulmonary Hypertension

Diagnosis and Screening

Treatment

Prognosis

Pulmonary hypertension is the term used to describe a group of disorders characterized by abnormally high pressures in the pulmonary arteries. Initial evaluation is focused on identifying the cause, which helps guide appropriate treatment. Pulmonary hypertension is often a feature of advanced common diseases, such as chronic obstructive pulmonary disease and left heart disease, and treatment is focused primarily on the underlying disease. More rarely, pulmonary hypertension results from chronic organized thromboemboli or a primary vasculopathy. The former requires evaluation for surgical intervention, and the latter is treated with advanced medical therapies.

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The pulmonary vascular bed is normally a low-resistance, high-capacitance circuit capable of accommodating the entire cardiac output at pressures that are approximately 15%–20% of those found in the systemic circulation. In pulmonary hypertension (PH), elevated pulmonary arterial pressure places a burden on the normally thin-walled right ventricle as it works to maintain normal output. Without effective therapy, progressive right heart dysfunction leads to escalating symptoms and is often fatal. PH frequently results from common left-sided cardiac diseases or lung diseases. Less frequently, it is caused by a disease process intrinsic to the pulmonary vasculature itself. Differentiating among the several causes of PH requires methodical evaluation and is essential because management varies according to the underlying cause and misapplication of therapy can cause serious harm.

Diagnosis and Screening

What is PH, and what causes it?

Normal pulmonary arterial systolic pressure (PASP) ranges from 15–30 mm Hg, and normal diastolic pressure ranges from 4–12 mm Hg; mean values range from 9–18 mm Hg. According to the current definition, PH is present when the mean pulmonary arterial pressure (mPAP) is 25 mm Hg or higher. It is currently classified by the World Health Organization (WHO) into 5 categories of disease (see the Box: Causes of Pulmonary Hypertension), each differing in the mechanism responsible for the elevated pulmonary arterial pressure, the natural history, and the approach to treatment. Pulmonary arterial hypertension (PAH) (WHO group 1) has a unique hemodynamic definition that identifies patients with pulmonary vascular pathology in the precapillary pulmonary arterioles. To meet the hemodynamic definition of PAH, the mPAP must be 25 mm Hg or higher and the pulmonary capillary wedge pressure (PCWP) must be 15 mm Hg or lower. A newer definition with a lower mPAP of 20 mm Hg has also been proposed. To meet criteria for PAH, patients with an mPAP between 21 and 24 mm Hg must also have a PCWP of 15 mm Hg or lower and a pulmonary vascular resistance (PVR) greater than 3 Wood units (1). This new hemodynamic definition was developed in an effort to diagnose patients earlier in their disease course. This is of particular interest for patients at higher risk for PAH, such as those with an underlying connective tissue disease (for example, progressive systemic sclerosis [scleroderma]).

Causes of Pulmonary Hypertension*

Pulmonary arterial hypertension (WHO group I)
Pulmonary hypertension due to left heart disease (pulmonary venous hypertension) (WHO group II)
Pulmonary hypertension due to chronic lung diseases and/or hypoxia (WHO group III)
Pulmonary hypertension due to embolic disease (e.g., chronic thromboembolic pulmonary hypertension, tumor embolism) (WHO group IV)
Miscellaneous causes (e.g., sarcoidosis, lymphatic obstruction) (WHO group V)

** Adapted from the current WHO classification. Note that pulmonary arterial hypertension requires catheterization-confirmed pulmonary hypertension and exclusion of all other forms of pulmonary hypertension listed. WHO = World Health Organization.*

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The most common cause of PH is left heart disease that results in left atrial hypertension and chronically elevated pulmonary venous pressures. Common causes of left heart disease that lead to elevated pulmonary venous pressures include left ventricular systolic or diastolic dysfunction and mitral or aortic valvular diseases. PVR may become modestly elevated with long-standing pulmonary venous hypertension. It is important to note that these left heart processes may become more pronounced and more symptomatic with exertion and/or increased heart rate.

Chronic hypoxemic lung disease may involve destruction of lung parenchyma, entrapment of pulmonary vasculature, and hypoxemic pulmonary vasoconstriction and may lead to PH in some patients. The most common example is chronic obstructive pulmonary disease (COPD). Fibrotic lung diseases, such as idiopathic pulmonary fibrosis or diffuse parenchymal lung diseases due to collagen vascular disorders (for example, scleroderma or systemic lupus erythematosus), also cause PH. Obstructive sleep apnea is also included in this category and can cause PH that typically is milder than what is observed in WHO group I PAH. Although the PH seen in these disorders is often mild, more profound disease does occur, and a sufficiently reliable method of determining the extent to which patients have PH in excess of the severity of hypoxemic lung disease is unavailable. The presence of PH in most chronic lung diseases portends a worse outcome. Whether the PH is causative or simply an indicator of the severity of parenchymal lung disease is unclear.

Chronic thromboembolic PH develops in up to 4% of patients after pulmonary embolism (2). Venous thromboembolic events may go unrecognized until progressive symptoms lead to recognition of PH and an evaluation of its cause.

In the absence of left-sided heart disease, chronic hypoxemic lung disease, or chronic thromboembolic disease, PH may be due to an intrinsic pulmonary vasculopathy termed "pulmonary arterial hypertension." This involves progressive intimal, medial, and adventitial vascular derangements that increase PVR. It may be caused by genetic abnormalities or seen in association with known risk factors, including collagen vascular disease (for example, systemic sclerosis); HIV infection; liver disease; congenital heart disease with left-to-right shunt; or a history of use of stimulant drugs, such as anorectic agents or methamphetamines. In the absence of an identifiable risk, PAH is termed "idiopathic."

Who should be screened?

Although prospective studies have not shown improved outcomes with screening, expert consensus recommendations include screening for PH in patients with scleroderma spectrum disorders. Patients with scleroderma disorder and a corrected D_{LCO} less than 80% require annual screening for PAH. For patients who carry mutations for a heritable form of PAH, annual screening echocardiography is recommended. Unfortunately, routine genetic counseling and genetic testing are less widely available in the United States than in other parts of the world. Screening for PH is necessary in patients with portal hypertension being considered for organ transplantation because perioperative mortality is increased with elevations in mPAP and effective therapy may be required before transplantation can be safely pursued.

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What are the symptoms?

Progressive dyspnea is the most common symptom of PH. It is the initial symptom in more than half of patients with PH and ultimately occurs in approximately 85% (3). Because exertional dyspnea is a common symptom and PH is relatively uncommon, a high index of suspicion is needed to identify patients with the condition. Even as awareness of the disease has increased, delay from symptom onset to diagnosis is still considerable, with 20% of patients reporting symptoms for more than 2 years before a diagnosis of PAH is made.

Other symptoms include fatigue (26%), chest pain (22%), presyncope or syncope (17%), lower-extremity edema (20%), and palpitations (12%) (3, 4). Ortner syndrome is a rare symptom that involves hoarseness from compression of the left laryngeal nerve by an enlarged pulmonary artery.

What are the physical examination findings?

Physical examination findings may be unremarkable in early PH. As the condition progresses, right heart strain and ultimately right heart failure will develop. Cardiac examination may be notable for elevated jugular venous pressure, a right ventricular parasternal heave or subxiphoid thrust, a loud P2, a right-sided S3 or S4, and a holosystolic tricuspid regurgitant murmur heard best at the lower left sternal border. In contrast to mitral regurgitation, the murmur of tricuspid regurgitation becomes louder after inspiration due to increased venous return to the right heart (Carvallo sign). With development of right heart failure, patients may manifest peripheral edema and/or ascites. Hepatomegaly due to hepatic congestion is common, and when there is significant tricuspid regurgitation, a pulsatile liver may be palpated.

Some physical findings suggest underlying conditions responsible for PH, such as pulmonary edema; rales; wheezing; or other signs of left-sided heart failure, interstitial lung disease, or significant obstructive lung disease (the most common causes of PH). Signs suggestive of liver disease (such as palmar erythema, jaundice, or caput medusa), collagen vascular disease (such as sclerodactyly, telangiectasias, or other rashes), or HIV infection might indicate a cause of PAH. The presence of these findings is helpful in directing testing toward specific causes of elevated pulmonary pressures, although none are sufficiently sensitive to allow exclusion of a diagnosis.

What is the role of echocardiography in patients with suspected PH?

Echocardiography is one of the best tests to evaluate for possible PH. Indeed, PH is often first recognized as a potential diagnostic possibility when noted on an echocardiogram ordered for evaluation of dyspnea or a cardiac murmur. PASP can be estimated via echocardiography by adding an estimated right ventricular pressure calculated from tricuspid valve regurgitant flow velocity to an estimate of central venous pressure that is often generated from the appearance of the inferior vena cava. A close approximation of PASP is possible in most patients but is limited when an accurate tricuspid regurgitation envelope cannot be obtained. Right atrial or ventricular enlargement, hypertrophy, or decreased right ventricular function is more important than the actual estimated PASP because these findings usually indicate more severe disease regardless of the cause. Severe elevations in right ventricular pressure may cause leftward deviation of the interventricular septum ("D sign") (**Figure 1**).

Of note, echocardiography may also provide information that suggests the cause of PH and the patient's symptoms (which may not be due to the PH itself). The presence of pulmonary venous hypertension causing elevations in PASP may be suggested by left atrial enlargement, left-sided valvular heart disorders (such as mitral or aortic regurgitation or stenosis), or left ventricular systolic or diastolic dysfunction. Regional wall motion abnormalities or ventricular dilatation may suggest ischemic heart disease or other cardiomyopathies. Atrial or ventricular septal defects may suggest the presence of congenital heart disease and may require administration of agitated saline (and an echocardiographic "bubble" study) to identify.

Although estimation of PASP by echocardiography is useful when evaluating for PH, it is inadequate to precisely assess disease severity or to gauge the response to therapy. When specific treatment of certain types of PH is being considered, right heart catheterization is mandatory. The echocardiogram alone cannot definitively diagnose PAH.

What other tests should be ordered in the evaluation of PH?

Some tests are required to establish or exclude potential causes of PH. Ventilation–perfusion scanning should be done to rule out chronic thromboembolic disease, even when there is no known history of pulmonary embolism, because such disease is frequently unrecognized. Computed tomography pulmonary angiography is not considered sufficiently sensitive to exclude this important and potentially reversible cause of PH. Chest computed tomography may be useful when there is suspicion for diffuse parenchymal lung disease because of clinical, pulmonary function, or chest radiographic findings. A sleep study

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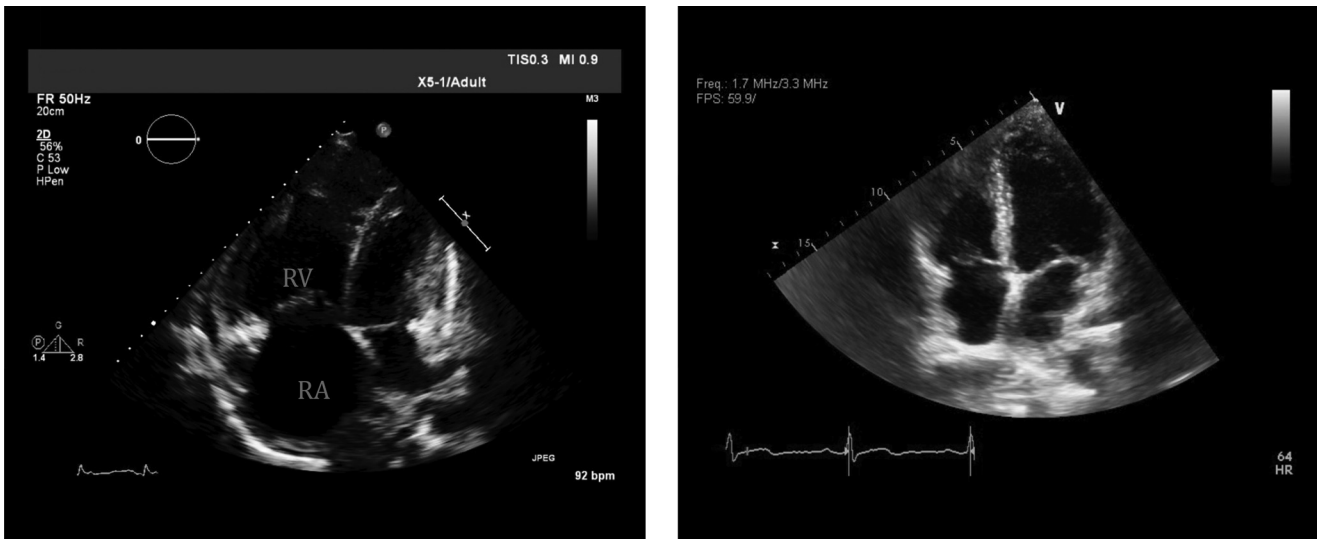
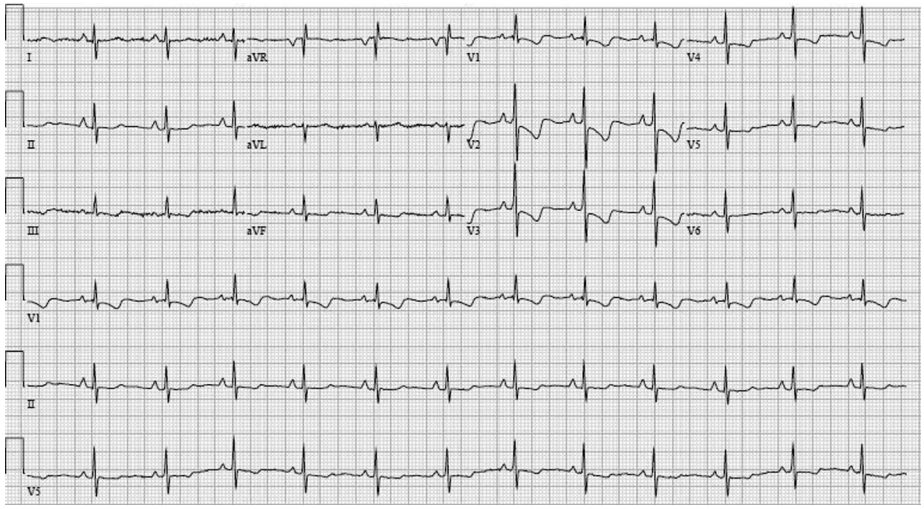
Figure 1. **Apical 4-chamber views of echocardiograms from a patient with idiopathic pulmonary arterial hypertension (*left*) and a healthy person (*right*).**



Dilatation of both the RA and RV in the patient with idiopathic pulmonary arterial hypertension is recognized when compared with the image from the healthy person. Other echocardiographic findings in patients with pulmonary hypertension can include RV hypokinesis, septal flattening or bowing toward the left ventricle, tricuspid regurgitation, pulmonary insufficiency, and midsystolic closure of the pulmonary valve. RA = right atrium; RV = right ventricle.

Figure 2. **Electrocardiogram of a 31-year-old woman presenting with dyspnea.**



The electrocardiogram shows right axis deviation, right atrial enlargement, and right ventricular hypertrophy with repolarization abnormality, suggesting pulmonary hypertension.

should be considered if there is any possibility of sleep apnea.

Additional testing is performed to help determine the specific cause or association of PAH and assess disease severity (see the Box: Evaluation of Pulmonary Hypertension). The electrocardiogram of a patient with PH may reveal right axis deviation, right atrial enlargement, or right ventricular hypertrophy (**Figure 2**). The chest radiograph may reveal enlargement of the right ventricle and pulmonary arteries (**Figure 3**).

Other tests are useful in assessing disease severity and in helping to guide the choice of therapy and response. Oxyhemoglobin saturation should be measured at rest

Evaluation of Pulmonary Hypertension

Autoantibody testing for collagen vascular disease
B-type natriuretic peptide or *N*-terminal pro–B-type natriuretic peptide measurement
Chest radiography
Complete blood count
Echocardiography
Electrocardiography
Electrolytes/creatinine measurement
HIV serologic testing
Liver function testing (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin)
Oxyhemoglobin saturation at rest and with exertion
Polysomnography
Pulmonary function testing (spirometry, lung volumes, diffusing capacity)
Radionuclide ventilation–perfusion imaging
Right heart catheterization
Six-minute walking distance

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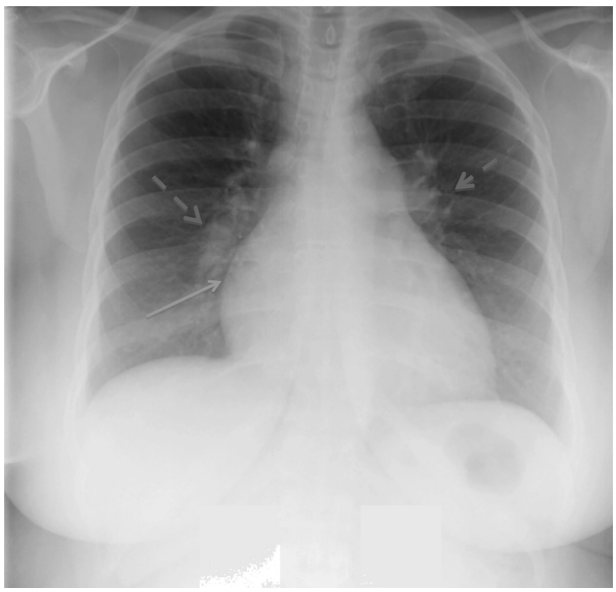
and with exertion. B-type natriuretic peptide (BNP) has been shown to correlate with disease severity in certain types of PH, specifically with PAH or with PH due to systolic left heart failure. Levels of BNP above 150 pg/mL in patients with PAH at the time of initial diagnosis correlate with worse outcomes, as do persistent BNP levels above 180 pg/mL after treatment is initiated (5). Elevated levels of *N*-terminal pro–BNP (NT-proBNP) above 1400 pg/mL have also been shown to correlate with worse prognosis (6, 7). Levels of BNP and NT-proBNP may be elevated in the setting of pulmonary arterial or pulmonary venous hypertension due to left heart disease and cannot be used to distinguish between the two. A 6-minute walking test provides an assessment of the functional impact of PH and correlates with prognosis. Serial testing may be useful in assessing response to therapy.

Which patients require cardiac catheterization?

Right heart catheterization is mandatory to establish the diagnosis of PAH and must be performed before initiation of any advanced medical therapies directed specifically toward the pulmonary vasculature. It also can help to identify previously unrecognized left heart dysfunction and pulmonary venous hypertension. Even when PH is related to left heart disease, right heart catheterization should be considered to confirm the diagnosis and severity of PH because this may affect treatment options regarding valvular heart disease and candidacy for heart transplantation. Similarly, knowing the hemodynamics in PH associated with chronic lung disease will influence decisions about open lung biopsy, treatment options, and the timing of consideration of lung transplantation. Right heart catheterization is a safe procedure in patients with PH; complication rates are only 1.1% and most frequently relate to venous access,

Figure 3. **Posteroanterior chest radiograph in a patient with idiopathic pulmonary arterial hypertension.**



The central pulmonary arteries are enlarged (*top arrows*), and the laterally shifted right heart contour (*bottom left arrow*) suggests right atrial and right ventricular enlargement.

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arrhythmia, and hypotension from vagal episodes. Overall procedure-related mortality is rare and is reported in 0.05% of cases (8).

How should right heart catheterization be done when PH is a consideration?

During right heart catheterization, presence of left-to-right shunts should be assessed via measurement of oxygen saturation in the central veins, right atrium, right ventricle, and pulmonary artery. An increase ("step-up") in oxyhemoglobin saturation at any of these levels suggests that a left-to-right shunt is present and oxygenated blood is being shunted into the right-sided circulation. If a step-up is detected, cardiac imaging is indicated to identify and quantify a congenital abnormality. Hemodynamics are assessed with particular attention to accurate measurement of pulmonary artery occlusion ("wedge") pressure. To eliminate the effect of respiration on pressure, all measurements, including PCWP, should be done at the end of exhalation and with equipment leveled at the midthoracic line. If accuracy is in doubt, left ventricular end-diastolic pressure should be measured simultaneously (9). Cardiac output measured using the estimated Fick method is generally reliable in this setting.

In addition to accurate measurement of hemodynamics, right heart catheterization allows for pulmonary vasoreactivity testing when the presence of PAH has been established (see the **Box**: Diagnosis of Pulmonary Arterial Hypertension). During the procedure, a short-acting pulmonary vasodilator, such as inhaled nitric oxide or intravenous adenosine, is used to identify a small subgroup of patients who may safely undergo a trial of calcium-channel antagonist therapy. The current criterion for vasoreactivity is a decrease in mPAP of more than 10 mm Hg to an absolute value less than 40 mm Hg without reduction in cardiac output (1).

When should a clinician consider consultation with a specialist in diagnosing PH?

Much of the assessment of PH focuses on correctly determining whether a patient has PAH, which may be amenable to pharmacotherapy. Recognition of when PH is caused by heart or lung disease is essential because treatment is focused on the underlying condition rather than the pulmonary vasculature per se.

PAH is a rare condition and is thus best treated with the assistance of a center with sufficient expertise. Patients should be referred to a specialized center if there is uncertainty about the diagnosis, if they have multiple comorbid conditions that may complicate diagnosis and/or treatment, or if they have high-risk features or New York Heart Association (NYHA) functional class III or IV heart failure. Benefits of referral to a specialized center include availability of advanced therapies;

Diagnosis of Pulmonary Arterial Hypertension

- Presence of pulmonary hypertension (mean pulmonary arterial pressure >25 mm Hg)
- Absence of pulmonary venous hypertension (left atrial or pulmonary artery occlusion ["wedge"] pressure <15 mm Hg)
- Elevated pulmonary vascular resistance (>3 Wood units)
- Exclusion of significant chronic hypoxemic lung disease (e.g., severe chronic obstructive pulmonary disease) or chronic thromboembolic disease

opportunities for patients to participate in clinical trials; and, when appropriate, evaluation for lung transplantation.

Diagnosis and Screening... PH is caused by disorders that result in elevated pulmonary pressures. Physical examination and diagnostic testing are targeted at confirming the presence of elevated pulmonary pressures and identifying a cause. Echocardiography is important to evaluate possible PH. Most PH detected by echocardiography is caused by chronic left-sided cardiac abnormalities (both ventricular and valvular) or chronic pulmonary disease (such as COPD). Echocardiography, chest radiography, ventilation–perfusion scanning, and pulmonary function and blood testing are required to evaluate potential causes. Other tests, such as sleep studies, may also be appropriate. Measurement of oxyhemoglobin saturation, 6-minute walking distance, and blood BNP level help to assess disease severity. Right heart catheterization is mandatory to establish the diagnosis of PAH and to help guide therapy directed toward the pulmonary vasculature. Echocardiographic screening for PH is recommended in patients with a concerning family history or scleroderma or for evaluation for possible liver transplantation.

CLINICAL BOTTOM LINE

Treatment

What is the approach to treatment?

Appropriate treatment relies on identification of the cause of PH, and for patients with chronic cardiac or pulmonary disease, therapy is largely focused on treating the underlying condition. This usually leads to an improvement in symptoms and pulmonary hemodynamics.

Oxygen therapy should be prescribed at flow rates sufficient to maintain an oxygen saturation of 90% or higher at rest, with exertion, and during sleep (10). In patients with advanced Eisenmenger physiology in whom there is a significant right-to-left shunt, supplemental oxygen has not been shown to be beneficial.

Regardless of its cause, when PH results in right heart dysfunction, appropriate use of diuretics is essential. Although few data regarding the optimum regimen exist, diuretic therapy (coupled with salt restriction and close weight surveillance) is essential to minimize fluid overload and consequent dyspnea in patients with symptoms of right heart dysfunction.

How should patients with PH due to left heart disease be treated?

PH associated with left heart disease is the most common form encountered in clinical practice. Recent guidelines have recommended a more nuanced approach in this group of patients, recognizing that there are some in whom chronically elevated pulmonary venous pressures result in a vasculopathy within the precapillary vessels.

Hemodynamic definitions of this group now break down into isolated postcapillary PH (mPAP >20 mm Hg, PCWP >15 mm Hg, and PVR <3 Wood units) and combined precapillary and postcapillary PH (mPAP >20 mm Hg, PCWP >15 mm Hg, and PVR ≥3 Wood units) (11). Although these newer definitions have been implemented, there is still no evidence to support use of PH-targeted therapies in patients with either of

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these profiles if they result from left heart disease.

Thus, the presence of PH in left heart disease should still be viewed as a consequence of left heart disease, and treatment should be directed toward this rather than toward directly attempting to reduce pulmonary arterial pressure. Prostacyclin analogues, endothelin-receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, and soluble guanylate cyclase (SGC) stimulators have been studied in the treatment of left heart failure and/or PH with left heart disease, with disappointing results (12–14).

PH secondary to left-sided valvular heart disease, particularly mitral stenosis, has been well studied. After correction of the mitral valve disease, pulmonary arterial pressure often returns toward normal. The response can occur immediately or can take up to 6 months to manifest (15).

How should patients with PH due to lung disease be treated?

The only proven effective therapy for PH associated with COPD is supplemental oxygen (16). Treatment should be directed at optimizing treatment of underlying sleep apnea, COPD, or lung disease; utilizing supplemental oxygen to avoid periods of hypoxia; and enrollment in pulmonary rehabilitation as appropriate (17). Sleep apnea should be aggressively treated to minimize nocturnal desaturation and its promotion of PH via hypoxic vasoconstriction.

The use of PAH therapy in PH secondary to lung disease is not currently recommended (18). Clinical trials have shown no benefit of pulmonary vasodilators in diffuse parenchymal lung disease and COPD, and these drugs can worsen ventilation–perfusion matching and result in more severe hypoxia (19, 20). Trials of the endothelin-receptor antagonist ambrisentan and the SGC stimulator riociguat in patients with idiopathic pulmonary fibrosis were terminated early due to lack of benefit and potential for harm (21). A clinical trial of inhaled treprostinil in patients with PH and diffuse parenchymal lung disease is under way and may influence the clinical approach to such patients.

How should patients with chronic thromboembolic PH be treated?

Chronic thromboembolic PH (CTEPH) is distinct from other forms of PH because a surgical procedure, pulmonary thromboendarterectomy (PTE), is the treatment of choice and may be curative (22). For patients with CTEPH who are not candidates for PTE or for those with residual PH after PTE, treatment with balloon pulmonary angioplasty (BPA) at an experienced center may be recommended. BPA is a percutaneous procedure that uses angioplasty techniques to disrupt organized thromboemboli in order to restore pulmonary blood flow in chronically obstructed territories. If a diagnosis of CTEPH is suspected, patients should receive effective anticoagulation and be referred for evaluation at an expert center. Initiation of medical therapy directed at the PH should not delay evaluation at an expert center for mechanical treatment with PTE or BPA. Most patients with surgically accessible disease will have sustained improvement in symptoms after successful PTE, and at experienced centers, surgical mortality is less than 5% (23, 24). For patients with residual PH after PTE or patients who are not candidates for surgery, the SGC stimulator riociguat has demonstrated improvement in hemodynamic end points and functional outcomes, such as 6-minute walking

distance, that are maintained to at least 1 year (25, 26).

What drugs are available for treatment of PAH?

Therapy for PAH is generally divided into "background" therapy and PAH-specific drugs. Background therapy includes use of diuretics and supplemental oxygen as described previously.

Use of calcium-channel antagonists in PAH should be limited to patients who have a positive response to vasoreactivity testing at the time of right heart catheterization. Although only a small number (estimated to be <10%) experience benefit, those who do frequently have sustained response for years and an excellent prognosis. These drugs should not be used unless vasoreactivity at right heart catheterization is clearly demonstrated because hemodynamic instability, worsened symptoms, or death may occur if the drugs are prescribed empirically.

Warfarin has been evaluated in observational studies of idiopathic, heritable, and anorexigen-associated PAH and has been associated with improved outcomes. However, recognizing the lack of firmly established benefit and the potential for harm, expert organizations indicate that warfarin can be considered in patients with these 3 forms of PAH. There is no established consensus on the target international normalized ratio. Benefits of warfarin use for other causes of PH are less clear, and it is generally not used in this setting. There are no data on use of newer anticoagulants in lieu of warfarin in PAH.

Currently approved PAH therapies target 3 molecular pathways implicated in disease pathogenesis (**Table 1**). The choice of agent and the decision to use combinations of advanced PAH therapies

Table 1. **Advanced Therapies for Pulmonary Arterial Hypertension**

Therapy	*Examples and Doses*	*Mechanism of Action*	*Comments/Common Adverse Effects*
Prostacyclins and prostacyclin-receptor agonists	Epoprostenol: Initiated at 2 ng/kg/min intravenously and titrated to symptoms, hemodynamic response, and exercise capacity Iloprost: 2.5–5 mcg inhaled 6–9 times daily Treprostinil: Multiple delivery methods available (continuous intravenous or subcutaneous infusion; intermittent inhaled and oral formulations) Selexipag: Start 200 mcg twice daily orally and increase weekly to maximum tolerated dose or maximum dose of 1600 mcg twice daily	Stimulate intracellular production of cAMP	Headache, flushing, hypotension, masticatory jaw pain, nausea, diarrhea, anorexia, rash, arthralgia Risk for central venous catheter–related infection with intravenous infusion Risk for cellulitis and pain with subcutaneous infusion Cough may occur with inhaled therapy
Endothelin-receptor antagonists	Ambrisentan: 5–10 mg orally daily Bosentan: 62.5 mg orally twice daily for 4 wk, then 125 mg orally twice daily if liver function test results are normal Macitentan: 10 mg orally daily	Block endothelin-1 receptors on vascular smooth muscle	Hepatotoxicity, worsened fluid retention, headache, anemia Contraindicated in pregnancy (FDA category X)
Nitric oxide pathway agents			
PDE5 inhibitors	Sildenafil: 20 mg orally 3 times daily Tadalafil: 40 mg orally once daily	Inhibit breakdown of cGMP in vascular smooth muscle	Headache, flushing, dyspepsia, epistaxis, hypotension (if used concomitantly with nitrates) Sildenafil has been titrated up to 80 mg 3 times daily in clinical trials
SGC stimulator	Riociguat: Start 0.5–1 mg 3 times daily and increase by 0.5 mg every 2 wk until maximum tolerated dose or dose of 2.5 mg 3 times daily is reached	Stimulates cGMP	Hypotension, dyspepsia Contraindicated in pregnancy (FDA category X)

cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; FDA = U.S. Food and Drug Administration; PDE5 = phosphodiesterase type 5; SGC = soluble guanylate cyclase.

Table 2. **Assessment of Risk in Pulmonary Arterial Hypertension***

Determinants of Prognosis (Estimated 1-Year Mortality)	*Low Risk (<5%)*	*Intermediate Risk (5%–10%)*	*High Risk (>10%)*
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO functional class	I, II	III	IV
6-minute walking distance	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak V_{O_2} >15 mL/min/kg (>65% of predicted) V_E/V_{CO_2} slope <36	Peak V_{O_2} 11–15 mL/min/kg (35%–65% of predicted) V_E/V_{CO_2} slope 36–44.9	Peak V_{O_2} <11 mL/min/kg (<35% of predicted) V_E/V_{CO_2} slope >45
Plasma NT-proBNP levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area <18–26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 SV_{O_2} >65%	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 SV_{O_2} 60%–65%	RAP >14 mm Hg CI ≤2.0 L/min/m^2 SV_{O_2} <60%

BNP = B-type natriuretic peptide; CI = cardiac index; CMR = cardiovascular magnetic resonance; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RA = right atrium; RAP = right atrial pressure; SV_{O_2} = mixed venous oxygen saturation; V_{CO_2} = volume of exhaled carbon dioxide; V_E = volume of expired air; V_{O_2} = oxygen consumption; WHO = World Health Organization.
** Adapted with permission of Oxford University Press from Galiè N, Humbert M, Vachiery JL, et al; ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119.*

are driven largely by the severity of illness and risk (27).

The severity of illness is determined by integrating clinical variables (such as functional status and 6-minute walking distance) with laboratory indicators of heart failure (NT-proBNP level, high-risk features on echocardiogram [pericardial effusion], hemodynamic evidence of right heart failure [elevated right atrial pressure and reduced cardiac index], or indicators of right heart impairment [such as enlargement or dysfunction on echocardiogram or measured hemodynamic values]) (**Table 2**). Many risk assessment tools have been developed, each incorporating different variables (some fixed and some modifiable) and scoring systems. Although these models are most powerful at predicting outcomes when used at the time of initial diagnosis, there is growing evidence that they can predict survival on subsequent follow-up as well.

Current guidelines support the use of initial monotherapy in patients who are in the low-risk category. However, for most patients with newly diagnosed PAH, initial combination therapy is recommended (27, 28). Follow-up must be performed to assess clinical response to therapy. If patients remain at intermediate or high risk after 3–6 months, therapy should be escalated until they achieve low-risk status. All patients with NYHA functional class III or greater should be considered for parenteral prostacyclin therapy, especially those who remain at high risk despite other PAH-targeted therapies.

Prostacyclins and prostacyclin-receptor agonists

Prostacyclins have potent vasodilatory, antiplatelet, and antiproliferative properties, and their synthesis is reduced in patients with PAH. Drugs stimulating the prostacyclin pathway for PAH are available in the United States as continuous intravenous or subcutaneous infusions, inhaled therapy, and oral agents.

Intravenous epoprostenol was the first drug approved for treatment of PAH after a landmark 1996 study showed improved survival (29), and it is generally viewed as the most potent therapy for PAH. Additional studies have shown improvements in symptoms, exercise capacity, and hemodynamics. Epoprostenol has a short half-life (3-5 minutes) and must be administered by continuous intravenous infusion, ideally through a tunneled catheter. Treprostinil is an analogue of epoprostenol that has a longer half-life (about 4.5 hours) and is delivered by continuous intravenous or subcutaneous infusion (30).

Both intravenous and subcutaneous infusion therapy require that patients and families be capable of reconstituting medication in a sterile manner, maintaining clean catheter sites, and making frequent adjustments in therapy. A required central venous catheter poses a risk for infection. Adverse effects of subcutaneous therapy include cellulitis and infusion site pain (31). Because of the complexities of this therapy, use should be reserved for highly experienced centers.

The inhaled prostacyclin analogues iloprost and treprostinil require repeated administrations through specialized nebulizer devices while the patient is awake (32, 33). Adverse effects include flushing, headache, diarrhea, leg pain, and jaw pain. Cough may occur with inhaled therapy.

Selexipag is an oral prostacyclin-receptor agonist that was found to reduce risk for a composite morbidity and mortality end point by 40% in the largest randomized controlled trial in PAH to date (34). Despite these encouraging results, selexipag typically is used as add-on therapy with other oral PAH agents and should not be used as an alternative to parenteral prostacyclin in high-risk patients due to its relatively lower potency. Treprostinil is also now available as an oral agent to treat PAH (35).

Endothelin antagonists

Endothelin-1 is a potent endogenous vasoconstrictor and mitogen when present at high levels, and its receptors are overexpressed within the pulmonary vasculature of patients with PAH. The oral endothelin-receptor antagonists bosentan, ambrisentan, and macitentan have been found to improve exercise capacity, functional class, hemodynamics, and time to clinical worsening in randomized trials (36–42). All drugs in this class are teratogens, and women of childbearing age require effective contraception and monthly pregnancy tests. Hepatotoxicity can occur in patients receiving bosentan, so use of ambrisentan and macitentan, which are less hepatotoxic, is preferable. Monthly liver function testing is required with use of bosentan but not ambrisentan or macitentan. All drugs in this class can cause mild reductions in hemoglobin level of approximately 1 g/dL.

Nitric oxide pathway agents

The PDE5 inhibitors potentiate the vasodilatory effects of cyclic guanosine monophosphate by inhibiting its breakdown. The oral PDE5 inhibitors sildenafil and tadalafil improve exercise capacity and hemodynamics in patients with PAH (43–47). The current U.S. Food and Drug Administration–approved dose of sildenafil for PAH is 20 mg 3 times daily, although doses up to 80 mg 3 times daily have been used in clinical trials. Tadalafil is administered once daily at a dose of 40 mg.

Riociguat, an SGC stimulator, is also approved to treat patients with PAH (48, 49). Riociguat is a thrice-daily oral medication that requires effective contraception and monthly pregnancy testing for women of childbearing age because of its teratogenic effects. Because of adverse effects, patients should not receive PDE5 inhibitors and SGC stimulators concurrently, and adequate washout must be observed if patients transition between these agents.

Coadministration of nitrate medications with PDE5 inhibitors and SGC stimulators can cause severe systemic hypotension, and patients must be educated about this risk.

What is the role of lung transplantation?

Referral for lung transplantation evaluation in PAH is appropriate if patients do not improve after initiation of PH-targeted therapies. For patients with severe right ventricular failure or rapidly progressive disease, referral for lung transplantation should be considered earlier and should not be delayed while waiting for a response to PAH therapy. If a patient improves or stabilizes in response to aggressive medical therapy, transplantation may be deferred.

What is the role of exercise?

It is important to avoid and, to the extent possible, reverse the physical deconditioning that may occur in patients who become sedentary due to exercise limitations. PH is not a contraindication to judicious exercise, and patients should be encouraged to remain active within acceptable symptom limits. Mild breathlessness is acceptable, but patients should avoid exertion that leads to severe breathlessness, exertional dizziness, near syncope, or chest pain. Isometric exercises (straining against a fixed resistance) are discouraged because they can cause exertional syncope.

Patients with PH due to heart failure or advanced lung disease can participate in a structured rehabilitation program. Monitored exercise programs for patients with stable PAH have shown improvements in exercise capacity and quality of life and can serve as an important adjunct to medical therapy.

Treatment... The therapeutic approach to PH differs according to the underlying pathology, and misapplication of therapy appropriate to one form of PH in the care of a patient with another form can be harmful. Regardless of the cause, patients should be evaluated for the need for supplemental oxygen, and those with symptoms of right heart failure should be treated with diuretics and salt restriction. Therapy for patients with PH due to left heart disease or chronic hypoxemic lung disease involves aggressive treatment of those underlying disorders and not treatment of the PH per se. Patients with CTEPH require evaluation for PTE, BPA, or medical therapy at an experienced center as well as life-long anticoagulation. Patients with PAH should have right heart catheterization with vasodilator testing at an experienced center and should not be treated empirically with calcium-channel antagonists. Advanced therapies for PAH include prostacyclins, endothelin-receptor antagonists, PDE5 inhibitors, and an SGC stimulator. Exercise is important for all patients. Lung transplantation may be required for patients with advanced disease that does not respond to medical therapy.

CLINICAL BOTTOM LINE

Prognosis

What is the prognosis of PH?

PH is considered a negative prognostic sign in many conditions, including the most commonly associated ones, such as heart failure and COPD. In the case of heart failure, elevated pulmonary arterial pressure on right heart catheterization has been shown to be a powerful predictor of mortality, particularly in the setting of myocarditis or decreased right ventricular ejection fraction. Likewise, more severe PH suggests a poorer prognosis in patients with COPD. Treatment directed at PH has not been linked to improved outcomes in either of these conditions.

Historically, PAH has carried a dismal prognosis. The National Institutes of Health Registry on Pulmonary Hypertension enrolled 187 patients with idiopathic PAH starting in 1981 and reported a median survival of 2.8 years, with an estimated 1-year survival of 68% (4). Recent outcomes obtained during the current era of disease-specific therapeutics are significantly improved, but PAH remains a highly morbid disease. Based on data from 2716 patients enrolled in the multicenter observational REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) Registry, survival rates were 85%, 68%, 57%, and 49% at 1, 3, 5, and 7 years, respectively (50, 51).

Several scoring and risk assessment tools have been developed. These tools consistently indicate a worse prognosis in PAH with presence of more advanced NYHA functional class, shorter 6-minute walking distance, and persistently elevated BNP or NT-proBNP level. A poorer prognosis has also been noted in patients in whom PAH is associated with connective tissue disease or portal hypertension (portopulmonary hypertension) (52, 53). Several factors may contribute to the worse prognosis of patients with portopulmonary hypertension, including complications of concomitant liver disease and longer delays in instituting advanced therapies for PAH.

In the Clinic
Tool Kit

Pulmonary Hypertension

Patient Information

https://medlineplus.gov/pulmonaryhypertension.html
https://medlineplus.gov/spanish/pulmonaryhypertension.html
Information and handouts in English and Spanish from the National Institutes of Health's MedlinePlus.

www.nhlbi.nih.gov/health-topics/pulmonary-hypertension
Information from the National Heart, Lung, and Blood Institute.

www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/pulmonary-hypertension-high-blood-pressure-in-the-heart-to-lung-system
Information from the American Heart Association.

https://phassociation.org/patients
Information on living with pulmonary hypertension from the Pulmonary Hypertension Association.

Information for Health Professionals

https://erj.ersjournals.com/content/53/1/1801913
Hemodynamic definitions and updated clinical classification of pulmonary hypertension from the 2018 proceedings of the 6th World Symposium on Pulmonary Hypertension.

https://academic.oup.com/eurheartj/article/37/1/67/2887599
2015 guidelines for diagnosis and treatment of pulmonary hypertension from the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society.

WHAT YOU SHOULD KNOW ABOUT PULMONARY HYPERTENSION

What Is Pulmonary Hypertension?

Pulmonary hypertension (PH) is when you have high blood pressure in the arteries that carry blood to your lungs. This makes your heart work harder than usual, which can weaken it over time. PH is a progressive disease that requires ongoing management and does not currently have a cure.

What Causes It?

PH is usually caused by another medical condition. Heart disease, chronic obstructive pulmonary disease, pulmonary fibrosis, pulmonary embolism, lupus, and obstructive sleep apnea may lead to PH. More rarely, pulmonary arterial hypertension (PAH) can be genetic or can happen with no known cause.

What Are the Signs and Symptoms?

- Shortness of breath during routine activities (most common)
- Tiredness
- Chest pain
- Fainting or feeling lightheaded
- Leg or ankle swelling
- Racing heartbeat

The average patient has symptoms for 2 years before a diagnosis of PH is made. Younger patients with unexplained, progressive shortness of breath should be evaluated for PH.

How Is It Diagnosed?

- Your doctor will ask about your symptoms, other medical conditions, and family history. He or she will conduct a physical examination to look for signs of PH and run tests to determine the cause and severity of disease.
- Tests, like an echocardiogram, will estimate the pressure in your pulmonary arteries and evaluate your heart function. Pulmonary function testing measures how your lungs are working. Other tests could include chest x-rays, lung scans, blood tests, and a sleep study if sleep apnea is suspected.
- If tests show you might have PH, you may need cardiac catheterization to confirm the diagnosis and help guide treatment. This procedure directly measures the pressure in your heart and pulmonary arteries and shows how your heart is pumping blood to the rest of your body.

- If you are diagnosed with PH, you may be asked to do a walking test so your doctor can see how severe your disease is by monitoring your oxygen level and heart during exercise.

How Is It Treated?

- Treatment depends on the cause and is generally focused on aggressively treating the underlying medical condition.
- If you have PH, you will benefit from mild to moderate exercise and should be evaluated to see if you need supplemental oxygen. You should consult your physician about the best type of exercise program for you.
- Treatment may include diuretics, anticoagulants, vasodilators, and more advanced therapies. If you have advanced PH that does not respond to treatment, a lung transplant may be recommended.
- The goal is to reduce symptoms and address diseases or conditions that worsen PH.
- PH has no cure, but early treatment may slow disease progression and control symptoms.

Questions for My Doctor

- What is the cause of my PH?
- What changes can I make in my life to help improve my symptoms?
- Do I need to take medicine?
- Do I need oxygen therapy?
- What are the risks or side effects of treatment?
- Can I keep doing the things I like to do?
- What types of exercise are best for me?
- How often should I have follow-up visits?
- Will I need to see any other doctors?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

MedlinePlus
https://medlineplus.gov/pulmonaryhypertension.html

Pulmonary Hypertension Association
https://phassociation.org/patients/aboutph

Patient Information