In the Clinic

Pulmonary Hypertension

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CME Objective: To review current evidence for the diagnosis and screening, treatment, prognosis, and practice improvement of pulmonary hypertension.

The information contained herein should never be used as a substitute for clinical judgment.

Annals of Internal Medicine

The pulmonary vascular bed is normally a low-resistance, high-capacitance circuit capable of accommodating the entire cardiac output at pressures approximately 15%–20% of those 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 blood flow. Without effective therapy, right heart dysfunction leads to progressive symptoms and is often fatal. Pulmonary hypertension is frequently a result of common left-sided heart or lung diseases. Less frequently, it results from a disease process intrinsic to the pulmonary vasculature itself. Differentiating among the several causes of PH requires methodical evaluation. Differentiation is essential because management varies according to the underlying cause, and misapplication of therapy can cause serious harm.

Diagnosis and Screening

What is pulmonary hypertension and what causes it?

Normal pulmonary arterial systolic pressure (PASP) ranges from 15–30 mm Hg and diastolic pressure from 4–12 mm Hg; mean values range from 9–18 mm Hg. By current definition, "pulmonary hypertension" is present when the mean pulmonary arterial pressure is > 25 mm Hg. It is currently classified by the World Health Organization (WHO) into 5 categories of disease (see the Box: Causes of Pulmonary Hypertension), each of which has a different mechanism responsible for the elevated pulmonary arterial pressure, a different natural history, and a different approach to treatment.

The most common cause of PH is left heart disease, including left-sided systolic dysfunction of various causes (e.g., ischemic and other cardiomyopathies). An important and frequently underappreciated cause of PH is left-sided heart failure with a preserved ejection fraction (with or without diastolic dysfunction). Mitral or aortic valve disease (stenosis or regurgitation) may also cause PH. In each case, it is the result of pulmonary venous hypertension, which manifests as either elevated left ventricular end-diastolic pressure or pulmonary artery occlusion ("wedge") pressure. Although usually normal in this setting, pulmonary vascular resistance may become modestly elevated with long-standing pulmonary venous hypertension. It is important to appreciate 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 such disease is chronic obstructive pulmonary disease (COPD). Fibrotic lung diseases, such as idiopathic pulmonary fibrosis and sarcoidosis, or interstitial lung diseases due to collagen vascular disorders, such as scleroderma or systemic lupus erythematosis, also cause PH. Obstructive sleep apnea also causes PH and is included in this category. 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 PH may be attributed to the severity of hypoxemic lung disease is unavailable.

Chronic thromboembolic PH develops in up to 4% of patients after pulmonary embolism (1). Venous thromboembolic events may go unrecognized until progressive symptoms lead to recognition of PH and an evaluation of its cause.

Causes of Pulmonary Hypertension*

I. Pulmonary arterial hypertension
- Heritable/genetic abnormalities
- Idiopathic pulmonary arterial hypertension
- Associated with known risk factors (e.g., collagen vascular diseases, anorectic agent use, HIV infection, liver disease)

II. Pulmonary hypertension due to left heart disease (pulmonary venous hypertension)
- Systolic or diastolic left heart dysfunction
- Mitral or aortic valve disorders

III. Pulmonary hypertension due to chronic hypoxemic lung disease
- Obstructive lung disorders (e.g., chronic obstructive pulmonary disease)
- Interstitial lung disease (e.g., idiopathic pulmonary fibrosis, interstitial lung disease due to collagen vascular disorders)
- Sleep-disordered breathing (e.g., obstructive sleep apnea)

IV. Pulmonary hypertension due to embolic disease (e.g., chronic thromboembolic pulmonary hypertension, tumor embolism)

V. Miscellaneous causes of pulmonary hypertension (e.g., sarcoidosis, lymphatic obstruction)

*Adapted from current World Health Organization classification, which divides pulmonary hypertension into groups I–V as noted above. Note that pulmonary arterial hypertension requires catheterization-confirmed pulmonary hypertension together with exclusion of all other forms of pulmonary hypertension listed.

In the absence of left-sided heart, chronic hypoxemic lung, or chronic thomboembolic diseases, PH may be due to an intrinsic pulmonary vasculopathy termed "pulmonary arterial hypertension" (PAH). This type of hypertension involves progressive intimal, medial, and adventitial vascular derangements that increase pulmonary vascular resistance. It may be caused by genetic abnormalities or seen in association with known risk factors, including collagen vascular disease (e.g., scleroderma), HIV infection, liver disease with portal hypertension, or a history of anorectic drug use. In the absence of an identifiable risk, PAH is termed idiopathic.

The terms "primary" and "secondary" PH are historical; their use is now discouraged because they suggest clinically inappropriate groupings of disorders and may thus promote inadequate therapeutic decision making.

Who should be screened?

Although prospective studies have not demonstrated improved outcomes with screening, expert consensus recommendations include screening for PH in patients with systemic sclerosis or a family history of a heritable form of PAH. The optimum screening interval in this setting has not been adequately studied, although annual screening has been recommended (2). Screening for PH is necessary in patients with portal hypertension being considered for organ transplantation because perioperative mortality is increased with elevations in mean PA pressure and effective therapy may be required before transplantation can be safely pursued.

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, particularly those who present at a younger age and patients diagnosed with concurrent asthma. Even as awareness of the disease has increased, delay from symptom onset to diagnosisis is still considerable, with 20% of patients reporting symptoms for > 2 years before a diagnosis of PAH is made (3).

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

What are the physical examination findings?

The physical examination may be surprisingly unremarkable in early PH. As the condition progresses, the findings of 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 the 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 pulmonary hypertension, such

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as pleural effusion; 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 (e.g., palmar erythema, jaundice, caput medusa), collagen vascular disease (e.g., sclerodactyly, telangiectasias, or other rashes), or HIV infection might point toward 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 patients with suspected pulmonary hypertension?

The echocardiogram is one of the best tests to evaluate for possible PH. Indeed, PH is often first recognized as a potential diagnostic issue when noted on an echocardiogram ordered for evaluation of dyspnea or a cardiac murmur. PASP can be estimated with use of 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 septalum ("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 (e.g., mitral or aortic regurgitation or stenosis), or

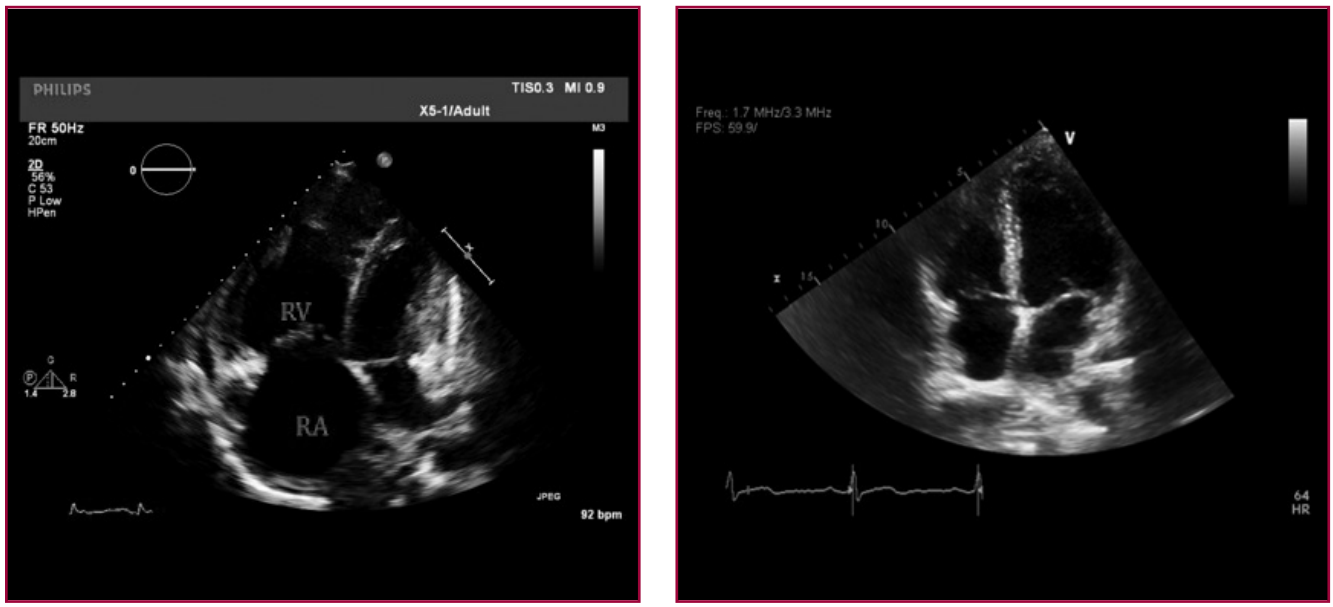

Figure 1. Apical 4-chamber view of an echocardiogram from a patient with idiopathic pulmonary arterial hypertension (*left panel*). Dilatation of both the right atrium (*RA*) and right ventricle (*RV*) is appreciated when compared with an apical four chamber view from a healthy individual (*right panel*). 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.

left ventricular systolic or diastolic dysfunction. Regional wall motion abnormalities or ventricular dilatation may suggest ischemic heart disease, ventricular dilatation, or other cardiomyopathies. Atrial or ventricular septal defects may point to congenital heart disease and may require administration of agitated saline (and an echocardiographic "bubble" study) to appreciate.

Although estimation of PASP by echocardiography is useful when evaluating for PH, it is inadequate to assess precise 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 pulmonary hypertension?

Some tests are required to establish or exclude certain 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 interstitial lung disease because of clinical, pulmonary function, or chest radiographic findings. A sleep study should be considered if there is any possibility of sleep apnea.

Additional testing is done 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 and with exertion. Brain 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 > 150 pg/mL

Evaluation of Pulmonary Hypertension

- Autoantibody testing for collagen vascular disease
- Brain natriuretic peptide or N-terminal brain natriuretic peptide measurement
- Chest radiography
- Complete blood count
- Echocardiography
- Electrocardiography
- Electrolytes/creatinine measurement
- HIV serologic testing
- Liver function testing (alanine transaminase, aspartate transaminase, 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

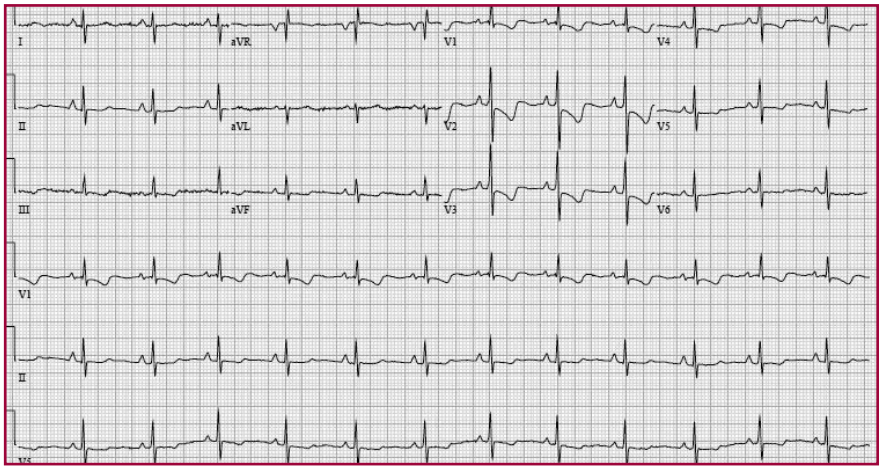

Figure 2. Electrocardiogram of a 31-year-old woman presenting with dyspnea, demonstrating right axis deviation, right atrial enlargement, and right ventricular hypertrophy with repolarization abnormality, suggesting pulmonary hypertension.

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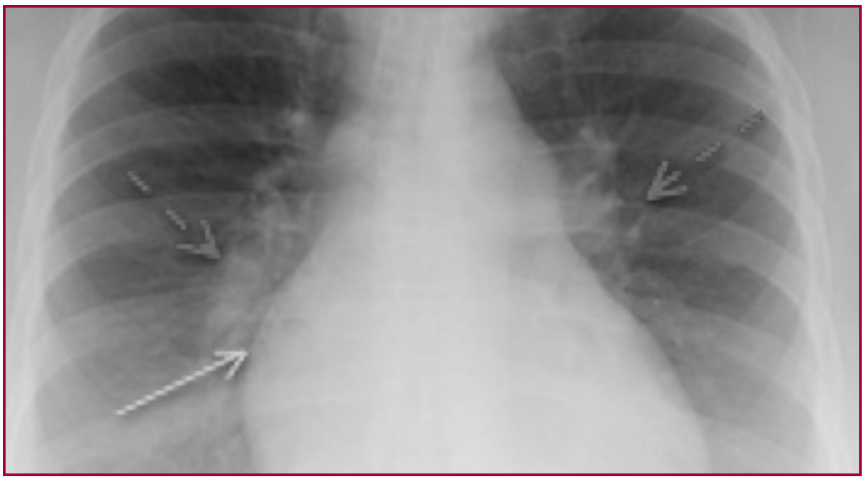

Figure 3. Posteroanterior chest radiograph in a patient with idiopathic pulmonary arterial hypertension. Central pulmonary arteries are enlarged (*top arrows*), and the laterally shifted right heart contour (*bottom left-hand arrow*) suggests right atrial and right ventricular enlargement.

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in patients with PAH at the time of initial diagnosis correlate with worse outcomes, as do persistent BNP levels > 180 pg/mL after treatment is initiated (5). Elevated levels of the N-terminal portion of BNP (NT-Pro BNP) > 1400 pg/mL have also been shown to correlate with worse prognosis (6, 7). Levels of BNP and NT-Pro BNP may both be elevated in the setting of either pulmonary arterial and 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?

Patient in whom PH is clearly referable to left heart disease or chronic pulmonary disease may not require right heart catheterization to confirm PH because its presence generally does not alter the approach to therapy, which is best directed at the underlying cause. In contrast, right heart catheterization is mandatory to establish the diagnosis of PAH and must be done before any advanced medical therapies directed specifically toward the pulmonary vasculature. In addition, right heart catheterization is often helpful in identifying previously unrecognized left heart dysfunction and pulmonary venous hypertension. Right heart catheterization is a safe procedure in patients with PH; complication rates are only 1.1% and most frequently relate to venous access, arrhythmia, and hypotension from vagal episodes. Overall procedure-related mortality is rare and is reported in 0.05% of cases (8). Left heart catheterization is often done concurrently in the evaluation of the patient's symptoms, particularly in patients at risk for coronary artery disease (2, 9).

All patients with a high clinical suspicion of PAH as the cause of PH should undergo right heart catheterization. The presence of comorbid conditions, such as severe interstitial lung disease, COPD, or left heart disease, that precludes a diagnosis of PAH and the use of PAH-specific therapies may temper the decision to proceed with right heart catheterization. However, no PAH-specific therapies should be initiated without right heart catheterization because of the potential for adverse effects if PAH-specific therapies are used in non-WHO group I PAH.

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

During right heart catheterization, assessment for possible left-to-right shunts should be made with 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. 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 pulmonary capillary wedge pressure, should be taken at the end of exhalation and with equipment leveled at the mid-thoracic line. If accuracy is in doubt, left ventricular end-diastolic pressure should be measured simultaneously (10). 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, IV epoprostenol, or IV adenosine, is used to identify a small subgroup of patients who may safely undergo a trial of therapy with calcium-channel antagonists. The current criterion for patients who are "vasoreactive" is a decrease in mean pulmonary arterial pressure of more than 10 mm Hg to an absolute value of less than 40 mm Hg without reduction in cardiac output (2, 9).

When should a clinician consider consultation with a specialist in diagnosing pulmonary hypertension?

Much of the assessment of PH focuses on correctly determining whether a patient has PAH, which may be amenable to available 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.

Pulmonary arterial hypertension is a rare condition and thus best treated with the assistance of a center with sufficient expertise. Patients should be referred to a specialized center if there is uncertainty regarding the diagnosis, they have multiple comorbid conditions that may complicate diagnosis and/or treatment, or they have high-risk features or are New York Heart Association (NYHA) functional class III or IV. Benefits of referral to a specialized center include the availability of advanced therapies; opportunities for patients to participate in clinical trials; and when appropriate, evaluation for lung transplantation.

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

Diagnosis and Screening... Pulmonary hypertension 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 help to assess disease severity. Diagnosis requires right heart catheterization, which is mandatory if therapy is to be directed at PH itself, as in the case of PAH. 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

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What is the approach to treatment of pulmonary hypertension?

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 ≥ 90% at rest, with exertion, and during sleep (9).

Regardless of its cause, when PH results in right heart dysfunction, aggressive yet judicious 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 who have symptoms of right heart dysfunction.

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

Pulmonary hypertension associated with left heart disease is the most common form of PH encountered in clinical practice. It is defined by a mean pulmonary arterial pressure > 25 mm Hg in the presence of an abnormally elevated pulmonary capillary wedge pressure (>15 mm Hg).

The presence of PH in left heart disease should be viewed as a consequence and possible symptom of left heart disease, and treatment should be directed toward its cause rather than toward directly attempting to reduce pulmonary arterial pressure. Treatments of systolic and diastolic heart failure have been reviewed elsewhere (11, 12). Optimum therapy of systolic heart failure generally includes angiotensin-converting enzyme inhibitors; beta-adrenergic antagonists; and diuretics and may also involve cardiac resynchronization, implantable cardioverter defibrillator placement, and digitalis. Treatment of heart failure with a preserved ejection fraction (diastolic dysfunction) is overall less frequently associated with overt volume overload but rather requires tight control of systemic hypertension and heart rate with such agents as beta-adrenergic antagonists and at times diuretics.

Several drugs that are appropriate for treatment of PAH, prostacyclin analogues and endothelin antagonists, have been studied in the treatment of left heart failure with reduced ejection fraction and have both been shown to be associated with higher mortality, more frequent hospital admission, or increased fluid retention (13, 14), emphasizing the importance of differentiation between PH due to left heart disease with pulmonary venous hypertension and PAH.

Although a small study of the phosphodiesterase-5 (PDE5) inhibitor sildenafil in left heart failure showed improvements in hemodynamics and a measure of exercise capacity (15), a larger study of patients with diastolic heart failure found no benefit (15a). Routine use of PDE5 inhibitors is not recommended in PH caused by left heart disease.

Pulmonary hypertension 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 (16).

How should patients with pulmonary hypertension due to lung disease be treated?

The only proven effective therapy for PH associated with COPD is

supplemental oxygen (17). Treatment should be directed at optimizing treatment of underlying sleep apnea, COPD, and idiopathic lung disease, utilizing supplemental oxygen to avoid periods of hypoxia, and enrollment in pulmonary rehabilitation as appropriate (18). 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 recommended (2, 9). Clinical trials have failed to show any benefit of pulmonary vasodilators in idiopathic lung disease and COPD, and these drugs can worsen ventilation–perfusion matching and cause more severe hypoxia (19–21). A recent trial of endothelin-receptor antagonist ambrisentan therapy in patients with idiopathic pulmonary fibrosis was terminated early due to lack of benefit and potential for harm (22).

How should patients with chronic thromboembolic pulmonary hypertension be treated?

Chronic thromboembolic PH (CTEPH) is distinct from other forms of PH because surgical pulmonary thromboendarterectomy (PTE) is the treatment of choice and may be curative (23). If a diagnosis of CTEPH is suspected, patients should receive effective anticoagulation and be referred for evaluation to an expert center. Medical therapy directed at the PH itself has a limited role and should not delay evaluation for possible thromboendarterectomy, which should only be done at expert centers with experience in both the surgical procedure and postoperative management.

Most patients with surgically accessible disease will have a sustained improvement in symptoms after successful surgery. At experienced centers, surgical mortality is less than 5% (24).

What drugs are available for the treatment of pulmonary arterial hypertension?

Therapy for PAH is generally divided into "background" therapy and PAH-specific drugs. Background therapy includes the use of diuretics and supplemental oxygen as described above (What is the approach to treatment of PH?). In addition, in PAH, calcium-channel antagonists, anticoagulants, and digoxin are often considered.

Vasodilator testing during right heart catheterization at an expert center is required for appropriate patients with PAH to identify those who may safely undergo a therapeutic trial of calcium-channel antagonists. Although only a small number experience benefit (estimated to be <10%), 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, and death may occur.

Warfarin has been evaluated in observational studies of idiopathic PAH, heritable PAH, and anorexogen-associated PAH and has been associated with improved outcomes. However, recognizing the lack of firmly established benefit and the potential for harm, expert organizations recommend a lower target international normalized ratio (1.5–2.5) than is used in patients treated with warfarin for atrial fibrillation or venous thromboembolism (25, 26). Warfarin use for other forms of PH is less clear, and it is generally not employed in this setting. There are no data on use of newer anticoagulants in lieu of warfarin in PAH.

In PAH, digoxin has been shown to acutely increase cardiac output; however, there are few long-term data to support its use (27).

Three classes of medication are approved to treat PAH (but not other

34. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med. 1990;112:485-91. [PMID: 2107780]
35. Gomberg-Maitland M, Tapson VF, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005;172:1586-9. [PMID: 16151039]
36. Doran AK, Ivy DD, Barst RJ, Hill N, Murali S, Benza RL; Scientific Leadership Council of the Pulmonary Hypertension Association. Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract Suppl. 2008:5-9. [PMID: 18638170]
37. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006;174:1257-63. [PMID: 16946127]
38. Olschewski H, Simonneau G, Galiè N, et al; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347:322-9. [PMID: 12151469]
39. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med. 1993;328:1732-9. [PMID: 8497283]
40. Channick RN, Simonneau G, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet. 2001;358:1119-23. [PMID: 11597664]

Table 1. Advanced Therapies for Pulmonary Arterial Hypertension

Drug Class	*Examples*	*Dose*	*Mechanism of Action*	*Comments/Common Adverse Effects*
Prostacyclin derivatives	Epoprostenol	Initiated at 2 ng/kg/min IV and titrated to symptoms	Stimulates intracellular production of cAMP	Headache, flushing, hypotension, masticatory jaw pain, nausea, diarrhea, anorexia, rash, arthralgia. Risk for central venous catheter–related infections with intravenous infusion. Risk for cellulitis and pain with SQ infusion. Cough may occur with inhaled therapy
	Iloprost	2.5–5 mcg inhaled 6–9 times/d		
	Treprostinil	SC or IV: initially, 1.25 ng/kg/min infusion and titrated to symptoms. Inhaled: initially, 18 mcg 4 times/d, up-titrated to 54 mcg 4 times/d		
Endothelin- receptor antagonists	Ambrisentan	5–10 mg orally daily	Blocks endothelin-1 receptors on vascular smooth muscle	Contraindicated in pregnancy (FDAcategory X), hepatotoxicity, worsened fluid retention, headache, anemia
	Bosentan	62.5 mg orally 2 times/d for 4 weeks, then 125 mg orally 2 times/d if liver function tests are normal		
Phosphodiesterase-5 inhibitors	Sildenafil	20 mg orally 3 times/d	Inhibits the 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 TID in clinical trials
	Tadalafil	40 mg orally once/d		

cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; FDA = U.S. Food and Drug Administration.

types of PH), collectively termed "advanced therapies" (Table 1). Each therapy targets a different cellular pathway implicated in the pathogenesis of PAH.

The choice of advanced PAH therapy is driven largely by the severity of illness and risk. The severity of illness is determined by integrating clinical variables (e.g., functional status and 6-minute walking distance) with indicators of right heart impairment (e.g., enlargement or dysfunction on echocardiogram, measured hemodynamic values) (Table 2). Pulmonary arterial hypertension registry data have recently led to development of a clinical calculator that may be useful to assess patient risk (28, 29). In general, oral therapies are initiated for patients at low risk, whereas prostenoid therapies are considered for more advanced and higher-risk disease (e.g., in patients with more severe functional class III or class IV symptoms).

Prostacyclins

Prostacyclins have potent vasodilatory, antiplatelet, and antiproliferative properties and their synthesis is reduced in patients with PAH. Prostenoid drugs for PAH are available in the United States as continuous IV or SQ infusions or inhaled therapy; oral analogues of these agents are currently under investigation.

Epoprostenol was the first drug approved for the treatment of PAH after a landmark 1996 study demonstrating improved survival (30) and is generally viewed as the most potent therapy for PAH. Additional studies have demonstrated improvements in symptoms, exercise capacity, and hemodynamics (31–34). Epoprostenol has a short half-life (3–5 min) and must be administered by continuous IV infusion, ideally through a tunneled catheter. Treprostinil is an analogue

41. Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet. 2008;371:2093-100. [PMID: 18572079]
42. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346:896-903. [PMID: 11907289]
44. Galié N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46:529-35. [PMID: 16053970]
45. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117:3010-9. [PMID: 18506008]

of epoprostenol with a longer half-life (about 4.5 h) delivered by continuous IV or SQ infusion (35).

Both IV and SQ infusion therapy requires patients and families capable of reconstituting medication in a sterile manner, maintaining clean catheter sites, and making frequent adjustments in therapy. The required central venous catheter poses a risk for infection. Adverse effects of SQ therapy include cellulitis and infusion site pain (36). Because of the complexities of this therapy, use should be reserved for highly experienced centers.

Inhalational formulations of prostenoid therapy are iloprost and treprostinil, which require repeated administrations while the patient is awake (37, 38). Side effects include flushing, headache, diarrhea, leg pain, and jaw pain. Cough may occur with inhalational therapy.

Endothelin antagonists

Endothelin-1 is a potent endogenous vasocontrictor and mitogen present at high levels and whose receptors are overexpressed within the pulmonary vasculature of patients with PAH (39). The oral endothelin-receptor antagonists bosentan and ambrisentan improve exercise capacity, functional class, hemodynamics, and the time to clinical worsening in randomized trials (40–46). Both drugs are teratogens, and women of child-bearing age require monthly pregnancy tests. Elevations in liver transaminases occur, and monthly monitoring is required with bosentan and recommended by expert panels for both agents. Both bosentan and ambrisentan can cause mild reductions in hemoglobin of approximately 1 g/dL.

Phosphodiesterase-5 inhibitors

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 (47–52). The current U.S. Food and Drug Administration–approved dose of sildenafil 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. Coadministration of nitrate medications can cause severe systemic hypotension. Patients treated with PDE5 inhibitors must be educated regarding this risk.

Table 2. Assessment of Risk in Pulmonary Arterial Hypertension*

Variable	*Lower Risk/Better Prognosis*	*Higher Risk/Poorer Prognosis*
Clinical right heart failure	No evidence	Yes evidence
Symptom progression	Gradual	Rapid
WHO functional class	II, III	IV
Six-minute walk distance	Longer (> 400 meters)	Shorter (< 300 meters)
Cardiopulmonary exercise testing	VO_2 maximum > 10.4 ml/kg/min	VO_2 maximum < 10.4 mL/kg/min
Echocardiogram	Minimal right ventricular dysfunction	Significant right ventricular enlargement/dysfunction; pericardial effusion
Hemodynamics	Right atrial pressure < 10 mm Hg; cardiac index > 2.5 L/min/m^2	Right atrial pressure > 20 mm Hg; cardiac index < 2.0 liters/min/m^2
Brain natriuretic peptide†	Minimally elevated	Markedly elevated

WHO = World Health Organization.

**Adapted from McLaughlin VV, Archer SL, Badesch DB, et al. J Am Coll Cardiol. 2009;53:1573-619.*

†May be affected by renal function, weight, age, and sex. Few data are available to guide numerical cut-offs.

Is there a role for combination therapy in pulmonary arterial hypertension?

The current model of PAH treatment relies on sequential addition of advanced therapies. Initial therapy is chosen by assessing illness severity and patient functional class, and integrating patient preferences and the adverse effect profiles of the medications being considered. If PAH worsens despite optimum dosing of a single agent, therapies are usually added until treatment goals are reached.

There have been at least 7 randomized, controlled trials examining the sequential addition of therapy and together demonstrate that improvements in 6-minute walking distance and in delaying clinical worsening

46. Oudiz RJ, Galiè N, Olschewski H, et al; ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54:1971-81. [PMID: 19909879]
47. Rubin LJ, Badesch DB, Fleming TR, et al; SUPER-2 Study Group. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. Chest. 2011;140:1274-83. [PMID: 21546436]
48. Badesch DB, Hill NS, Burgess G, et al; SUPER Study Group. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. J Rheumatol. 2007;34:2417-22. [PMID: 17985403]
49. Simonneau G, Rubin LJ, Galiè N, et al; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008;149:521-30. [PMID: 18936500]
50. Galiè N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353:2148-57. [PMID: 16291984]

may be possible with these approaches (37, 49, 51, 53–57). However, data are less than robust in guiding treatment decisions when combination therapy is used and the optimum and safest approaches have not been established. Investigations are currently examining the impact of initial combination therapy vs. monotherapy or sequential addition of therapies.

What is the role of lung transplantation?

Patients with severe PH and comorbid COPD or interstitial lung disease usually have late-stage respiratory disease and may be considered for lung transplantation to treat the underlying pulmonary condition.

Referral for lung transplantation evaluation in PAH is appropriate when patients have progressive disease that is severe enough to require parenteral therapy. If a patient improves or stabilizes in response to aggressive medical therapy, transplantation may be deferred until deterioration despite maximum medical therapy occurs.

What is the role of exercise?

It is important to avoid and to the extent possible reverse the deconditioning that may occur in patients with exercise limitation who become sedentary. Pulmonary hypertension 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 (2, 9).

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 demonstrated improvements in exercise capacity and quality of life and can serve as an important adjunct to medical therapy (58, 59).

Treatment... The therapeutic approach to PH differs according to underlying pathology, and misapplication of therapy appropriate to one form of PH in the care of a patient with another cause of PH is potentially harmful. Regardless of 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 either left heart or chronic hypoxemic lung disease involves aggressive treatment of those underlying disorders, and not treatment of the PH per se. Patients with chronic thromboembolic PH require evaluation for possible thromboendarterectomy at an experienced center as well as anticoagulation therapy. 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, and PDE5 inhibitors. 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 pulmonary hypertension?

Pulmonary hypertension 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

51. Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119:2894-903. [PMID: 19470885]
52. Barst RJ, Oudiz RJ, Beardsworth A, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2011;30:632-43. [PMID: 21256048]
53. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010;55:1915-22. [PMID: 20430262]
54. Zhu B, Wang L, Sun L, Cao R. Combination therapy improves exercise capacity and reduces risk of clinical worsening in patients with pulmonary arterial hypertension: a meta-analysis. J Cardiovasc Pharmacol. 2012;60:342-6. [PMID: 22691882]
55. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. Eur Respir J. 2004;24:353-9. [PMID: 15358690]
56. Hoeper MM, Leuchte H, Halank M, et al. Combining inhaled iloprost with bosentan in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2006;28:691-4. [PMID: 17012628]

myocarditis or decreased right ventricular ejection fraction (60, 61). Likewise, more severe PH connotes a poorer prognosis in patients with COPD. In neither of these conditions has treatment directed at PH been linked to improved outcomes.

Because effective therapy is relatively new, the prognosis of untreated PAH has been evaluated as recently as the 1980s. 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). More recently, prognostic data obtained during the current era of therapeutics have become available. Based on data from 2716 patients enrolled in the multicenter observational Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) Registry, a risk calculator for patients with PAH has been developed and validated (29).

Several studies have shown that prognosis in PAH is worse in the presence of more advanced NYHA/WHO functional class or shorter 6-minute walking distance. A poorer prognosis has also been noted in patients in whom PAH is associated with connective tissue disease or portal hypertension (i.e., portopulmonary hypertension) (62). Several factors may contribute to the worsened prognosis of patients with portopulmonary hypertension, including complications of concomitant liver disease and greater delays in instituting advanced therapies for PAH.

What should patients be taught about pulmonary hypertension?

Patients should be educated that PH is not a single disease and that it is distinct from systemic hypertension. Regardless of the cause, the presence of significant PH almost always connotes significant systemic disease that requires ongoing, closely coordinated medical care and close attention to salt intake, fluid balance, and home weight monitoring.

Patients with PAH may need to self-administer complex medications, self-monitor for adverse effects or progression of disease, and help ensure that concomitant health care issues do not compromise or adversely interact with their PAH regimen. Patients should be informed of available information and peer support (see Tool Kit).

Practice Improvement

What do professional organizations recommend with regard to the care of patients with pulmonary hypertension?

Because treatment directed specifically at abnormal pulmonary hemodynamics is not advisable outside the setting of PAH, most treatment guidelines for patients with heart failure or cor pulmonale do not directly address the issue.

In contrast, several organizations have published consensus documents related to PAH. The American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association released a guideline on PH in 2009 that makes evidence-based clinical recommendations in several areas related to both PAH and non-PAH PH (9).

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society also issued comprehensive guidelines in 2009 that were endorsed by the International Society of Heart and Lung Transplantation (2).

The American College of Chest Physicians developed guidelines for

57. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Søndergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J. 2010;31:1124-31. [PMID: 20202971]
58. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114:1482-9. [PMID: 16982941]
59. Grünig E, Ehlken N, Ghofrani A, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration. 2011;81:394-401. [PMID: 21311162]
60. Cappola TP, Felker GM, Kao WH, Hare JM, Baughman KL, Kasper EK. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. Circulation. 2002;105:1663-8. [PMID: 11940544]
61. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37:183-8. [PMID: 11153735]
62. Hurdman J, Condliffe R, Elliot CA, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur Respir J. 2012;39:945-55. [PMID: 21885399]

63. Badesch DB, Abman SH, Ahearn GS, et al; American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:35S-62S. [PMID: 15249494]
64. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest. 2007;131:1917-28. [PMID: 17565025]

the treatment of PAH that were issued in 2004 and updated in 2007 (63, 64). A revision of these guidelines is in progress.

Do U.S. stakeholders consider management of patients with pulmonary hypertension when evaluating the quality of care physicians deliver?

Most patients with PH have underlying left heart disease or COPD. Multiple performance measures have been developed for these conditions, but none focus on the aspect of PH in these settings.

Similarly, there are no specific Centers for Medicare & Medicaid Services performance measures with regard to care of patients with PAH. However, there are several measures that may be relevant related to warfarin use and to monitoring electrolytes and renal function in patients receiving long-term diuretic therapy.

In the Clinic
Tool Kit

Pulmonary Hypertension

PIER Module

http://pier.acponline.org/physicians/diseases/d200/d200.html
PIER module on pulmonary hypertension from the American College of Physicians.

Patient Information

http://pier.acponline.org/physicians/diseases/d200/d200-pi.html
Patient information that appears on the next page for duplication and distribution to patients.
www.nlm.nih.gov/medlineplus/pulmonaryhypertension.html
www.nlm.nih.gov/medlineplus/tutorials/echocardiogram/htm/index.htm
www.nlm.nih.gov/medlineplus/spanish/tutorials/echocardiogramspanish/htm/index.htm
Resources related to pulmonary hypertension from the National Institutes of Health's MedlinePLUS, including an echocardiogram interactive tutorial in English and Spanish.
www.nhlbi.nih.gov/health/health-topics/topics/pah
Information on pulmonary hypertension, including treatment, from the NIH's National Heart, Lung, and Blood Institute.
www.phassociation.org/MedicalProfessionals
Information on caring for patients with pulmonary hypertension, from the Pulmonary Hypertension Association.

Clinical Guidelines

http://content.onlinejacc.org/article.aspx?articleid=1139633
Consensus document on pulmonary hypertension, from the American College of Cardiology and the American Heart Association in 2009.
http://journal.publications.chestnet.org/article.aspx?articleid=1082671
Practice guidelines on screening, early detection, and diagnosis of pulmonary arterial hypertension from the American College of Chest Physicians in 2004.
http://journal.publications.chestnet.org/article.aspx?articleid=1085181
Practice guidelines on medical therapy for pulmonary arterial hypertension, from the ACCP in 2007.

Diagnostic Tests and Criteria

http://pier.acponline.org/physicians/diseases/d200/tables/d200-t4.html
PIER list of laboratory tests for evaluating the causes, risk factors, comorbid conditions, and functional impairment in pulmonary hypertension.
http://pier.acponline.org/physicians/diseases/d200/tables/d200-tables.html
PIER list of tests used for detecting pulmonary hypertension.

THINGS YOU SHOULD KNOW ABOUT PULMONARY HYPERTENSION

What is pulmonary hypertension?

- Pulmonary hypertension (PH) means high blood pressure in the lungs.
- It occurs with narrowing of the arteries in the lungs, which carry blood from your heart to your lungs to pick up oxygen.
- Medical conditions that can lead to PH include heart and lung diseases or blood clots and connective tissue disease (such as lupus or scleroderma).
- Rarely, an inherited form of PH runs in families.

How is it diagnosed?

- Your doctor will conduct a thorough physical examination to look for signs or PH.
- Your doctor may order tests, such as an echocardiogram to estimate the pressure in your pulmonary arteries or a pulmonary function test to measure how your lungs are working.
- If these tests indicate that you may have PH, you will undergo cardiac catheterization, which directly measures the pressure in your heart and lungs and shows how your heart is pumping blood to the rest of your body.

What are the signs and symptoms?

- Tiredness and shortness of breath during routine activities.
- Chest pain and pain on the upper right side of the abdomen.
- Racing heartbeat and decreased appetite.
- Fainting or feeling lightheaded.
- Leg and ankle swelling.
- Blue tinted lips and skin.

How is it treated?

- Treatment may include medications, supplemental oxygen, lifestyle changes, and surgery.

- Your doctor will aim to reduce your symptoms and to address underlying diseases or conditions that exacerbate PH.
- Patients with advanced PH may undergo lung transplantation.
- PH has no cure, but earlier treatment can make it easier to control.

For More Information

www.phassociation.org/homepage
www.phassociation.org/page.aspx?pid=428
The Pulmonary Hypertension Association provides information about the disease, including information for newly diagnosed patients.

www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/What-is-Pulmonary-Hypertension_UCM_301792_Article.jsp
Information about pulmonary hypertension, including how pulmonary hypertension differs from high blood pressure, from the American Heart Association.

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Patient Information

CME Questions

MKSAP
MEDICAL KNOWLEDGE Self-Assessment Program

1. A 33-year-old woman is evaluated for a 2-year history of progressive dyspnea on exertion accompanied by weakness and fatigue. There is no seasonal variation to her symptoms. She reports difficulty falling asleep but has no history of nocturnal awakening, snoring, or daytime somnolence. She does not have dizziness or syncope. Her medical history is otherwise normal, and she takes no medications.

   On physical examination, temperature is 37.0°C (98.6°F), blood pressure 115/75 mm Hg, pulse rate is 108/min and regular, and respiration rate is 18/min at rest; body mass index (BMI) is 23. The neck veins are distended. Cardiac examination shows regular tachycardia and a prominent pulmonic component of S_2. The lungs are clear. There is bilateral edema of the legs. There are no rashes, the joints appear normal, and there is no clubbing of the digits.

   Laboratory studies, including a complete blood count, serum chemistries, and thyroid and coagulation studies, are normal. HIV testing is seronegative. Antinuclear antibody, rheumatoid factor, and ANCA studies are negative. Chest radiograph reveals prominent central pulmonary arteries, clear lungs, and normal heart size. Pulmonary function tests reveal a mildly decreased DLCO without evidence of airway obstruction or decreased lung volumes. Electrocardiogram shows right axis deviation. Transthoracic echocardiogram shows normal left ventricular size and function, a dilated right ventricle, and an estimated right ventricular systolic pressure of 40 mm Hg. Ventilation–perfusion scan is normal.

   Which of the following is the most appropriate diagnostic test to perform next?

   A. High-resolution chest computed tomography (CT)
   B. Pulmonary angiography
   C. Right heart catheterization
   D. Sleep study
   E. Transesophageal echocardiography

2. A 54-year-old woman is evaluated for a 1-year history of progressive dyspnea. Her symptoms have been progressively worsening, and she is now unable to walk more than a block without becoming significantly short of breath. Oxygen desaturation with ambulation was recently diagnosed, and she was prescribed supplemental oxygen during exertion. She recently developed ankle swelling but does not have chest pain, cough, lightheadedness, or other localizing symptoms. Medical history is significant only for a hysterectomy 3 years ago that was followed by a postoperative respiratory illness treated as pneumonia. Current medications are oxygen with exertion, 2 L/min by nasal prongs, and as-needed furosemide.

   On physical examination, temperature is 37.0°C (98.6°F), blood pressure is 118/72 mm Hg, pulse rate is 100/min and regular, and respiration rate is 18/min. BMI is 27. The lungs are clear. Cardiac examination reveals sinus tachycardia, an increased pulmonary component of S_2, and no murmurs. The liver is not enlarged. There is no clubbing of the digits. Ankle edema is noted bilaterally, and there are no venous cords or tenderness in the legs.

   Laboratory studies are normal except for a B-type natriuretic peptide level of 700 pg/mL. Arterial blood gas measurement breathing ambient air shows a pH of 7.41, PCO_2 of 38 mm Hg (5.1 kPa), and PO_2 of 62 mm Hg (8.2 kPa). Pulmonary function tests are normal except for a mild reduction in DLCO to 70% of normal. Electrocardiogram discloses sinus tachycardia and right ventricular hypertrophy. A chest radiograph shows mildly increased interstitial markings, normal inflation, and no evidence of infiltrate or effusion. Echocardiogram shows a normal left ventricular ejection fraction and an estimated pulmonary artery systolic pressure of 35 to 45 mm Hg.

   Which of the following is the most appropriate diagnostic study?

   A. Chest CT angiography
   B. D-dimer study
   C. Lower-extremity duplex ultrasonography
   D. Ventilation–perfusion scan

3. A 60-year-old man is evaluated for a 2-year history of fatigue and daytime sleepiness and an 8-month history of dyspnea that occurs only during moderate exercise. He does not smoke cigarettes and works inside the home. He has hypertension, and his only medication is hydrochlorothiazide.

   On physical examination, vital signs are normal. The patient is obese (BMI 33); the neck is short and thick (circumference 50.8 cm [20 in]), and the posterior airway is crowded. Jugular venous distention cannot be adequately assessed. There is increased intensity of P_2 with fixed splitting of S_2 and a grade 1–2/6 holosystolic murmur that increases with inspiration heard best along the left lower sternal border. Chest radiograph is normal. Spirometry, plethysmography, and arterial blood gases with the patient breathing ambient air are normal. Transthoracic echocardiography shows evidence of right ventricular hypertrophy and mild pulmonary hypertension. Right and left ventricular function are normal. A ventilation–perfusion scan is normal.

   Which of the following is the most appropriate management for this patient?

   A. Lung transplantation
   B. Nocturnal continuous positive airway pressure therapy
   C. Polysomnography
   D. Right heart catheterization

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program. Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.