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Principles and Practice of Hospital Medicine

Second Edition

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CHAPTER 237

Pulmonary Hypertension

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1. How does the classification system for pulmonary hypertension (PH) aid in understanding the pathophysiology, diagnostic evaluation, and treatments for this condition?
2. What signs and symptoms might increase the suspicion for elevated pulmonary arterial pressures?
3. What is a rational diagnostic approach to suspected PH?
4. What is the meaning of an elevated pulmonary pressure determined by echocardiography?
5. When should right heart catheterization be considered in the evaluation of suspected PH?
6. What are the key steps in the evaluation and management of acute right heart failure secondary to elevated pulmonary arterial pressure?
7. What are the common side effects of the medications used to treat PH?

INTRODUCTION

Pulmonary hypertension (PH) is simply defined as a mean pulmonary arterial pressure > 25 mm Hg at rest. However, this deceptively simple definition encompasses a broad spectrum of clinical entities. In this chapter, we will present an evidence-based approach to the care of the patient with elevated pulmonary arterial pressures. Table 237-1 lists landmark studies supporting the approach presented in this chapter.

DISEASE CLASSIFICATION, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY

The first step in understanding the myriad presentations of pulmonary hypertension is to comprehend the pathophysiologic differences that divide the major groups of this disorder. These groups, as defined by the 2013 Fifth World Symposium on Pulmonary Arterial Hypertension, are shown in Table 237-2.

■ GROUP I DISEASE

Group I disease, defined as pulmonary arterial hypertension (PAH), is characterized histologically by plexiform lesions occluding the pulmonary vasculature, in situ thrombosis, intimal proliferation, medial thickness and an apoptosis-resistant state producing a chaotic metabolism and mitochondrial structure, inflammation, and dysregulation of growth factors. This process results in decreased pulmonary vascular surface area, increased pulmonary vascular resistance, and functional disruptions of normal endothelial homeostasis. These perturbations are most notable in the prostacyclin, endothelin, nitric oxide, and serotonergic pathways regulating endothelial function. These pathways are the targets of current PAH therapy.

Group I PAH is most commonly idiopathic or heritable (in 80% of families with multiple cases of PAH, mutations in the bone morphogenic protein receptor type 2 can be identified), drug/toxin induced, or associated with other conditions, including collagen vascular disease (most notably, systemic sclerosis), HIV infection, portal hypertension, schistosomiasis, or congenital heart disease. This group also includes persistent pulmonary hypertension of the newborn and pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).

Idiopathic pulmonary arterial hypertension (IPAH, formerly, "primary pulmonary hypertension") is rare, but life threatening, with a prevalence of approximately 15 cases/million, an incidence of 2.4 cases/million/y, and a median survival of only 2.8 years without treatment. The vast majority of patients diagnosed with IPAH are in World Health Organization functional classes III and IV, which have been associated with a poorer prognosis.

Recent evidence suggests that PAH in systemic sclerosis may be diagnosed earlier by annual cardiopulmonary screening in asymptomatic patients with the SSc spectrum of diseases, although there is currently a lack of evidence-based data, especially in individual with a DLCO >60%. Screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH should include a 2-step approach using clinical assessment for the presence of telangiectasia, anti-centromere anti- bodies, PFT and DLCO measurements, electrocardiogram, and biomarkers (NT-proBNP and uric acid) in the initial stage, followed by echocardiography and consideration of RHC in patients with abnormal findings. The American College of Rheumatology recommends annual echocardiography and PFTs in these individuals because 10% of SSc patients will develop PH during the course of the disease.

TABLE 237-1 Evidence-based Key References: Pulmonary Hypertension

Topic	Supporting Literature
Epidemiology	Humbert M, Sitbon O, Chaaouat A, et al. Pulmonary hypertension in France: results from a national registry. Am J Resp Crit Care Med. 2006;173:1023-1030. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in patients with preserved ejection fraction: a community based study. J Am Coll Card. 2009;53:1119-1126. Badesch DB, Raskob G, Elliott G, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest. 2010;137(2):376-387.
Classification and pathophysiology	Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004;351:1655-1665. Gerald Simonneau MD, Michael A Gatzoulis MD PhD, et al. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol. 2013;62(25_S). doi:10.1016/j.jacc.2013.10.029. Marius M. Hoeper, MD, Harm Jan Bogaard, MD, et al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol. 2013;62(25_S):. doi:10.1016/j.jacc.2013.10.032. Overbeek MJ, Vonk MC, Boonstra A, et al. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. Eur Respir J. 2009;34(2):371-379.
Diagnosis: examination, laboratory	Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med. 1987;107:216-223. Dahlstrom U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? Eur J Heart Fail. 2004;6:281-287. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102:865-870.
Diagnosis: echocardiography, imaging	Aurigemma GP, Zile MR, Gaasch WH. Lack of relationship between Doppler indices of diastolic function and left ventricular pressure transients in patients with definite diastolic heart failure. Am Heart J. 2004;148:E12. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med. 2009;179:615-621. Chetty KG, Brown SE, Light RW. Identification of pulmonary hypertension in chronic obstructive pulmonary disease from routine chest radiographs. Am Rev Respir Dis. 1982;126:338-341. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48:680-684.
Treatment	Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;334:296-302. Nazzareno Galiè MD, Paul A. Corris MD, et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2013;62(25_S):. doi:10.1016/j.jacc.2013.10.031. Jais X, D'Armini AM, Jansa P, et al. Bosentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFit. J Am Coll Cardiol. 2008;52:2127-2134. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353:2148-2157.
Complications	Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. Circulation. 1989;80:178-188. Kallen AJ, Lederman E, Balaji A, et al. Incidence of central line infection in pulmonary hypertension patients receiving prostanoids. Infect Control Hosp Epidemiol. 2008;29:332-339.

■ GROUP II DISEASE

Group II disease constitutes the most common cause of elevated pulmonary pressures: pulmonary venous hypertension. Pulmonary hypertension (PH) is a common complication of left heart disease (LHD) due to left ventricular systolic or diastolic heart failure with preserved ejection fraction, or valvular disease. Congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to Group 2. Compared to pulmonary arterial hypertension (PAH), patients with PH-LHD are older, female, with a history of systemic hypertension, and characteristics of the metabolic syndrome.

The current hemodynamic definition of PH-LHD combines a mean pulmonary artery pressure (mPAP) 25 mm Hg, a pulmonary artery wedge pressure (PAWP) >15 mm Hg, and a normal or reduced cardiac output (CO).

Due to the low sensitivity of traditional echocardiographic measures (eg, E/A ratio) for the diagnosis of left ventricular diastolic dysfunction, this disorder may be confused with IPAH in the absence of right heart catheterization showing an elevated pulmonary artery occlusion pressure. Although treatment of underlying cardiac disease including repair of valvular heart disease and aggressive therapy for HF with reduced or preserved ejection function are the mainstays of group II disease therapy, a small proportion of patients with long-standing pulmonary venous hypertension may develop physiology and histology consistent with group I disease; this is usually poorly responsive to traditional cardiac risk factor modification.

In severe HF, optimizing volume status is of critical importance and might require invasive monitoring. Moreover, the implantation of an LV assist device has been shown to lower pulmonary pressures through LV unloading without increasing the risk of postimplantation

TABLE 237-2 2013 Fifth World Symposium on Pulmonary Arterial Hypertension: Classification

Group I. Pulmonary arterial hypertension
• Idiopathic (formerly "primary pulmonary hypertension")
• Heritable
• Drug or toxin-induced (eg, anorexigens, rapeseed oil, l-tryptophan, methamphetamine, and cocaine)
• Associated conditions: collagen vascular disease, congenital heart disease, portal hypertension, HIV infection, schistosomiasis
• Associated with significant venous or capillary involvement
[a] Pulmonary veno occlusive disease
[a] Pulmonary-capillary hemangiomatosis
[a] Persistent pulmonary hypertension of the newborn
Group II. Pulmonary venous hypertension
• Left-sided systolic, diastolic, or valvular heart disease
• Congenital/Acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group III. Pulmonary hypertension associated with lung disease and/or chronic hypoxemia
• Chronic obstructive pulmonary disease
• Interstitial lung disease
• Mixed restrictive and obstructive lung diseases
• Sleep-disordered breathing
• Alveolar hypoventilation disorders
• Chronic exposure to high altitude
• Developmental abnormalities
Group IV. Chronic thromboembolic pulmonary hypertension
Group V. Pulmonary hypertension of unclear or multifactorial mechanisms
• Hematologic disorders: splenectomy, myeloproliferative disorders
• Systemic disorders: sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangiomatosis, vasculitis, neurofibromatosis, chronic hemolytic anemias
• Metabolic disorders: Gaucher's, glycogen storage disease, thyroid disease
• Other: tumoral compression of pulmonary vessels, fibrosing mediastinitis, chronic hemodialysis, segmental PH

Adapted, with permission, from Simmoneau G, et al. Updated clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol. 2013; 62(25 Suppl):D34-41.

RV failure. Treatment of patients with pulmonary venous hypertension with pulmonary vasodilators may result in pulmonary edema from sudden reduction of pulmonary vascular resistance and acutely increased preload overwhelming the compromised left ventricle. This underscores the importance of right heart catheterization to correctly characterize the etiology of pulmonary hypertension prior to starting therapy.

■ GROUP III DISEASE

Group III disease describes PH due to chronic lung disease and hypoxic vasoconstriction. This group most commonly presents with known pulmonary diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), obstructive sleep apnea (OSA), and/or obesity hypoventilation syndromes. The prevalence of pulmonary hypertension in COPD is related to the severity of the disease. Studies have shown that up to 90% of patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage IV disease have a mean pulmonary artery pressure of >20 mm Hg, with most ranging between 20 and 35 mm Hg. The presence of PH is a strong predictor of mortality in COPD. A 5-year survival rate of only 36% has been reported in COPD patients with mPAP values > 25 mm Hg. Combined pulmonary fibrosis and emphysema (CPFE) patients have an increased risk to develop PH, with estimates approaching 30% to 50%. In these patients normal or mildly subnormal lung volumes and the absence of airflow obstruction coexist with severe PH and markedly reduced DLCO. Treatment of the underlying lung disease and use of supplemental oxygen are the foundations of care for pulmonary hypertension associated with chronic hypoxemia. Because pulmonary vasodilators may elicit significant ventilation/perfusion mismatch and severe hypoxemia with in patients with underlying structural lung disease, these medications are currently only investigational in this patient population.

■ GROUP IV DISEASE

Group IV disease is caused by thromboembolic disease to the pulmonary circulation, generating chronic thromboembolic pulmonary hypertension (CTEPH). Definitive treatment of group IV disease due to thrombotic pulmonary emboli involves pulmonary arterial thromboendarterectomy (PEA).

Although computed tomography (CT) and magnetic resonance imaging (MRI) have evolved, VQ scan remains the preferred test for screening for chronic thromboembolic disease and this is the initial step in the diagnosis of CTEPH. Pulmonary angiography remains the gold standard for diagnosis of chronic thromboembolic disease and assessment of operability. For inoperable CTEPH and residual disease after PEA, medical therapy is recommended; riociguat is the first drug approved for treatment in this population.

■ GROUP V DISEASE

Group V disease is best described as a catch-all of miscellaneous causes of PH. These include diseases with multifactorial mechanisms (ie, hematologic disorders, metabolic disorders, sarcoidosis, etc) or disease states associated with external compression of pulmonary arteries, such as tumor, lymphadenopathy, or fibrosing mediastinitis (most commonly caused by radiation therapy for Hodgkin disease), chronic myeloproliferative (CML) disorders, end-stage renal disease treated with hemodialysis, and segmental PH (pediatric classification).

There may be overlap of disease classification in any of individual case of PH. Given the potential complications associated with improper use of pulmonary vasodilators in patients with group II-V disease, initiation of these agents (prostacyclins, phosphodiesterase inhibitors, endothelin receptor antagonists, soluble guanylyl cyclase agonists) should be restricted to specialists with experience in their use, only after a diagnostic group has been established for a particular patient.

■ DIAGNOSIS

Obtaining a correct diagnostic classification for any patient with suspected or established PH is essential for initiating proper treatment. An evidence-based approach to the diagnostic evaluation of suspected PH is paramount. Patients with PH most often present with nonspecific signs and symptoms, as exemplified by an average time from onset of symptoms to diagnosis of 2 years. The following discussion will present a general diagnostic algorithm (Figure 237-1) for a patient with suspected PH. Ultimately, the diagnosis of PH must be established by right heart catheterization (RHC) in all patients. PH is defined as PAP ≥ 25 mm Hg at rest measured by RHC.

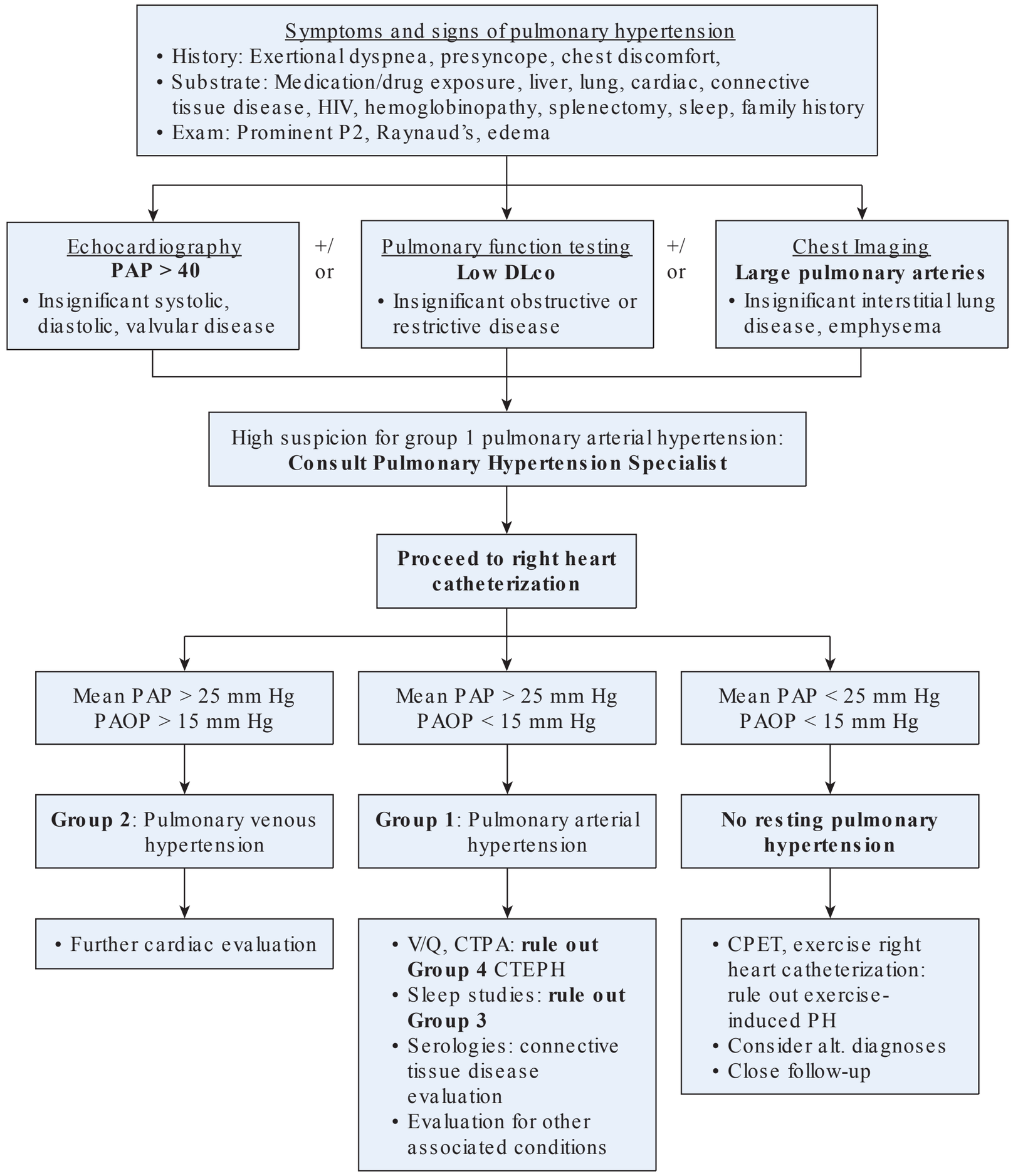

Figure 237-1 Algorithm for evaluation of suspected pulmonary hypertension.

■ SYMPTOMS

While PH often presents as an incidental echocardiographic finding of a high-velocity tricuspid regurgitant jet, certain presenting symptoms should also trigger evaluation for PH in the alert clinician. Due to their gradually progressive and nonspecific nature, PH symptoms are often misdiagnosed as asthma, cardiac ischemia, or left undiagnosed. However, exertional symptoms such as progressive exertional dyspnea, lightheadedness, syncope, or exertional chest pain should include pulmonary hypertension on their differential diagnosis. The presence of any of risk factors for the PH listed above (eg, exposure to toxins, anorexigens, selective serotonin reuptake inhibitor (SSRIs), diagnosis of systemic sclerosis, cirrhosis, HIV, connective tissue disease (CTD), congenital heart disease, congestive heart failure, COPD, sleep apnea, and pulmonary embolism) should further raise suspicion for PH. In fact, echocardiographic screening for PH in high-risk populations (such as those with a known genetic mutation, a first-degree relative with PAH, systemic sclerosis, the scleroderma (SSc) spectrum of disease, congenital heart disease, CTD, portal hypertension awaiting liver transplant) is advocated in the literature.

■ PHYSICAL EXAMINATION

Examination findings for PH are often subtle. Exertional oxygen desaturation may be the first sign of the diffusion limitation caused by reduction of the pulmonary arterial surface area. A prominent second heart sound is the most sensitive examination finding for PH, present in more than 90% of IPAH patients, but is nonspecific. Other nonspecific findings of PH include those of right heart strain such as right ventricular heave and tricuspid murmur (an increase in tricuspid regurgitation with inspiration is called Carvallo sign), and signs of right heart failure such as elevated jugular venous pressure, peripheral edema, and ascites. Examination should include an evaluation for signs of PH-associated disease with special attention paid to signs and symptoms of systemic sclerosis or Raynaud phenomenon, which are commonly associated with PH.

■ LABORATORY EVALUATION

Laboratory tests may be performed to help classify PH or aid in prognosis. Limited laboratory evaluation of a patient with suspected PH may include arterial blood gas analysis to differentiate an abnormal A-a gradient from chronic hypoventilation, HIV testing, tests of liver

TABLE 237-3 Test Characteristics of Echocardiography for the Diagnosis of Pulmonary Hypertension

Associated Condition	Sensitivity	Specificity
Portal hypertension	97%	77%
Systemic sclerosis	58%-90%	75%-96%
Chronic obstructive pulmonary disease	60%-78%	75%
Pulmonary fibrosis	77%	45%

function (albumin, coagulation), hepatitis serologies, and tests for connective tissue disease (ANA with anti-centromere pattern is associated with PH in limited systemic sclerosis). B-type natriuretic peptides (BNP, pro–NT-BNT) may be elevated in right heart strain of any etiology and BNP may be falsely negative in chronic diastolic CHF. However, in patients with known PH, persistently elevated BNP (> 180 pg/mL) after prostacyclin treatment is associated with poor prognosis, with median survival less than 12 months. The most current treatment guidelines recommend a "normal" BNP level as one potential treatment goal.

■ ECHOCARDIOGRAPHY

Echocardiography allows for the estimation of pulmonary arterial systolic pressure via application of a modified Bernoulli equation to the tricuspid regurgitant jet velocity [4 × (velocity)^2]. It also provides information of left ventricular function, valvular heart disease, intracardiac shunt, and right ventricular function. The ubiquity of echocardiography in the evaluation of patients with dyspnea, syncope or chest discomfort (all symptoms associated with PH), often results in incidental detection of elevated pulmonary pressures. Echocardiography is recommended as the initial screening tool for PH. However, it is important to appreciate its limitations as a diagnostic tool in PH. First, tricuspid regurgitation must be present for echocardiographic estimates of PA systolic pressures, and it is not present in approximately 25% of PH cases. Absence of tricuspid regurgitation does not exclude PH. Second, the test characteristics of echocardiography for the detection of PH range widely, based on the population screened (Table 237-3). In addition, echocardiographic estimates of pulmonary arterial systolic pressure have been shown to be within 10 mm Hg of right heart catheterization measurements only 48% of the time. Therefore, while echocardiography is certainly a valuable tool for the evaluation of subjects with PH, echocardiography can neither accurately rule in or out the diagnosis of PH. Direct measurement of cardiopulmonary parameters by cardiac catheterization must be performed in all patients with a high clinical suspicion of PH.

■ RIGHT HEART CATHETERIZATION

Right heart catheterization is the gold standard for the diagnosis of PH. PH treatment should not be instituted in the absence of RHC since it allows assessment of multiple hemodynamic factors essential in the diagnosis and treatment of PH. Patients with a high clinical suspicion of PH should be referred to a pulmonary or cardiology specialist with PH experience.

Interpretation of right heart catheterization values in the evaluation of pulmonary hypertension

- Right atrial pressure and right ventricular diastolic pressure provide an index of the degree of right heart failure; additionally a RA pressure > 20 mm Hg confers a poor prognosis.
- Filling pattern of the right ventricle provides an index of pericardial constrictive disease that can mimic PH.
- Mean pulmonary arterial pressure is used to diagnose the presence of PH (mean PAP > 25 mm Hg at rest).
- Pulmonary artery diastolic pressure-to-pulmonary artery occlusion pressure gradient is important in the analysis of the contribution of pulmonary venous hypertension (eg, CHF) to pulmonary hypertension. Pulmonary arterial occlusion pressure > 15 mm Hg with pulmonary arterial diastolic pressure-to-pulmonary artery occlusion pressure gradient < 5 mm Hg makes left heart disease the most likely etiology for elevated pulmonary pressures.
- Cardiac index < 2 L/min in pulmonary arterial hypertension is indicative of right heart failure and generally an indication for therapy with prostanoids.
- Vasodilator testing is used to determine the potential for responsiveness to calcium channel blocker therapy; however, vasoreactivity is present in less than 5% of patients with PAH (usually only patients with IPAH or HPAH).

■ ADDITIONAL TESTING

Chest x-ray

Plain chest films may increase the suspicion for PH: a descending branch of the right pulmonary artery > 20 mm is often associated with PH. Chest X-ray adds critical information as to the potential cause of PH. For example, a normal plain film in the setting of elevated pulmonary pressures suggests IPAH or CTEPH, or the presence of reticular opacities suggests PH secondary to interstitial lung disease or connective tissue disease.

Chest CT

Computed tomographic imaging of the chest may add additional information to the chest radiograph. Although a main pulmonary artery diameter > 33 mm may be associated with IPAH, this association does not appear as reliable in subjects with underlying parenchymal lung disease. CT scans are more sensitive than chest radiography in the diagnosis of underlying ILD.

V/Q scan

V/Q scanning has utility in the evaluation of CTEPH, where it has a greater sensitivity for the detection of chronic pulmonary thromboembolic disease than CTPA.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (cMRI) is increasingly being used for the assessment of right heart structure and volumes. In response to chronic PH, the right ventricle hypertrophies and dilates, leading to reduced function and stroke volume. Right ventricular end-diastolic volume index (RVEDVI) <84 mL/m^2, left ventricular end-diastolic volume index >40 mL/m^2, and a stroke volume index >25 mL/m^2 are associated with better survival in patients with IPAH. RVEDVI has been linked to be an independent predictor of mortality; no deaths were reported in patients with RVEDVI <84 mL/m^2. RV mass index <59 g/m^2 was linked to better survival in IPAH, and in patients with suspected scleroderma PAH, the ratio of RV to left ventricular end-diastolic mass >0.7 predicted worse survival. As right heart function is acknowledged as the main determinant of survival in PAH, cMRI may eventually provide consistent and valuable information regarding prognosis; however, further investigation is needed to assess the role of this modality in PH.

Electrocardiogram

ECGs of patients with PH may show signs of right heart strain and hypertrophy. These signs, right axis deviation, large R/S ratio > 1 in V1, R/S ratio < 1 in V5 or V6, P pulmonale, lack both sensitivity and specificity for routine use in diagnosis.

Pulmonary function testing

Pulmonary function testing (PFT) showing an isolated low diffusing capacity of the lung for carbon monoxide without anemia increases the suspicion for pulmonary vascular disease. In patients with known PH, PFTs may help in determining the diagnosis and severity of causes of secondary PH such as COPD and ILD.

Polysomnography

Sleep studies are indicated for the diagnosis and treatment of PH secondary to OSA.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing is valuable in the evaluation of unexplained dyspnea. Subjects with low maximum VO_2, low anaerobic threshold, low oxygen pulse, elevated ventilatory equivalent of CO_2 (VE/VCO_2), a large A-a gradient and increased dead space should undergo further evaluation for PH. This test may not be available in all centers.

Biopsy

Lung biopsy is rarely indicated after a diagnosis of PH has been established; usually only to confirm the suspicion of occult underlying causes such as pulmonary veno-occlusive disease.

TREATMENT

In general, treatment of group II-V disease is directed at the underlying disease pathology that has contributed to pulmonary hypertension (except as noted above for CTEPH).

Treatment goals do not differ for different PAH subgroups. Exceptions contain the limited utility of functional and biomarker goals in SSc-PAH and the importance of hemodynamic goals in patients with PAH related to portal hypertension being studied for liver transplantation.

Treatment of group I pulmonary hypertension is guided by findings on RHC and functional status. Multiple agents now exist in various drug classes for the treatment of group I PAH. The agents, indications, and common side effects are shown in Table 237-4. Below we present a brief discussion of the indications, mechanisms of action, and the major side effects of the currently approved treatments for group I PAH.

■ NITRIC OXIDE

Nitric oxide (NO) is a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle proliferation. Inhaled NO is potentially useful for PAH by controlling RV hypertrophy and augmenting downstream signaling targets, including but not limited to soluble guanylate cyclase and cyclic guanosine monophosphate, to reduce pulmonary vascular remodeling. Different formulations of inhaled NO are currently under investigation for treatment of PAH.

■ CALCIUM CHANNEL BLOCKERS

Dihydropyridine calcium channel blockers are not FDA-approved for use in pulmonary arterial hypertension and have been shown to be useful only in IPAH patients with positive vasoreactivity testing. This group encompasses < 5% of all patients with IPAH.

■ PROSTACYCLINS

Epoprostenol, treprostinil (in various formulations), beraprost and inhaled iloprost comprise the currently approved prostanoid medications for the treatment of PAH. These medications are analogues of prostacyclin, an endogenous vasodilator product of arachidonic acid metabolism in the vascular endothelium. Through stimulation of intracellular cAMP, prostacyclins inhibit smooth muscle proliferation and platelet aggregation. Intravenous epoprostenol is the only agent shown in a randomized controlled trial to confer a mortality benefit in PAH. Because of its short half-life, interruption of epoprostenol infusion may result in acute increases in pulmonary vascular resistance and hemodynamic collapse. For this reason, longer-acting medications such as treprostinil—with a half-life of hours rather than minutes—have been developed. Additionally, treprostinil may be administered subcutaneously, intravenously,

TABLE 237-4 Pulmonary Vasodilators

Pulmonary Vasodilator	NYHA Functional Status Indication	Route	T 1/2	Common Side Effects
Prostacyclins				
• Epoprostenol	II-IV	Intravenous	6 min	Hypotension, jaw/leg pain, flushing, headache, diarrhea, thrombocytopenia
• Treprostinil	II-IV	Intravenous, subcutaneous Inhaled	4 h	In addition to above, local reactions (SQ administration), bacteremia
• Iloprost	II-III	Inhaled	30 min	Bronchospasm, cough, trismus, flushing, hypotension
Endothelin Receptor Antagonists				
• Bosentan	III	Oral	5 h	Liver toxicity, headache, anemia, edema, flushing, hypotension
• Ambrisentan	II-III	Oral	9-15 h	Headache, edema, anemia, liver toxicity
• Macitentan	II-III	Oral	16 h	Headache, anemia, liver toxicity, sperm count decr, bronchitis
Phosphodiesterase-5 inhibitors				
• Sildenafil	II-III	Oral	4 h	Headache, diarrhea, flushing, hypotension, priapism, optic neuropathy
• Tadalafil	II-III	Oral	17.5 h	Same as sildenafil
Soluble guanylate cyclase stimulators				
• Riociguat	II-III	Oral	12 h	Headache, hemorrhage, hemoptysis, diarrhea, hypotension, anemia, vomiting

orally or inhaled. Inhaled iloprost and treprostinil have the theoretical advantage of improved V/Q matching compared with intravenous medications. In general, patients with right heart failure, NYHA functional class IV disease, and cardiac index of < 2 L/min generally require continuous intravenous prostacyclin therapy. Common side effects of the intravenous prostacyclins include thrombocytopenia and bleeding, jaw pain, leg pain, flushing, headache, nausea, and vomiting.

■ ENDOTHELIN-RECEPTOR ANTAGONISTS

Bosentan, ambrisentan, and macitentan represent the currently available endothelin-receptor antagonists in the United States and are widely used due to the ease of oral administration. Endothelin A receptors are located on vascular smooth muscle cells and mediate vasoconstriction and proliferation, while endothelin B receptors, located on endothelium, promote vasodilatation. While, it appears that, in vitro, the effects of endothelin A receptors are of greater importance than endothelin B receptors, in clinical practice, it is not clear that there are substantial differences among the ERAs since they have never been studied against one another. The nonselective endothelin-receptor antagonists bosentan and macitentan, as well as the selective endothelin A-receptor antagonist ambrisentan have all demonstrated ef cacy in the treatment of PAH. Liver toxicity is the most worrisome side effect (8%-12%) of bosentan; as such, liver function tests must be followed monthly. Ambrisentan and macitentan have a much lower incidence of liver toxicity (2%-3%); with these agents, liver function tests are followed as clinically indicated. Other side effects of this class include, nasal stuf ness, and edema. Ambrisentan has much few drug-drug interactions.

■ SOLUBLE GUANYLATE CYCLASE STIMULATORS

sGC stimulators augment cGMP production and are effective additionally in states in which endogenous NO is depleted. Riociguat, the first approved agent in this class, has a dual mechanism, operating in synergy with endogenous NO and also directly stimulating sGC autonomous of NO availability. Riociguat is approved by the FDA for treatment of both PAH and chronic thromboembolic pulmonary hypertension (CTEPH) patients.

■ PHOSPHODIESTERASE INHIBITORS

Sildenafil and tadalafil represent the FDA-approved phosphodiesterase 5 (PDE-5) inhibitors for the treatment of PAH. PDE-5 inhibition results in increased intracellular cGMP, which enhances vasodilatation and has antiproliferative effects. The PDE-5 inhibitors, like the ET antagonists, have been shown to improve 6-minute walk distance and functional status. Side effects include flushing, hypotension, headaches, and epistaxis.

■ ADJUNCTIVE THERAPY

Oxygen, systemic anticoagulation, diuresis, and digoxin represent adjunctive therapies for the long-term management of PAH. Although these therapies are not supported by clinical trials, they are recommended by societal guidelines. Use of anticoagulation has become controversial based on two recent analyses from PAH registries; further guidelines addressing this issue should appear shortly.

■ SURGICAL THERAPY

Prior to the advent of pulmonary vasodilator therapy, lung transplantation was common for patients with severe PAH. Other surgical therapies, including atrial septostomy and surgical or endovascular Potts procedures, may be considered for advanced cases not responsive to maximal medical therapy.

COMMON INPATIENT COMPLICATIONS OF PULMONARY HYPERTENSION

Right heart failure (worsening PAH) and complications of chronic indwelling central venous access are the common issues that arise in the inpatient care of patients with pulmonary hypertension. Triage of patients with right heart failure or complications of central venous access depends of the patient's hemodynamic stability, with hypotensive patients generally requiring ICU-level care, urgent cardiology or pulmonary consultation, and right heart catheterization to acutely assist in the management of pulmonary vasodilator therapy.

■ RIGHT HEART FAILURE

Patients with advanced PAH may present with right heart failure, which may range in severity from asymptomatic volume overload to shock. Unlike a right ventricular myocardial infarction, which often responds well to volume loading, the decompensated right ventricle generally responds poorly to volume loading. This is due to "ventricular interdependence." The right and left ventricle share the intraventricular septum, thus right ventricular pressure overload can cause the septum to shift into the left ventricle, decreasing left ventricle filling and cardiac output. Therefore, cardiogenic shock in the patient with PH and right ventricular failure is generally managed in the intensive care unit with potent pulmonary vasodilators (eg, intravenous epoprostenol, inhaled nitric oxide), diuresis, and, if necessary, inotropic, vasopressor, renal replacement support, and increasingly extracorporeal membrane oxygenation (ECMO) . Caution must be taken with the use of positive pressure ventilation and its acute reduction in preload, which may precipitate cardiovascular collapse in PH.

■ COMPLICATIONS OF CENTRAL VENOUS ACCESS

Patients with continuous infusions of prostacyclins often present with complications of central venous access. These include loss of access (causing acute discontinuation of pulmonary vasodilators), central line puncture (and risk of air embolism), and central line infection. Loss of venous access should be considered an emergency situation, due to risk of acute increases in pulmonary vascular resistance and cardiovascular collapse. Attempts must be made to gain venous access immediately; in this case, peripheral intravenous access can be used emergently, with transition to central venous access after stabilization.

Central line puncture is also managed by quickly establishing alternative venous access, clamping the indwelling line proximal to the puncture, and starting the prostacyclin infusion through the new catheter. Often, the indwelling central line may be repaired by experienced nursing personnel.

Central line infection and bacteremia occur at a rate of approximately one case every 5 years in patients receiving intravenous prostanoids. This rate appears to be lower than reports of indwelling catheters for other conditions. However, treprostinil is associated with approximately twice the risk of bloodstream infections as epoprostenol (although this risk has decreased dramatically with the use of epoprostenol diluent for treprostinil infusions). It is important to note that bacteremia associated with treprostinil is most often caused by Gram-negative organisms, unlike other line infections, and initial antibiotic coverage for Gram-positive and negative organisms, including Pseudomonas species, is necessary in these patients. Consultation of a surgical specialist for removal of tunneled venous lines is generally required only for staphylococcal infections or recurrent bacteremia.

- Central line infections associated with continuous treprostinil infusion are most commonly caused by Gram-negative organisms, including Pseudomonas species.

DISCHARGE PLANNING AND QUALITY IMPROVEMENT STRATEGIES

The involvement of outpatient specialized nursing services who provide ongoing education, central venous line care, and emotional support is critical to the care of patients with advanced pulmonary arterial hypertension. These nurses, along with the pulmonary hypertension specialist, should be involved in discharge planning for all PH patients with continuous intravenous infusions. As in all patients with high risk for right heart failure, daily weight assessment and plans for excessive fluid accumulation are helpful in avoiding readmission.

CONCLUSION

Pulmonary hypertension represents a broad spectrum of diseases which result in elevation of pulmonary arterial pressures. An understanding of the pathophysiologic mechanisms involved with this array of conditions is necessary for the successful care of patients with PH.

SUGGESTED READINGS

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