Chapter 12: Pulmonary Hypertension

12.1: Pulmonary Hypertension

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Learner Objectives

Upon completion of this module, the reader will be able to:
1. Summarize the current classification of pulmonary hypertension (PH).
2. Utilize the comprehensive diagnostic algorithm for a patient with suspected pulmonary arterial hypertension (PAH).
3. Discuss the current practice guidelines for the management of PAH.
4. Identify important predictors of survival and treatment goals for patients with PAH.

Introduction

PH is a complex disorder requiring a multidisciplinary approach. The term “pulmonary hypertension” refers to the presence of a high pulmonary vascular pressure and may be the end result of a variety of underlying disorders. By definition, PH is a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg. The definition of normal versus abnormal is based on several factors:

- The population mean resting mPAP is approximately 14 mm Hg, and 20 mm Hg encompasses two standard deviations above the mean.
- A value of 25 mm Hg is therefore definitively above the normal distribution of values.
- The value of 25 mm Hg has, by consensus, been used to identify candidates for participation in clinical trials and registries.

The definition for Group One, or PAH, also requires that left heart filling pressures (pulmonary capillary wedge pressure, left ventricular end-diastolic pressure [LVEDP], or left atrial pressure) be ≤15 mm Hg. Some definitions of PAH require that the calculated pulmonary vascular resistance (PVR) be ≥3 Wood units.2

Classification of Pulmonary Hypertension

The clinical classification of PH was revised most recently in 2008 at the Fourth World Symposium on Pulmonary Hypertension held in Dana Point, CA, and is depicted in Tables 1a and b.

Group One: Pulmonary Arterial Hypertension

Changes in classification have been made to reflect the evolving understanding of the clinical and pathologic manifestations of PAH. Notably, PAH should not be considered a disease itself, but it is one measurable sign (elevated pulmonary arterial blood pressure) of an underlying pulmonary vasculopathy for which the clinical context must be appropriately diagnosed. Clinical experience and analysis of formal disease registry databases make it increasingly clear that those diseases that are grouped together within Group One PAH (e.g., congenital heart disease [CHD], connective tissue disease [CTD]), have very different demographics, manifestations, and outcomes. The prevalence of Group One PAH is in the range of 15 to 50 cases per million.

Idiopathic Pulmonary Arterial Hypertension

Formerly referred to as primary pulmonary hypertension (PPH), idiopathic PAH (IPAH) is a rare disease of unknown etiology and is the most common type of Group One PAH in current registries. There is a female preponderance (2:1 in the National Institutes of Health [NIH] registry, 4:1 in the current REVEAL [Registry to Evaluate Early and Long-Term PAH Disease Management]). Although the mean age at diagnosis was 37 years in the NIH registry and about 50 years in more recent registries, IPAH can affect children and adults into their 70s.

Heritable Pulmonary Arterial Hypertension

Hereditary transmission of PAH has been reported in approximately 6-10% of patients with PAH. The most common mutation is that of the bone morphogenetic protein receptor type II (BMPR-II) gene, a member of the transforming growth factor-beta family. This mutation is characterized by incomplete penetrance and genetic anticipation. A second, less common mutation involves activin receptor-like kinase type 1; these patients often have coexistent hereditary hemorrhagic telangiectasia. Approximately 11-40% of patients thought to have IPAH without a family history are found to have BMPR-II mutations.

Drug- and Toxin-Induced Pulmonary Arterial Hypertension

An association between anorexigens (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) and PAH was initially observed in the 1960s when an epidemic of IPAH (then termed PPH) was noted in Europe after the introduction of aminorex fumarate. Structurally related compounds such as fenfluramine and dexfenfluramine were also demonstrated to be associated with the development of PAH in the 1980s and 1990s and have since been withdrawn from the market. Epidemiologic studies also have linked the development of PAH to rapeseed oil, L-tryptophan, and illicit drugs such as methamphetamine.

Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

The prevalence of PAH is greatest in those with the scleroderma spectrum of diseases, although PAH can occur in the setting of...
any of the CTDs. Two recent prospective studies, using echocardiography as a screening tool but requiring hemodynamic confirmation with right heart catheterization (RHC), found the prevalence of PAH in the scleroderma population to be approximately 8-12%. The high prevalence of PAH in patients with scleroderma serves as an opportunity for screening a high-risk group and instituting early therapy in those diagnosed with PAH. Currently, echocardiography is the most common screening tool; however, studies are underway to refine the screening process in this high-risk group. Patients with the scleroderma spectrum of disease may also be at higher risk for other types of PH, including diastolic dysfunction and hypoxemic lung disease.

**Pulmonary Arterial Hypertension Associated With Human Immunodeficiency Virus Infection**

PAH is a rare but well-established complication of human immunodeficiency virus (HIV) infection. Population studies of individuals infected with HIV suggest that the incidence of PAH is approximately 0.5% and is independent of the CD4 count or previous opportunistic infections. The mechanism is unknown, but the hemodynamics and clinical course are similar to those of IPAH. Routine screening for PAH in HIV is not recommended because of the relatively low prevalence in HIV patients. However, PAH should be considered in patients with HIV infection who have symptoms of dyspnea in whom another etiology cannot be found.

**Pulmonary Arterial Hypertension Associated With Portal Hypertension**

The development of PAH in association with elevated pressures in the portal circulation is known as portopulmonary hypertension. Portal hypertension, and not the underlying liver disease, is the risk factor. Hemodynamic studies have estimated the prevalence of PAH in these individuals at 2-6%, although the
Pulmonary Arterial Hypertension Associated With Congenital Heart Disease
PAH is a well-recognized complication of uncorrected increased pulmonary blood flow associated with congenital systemic-to-pulmonary shunts. Eisenmenger syndrome is defined as CHD with an initial large systemic-to-pulmonary shunt that induces progressive pulmonary vasculopathy with PAH and subsequent reversal of the shunt and central cyanosis. Eisenmenger syndrome occurs more frequently when blood flow is extremely high and the shunt exposes the pulmonary vasculature to systemic level pressures, such as occurs with a ventricular septal defect, patent ductus arteriosus, or truncus arteriosus (post-tricuspid valve shunts). However, PAH also may occur with low pressure-high flow abnormalities, such as with an atrial septal defect and can manifest years after closure, particularly if closure was late.

Pulmonary Arterial Hypertension Associated With Schistosomiasis
PH associated with schistosomiasis is diagnosed most commonly in endemic areas of South America and sub-Saharan Africa. Recent publications suggest that PH associated with schistosomiasis has clinical and histologic features similar to those of IPAH.

Pulmonary Arterial Hypertension Associated With Chronic Hemolytic Anemia
In relation to the chronic hemolytic anemias, PAH has been described most frequently in association with sickle cell disease (SCD). This population is also at risk for a number of other comorbidities that might contribute to the development of PH, including high cardiac output, thromboembolic disease, and restrictive lung disease.

Pulmonary Veno-Occlusive Disease and Pulmonary Capillary Hemangiomatosis
In rare instances, the typical histologic findings of PAH are associated with an occlusive venopathy (pulmonary veno-occlusive disease [PVOD]) or a microvasculopathy (pulmonary capillary hemangiomatosis [PCH]). In addition to the histology of PAH, these entities also exhibit the findings of pulmonary venous hypertension, including pulmonary hemosiderosis, interstitial edema, and lymphatic dilatation. Although the clinical presentation is usually indistinguishable from PAH, the rapid development of pulmonary edema after the administration of PAH-specific therapy is often a clue to the appropriate diagnosis because an increase in the pulmonary arterial flow has literally nowhere to go and results in alveolar edema.

Group Two: Pulmonary Hypertension Owing to Left Heart Disease
Left heart disease probably represents the most frequent cause of PH. Left-sided ventricular or valvular dysfunction may lead to chronic left atrial hypertension, with passive backward transmission of this pressure to the pulmonary vasculature leading to PH. Most commonly, the transpulmonary gradient is normal (<12 mm Hg), and the PVR is normal or near normal (<3 Wood units). Treatment should be directed to the underlying left heart disease.

On occasion, patients with longstanding elevated left heart filling pressures develop disproportionate PH, with elevated transpulmonary gradient and PVR, perhaps as a result of a reactive pulmonary vasculopathy. The efficacy and safety of PAH-specific therapies have not been studied adequately in this population.

Group Three: Pulmonary Hypertension Owing to Lung Diseases and/or Hypoxia
Mild PH often develops as a result of chronic alveolar hypoxia due to parenchymal lung disease, impaired control of breathing, or residence at high altitude. In such patients, the mPAP is often in the range of 25-35 mm Hg. A subgroup of patients with parenchymal lung diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis develop more severe PH with hemodynamic findings comparable to those of patients IPAH. As in PH owing to left heart disease, the efficacy and safety of PAH-specific therapy has not been studied adequately in this population.

Group Four: Chronic Thromboembolic Pulmonary Hypertension
While the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) is not known, approximately 4% of those who have suffered an acute pulmonary embolism will go on to develop CTEPH. On the other hand, approximately one half of those ultimately diagnosed with CTEPH do not have a history of an acute pulmonary embolism. The complexity of accurate diagnosis (including determination of surgical accessibility) and the difficulty of surgery require that patients suspected to have CTEPH be referred to a specialized center. Surgical candidacy depends on several factors including the location of the obstruction (proximal vs. distal), correlation of the hemodynamic impairment with the degree of obstruction on angiography, comorbidities, willingness of the patient, and experience of the surgeon.

Group Five: Pulmonary Hypertension With Unclear or Multifactorial Mechanisms
Group Five consists of several forms of PH for which the mechanism is either unclear or multifactorial. Included in this category are hematologic diseases (e.g., chronic myeloproliferative disorders), systemic diseases (e.g., sarcoidosis, histiocytosis X), metabolic disorders (glycogen storage disease, Gaucher disease), and other miscellaneous disorders.

Pathology & Pathophysiology of Pulmonary Arterial Hypertension
PAH is a syndrome resulting from restricted blood flow through the pulmonary circulation. PAH is a panvasculopathy predominantly affecting small pulmonary arteries and is characterized by intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation, and plexi-
form arteriopathy. An individual patient may manifest any or all of these lesions, and the distribution may be diffuse or focal. The PAH “phenotype” is characterized by endothelial dysfunction, a decreased ratio of apoptosis/proliferation in pulmonary artery smooth muscle cells, and a thickened, disordered adventitia in which there is excessive activation of adventitial metalloproteases. As with cancer and atherosclerosis, the “multiple-hit” theory has been generated to explain the pathobiologic progression of the disease.

The PAH endothelium is characterized by increased production of vasoconstrictor/mitogenic compounds, such as endothelin and thromboxane, and reduced production of vasodilators such as prostacyclin and nitric oxide. This imbalance favors vasoconstriction and signals smooth muscle cell activation, hyperplasia and hypertrophy, inhibition of apoptosis, fibroblast proliferation, collagen deposition, activation of proinflammatory cytokines, and angiogenesis. Other pathways that contribute to the pathogenesis of PAH are subjects of ongoing investigation.

The ability of the right ventricle (RV) to cope with increased PVR is a major determinant of functional capacity and prognosis in PAH. The RV initially responds to the increased afterload with myocardial hypertrophy. This adaptive response varies among individuals, with some compensating and others deteriorating, as manifested by RV dilatation and reduced ejection fraction, ultimately leading to RV failure and death.

**Clinical Diagnosis of Pulmonary Hypertension**

Given the multiple potential etiologies and contributing factors to the presence of PH, a methodical and extensive evaluation is warranted in most patients with common symptoms in whom this diagnosis is considered. Figure 1 illustrates the diagnostic algorithm.

**Symptoms**

The most common presenting symptoms of PH include exertional dyspnea/reduced exercise tolerance, chest pain, fatigue, and lightheadedness. Manifestations of more advanced disease include syncope and abdominal distension and lower extremity edema attributable to RV failure. The presence of risk factors for the development of PAH (e.g., CTD, family history, CHD, appetite suppressant use) should heighten awareness of the disorder.

In the NIH registry, the average time from onset of symptoms to diagnosis was two years. Unfortunately, current registries suggest that delay in diagnosis persists. In the REVEAL Registry, 21.1% of patients experienced symptoms for more than two years before PAH was recognized. Delay in diagnosis was most frequently observed in patients whose symptoms occurred at a younger age (before 36 years of age) and in those with COPD or obstructive sleep apnea. It appears that young people in whom cardiopulmonary disease is considered less likely to be present, or patients thought to have an alternative explanation for symptoms, are most at risk for delayed diagnosis.

**Signs**

The physical examination findings can be subtle or nonspecific, but certain findings should raise suspicion of PAH.

Physical examination features pertinent to the evaluation of PH are described in Tables 2a and b.

An accentuated pulmonic component of the second heart sound is present in the majority of patients with PAH due to the high pulmonary pressures resulting in more forceful closure of the pulmonic valve. At times, a loud P2 may be palpable along the left sternal border. P2 is not normally audible at the apical point of maximal impulse. If a split S2 is audible at the apex, then P2 must be accentuated, and the possibility of PAH should be further investigated. Physical examination findings are helpful to gauge the severity of PAH and to detect associated disorders, as summarized in Tables 2a and b.

**Clinical Evaluation**

**Electrocardiogram**

Although the electrocardiogram is neither sensitive nor specific for PAH, it is an inexpensive, noninvasive test that can provide valuable information. Common electrocardiographic findings include right atrial enlargement, right axis deviation, and RV enlargement, often with a strain pattern (Figure 2).

**Chest X-Ray**

Findings on chest X-ray that suggest the presence of PH include enlarged main and hilar pulmonary artery shadows with “pruning” or attenuation of the peripheral vasculature and RV enlargement, which is best appreciated on the lateral view (Figure 3). Other findings on chest X-ray may suggest an associated diagnosis, such as hyperinflation with flat diaphragm (COPD) or pulmonary venous congestion (left heart disease).

**Echocardiography**

If PH is suspected based on the history, risk factor assessment, and physical examination, the echocardiogram is the next appropriate study. Echocardiography also serves as the most useful noninvasive screening test for PH in at-risk populations (e.g., scleroderma, CHD). The Doppler echo can simultaneously provide an estimate of the RV systolic pressure, identify functional and morphologic sequelae of PH, and give clues to other potential cardiac etiologies of PH. Common echocardiographic features of PAH include the following:

- Right atrial enlargement
- RV enlargement and dysfunction
- Small, underfilled left heart chambers
- Interventricular septal flattening
- Tricuspid regurgitation with elevated tricuspid regurgitant velocity
- Reduced tricuspid annular plane systolic excursion

A saline contrast injection can verify an intracardiac right-to-left shunt. One must acknowledge the limitations of the estimated RV systolic pressure, as there are multiple potential sources of error in this measurement. In any patient, the estimated RV systolic pressure must be put into context with the patient’s
Figure 1
Diagnostic Approach to Pulmonary Arterial Hypertension

General guidelines for the evaluation of pulmonary hypertension (PH). Since the suspicion of PH may arise in various ways, the sequence of tests may vary. However, the diagnosis of PAH requires that certain data support a specific diagnosis. In addition, the diagnosis of IPAH is one of excluding all other reasonable possibilities. Pivotal tests are those that are essential to establishing a diagnosis of any type of PAH either by identification of criteria of associated disease or exclusion of diagnoses other than IPAH. All pivotal tests are required for a definitive diagnosis and baseline characterization. An abnormality of one assessment (such as obstructive pulmonary disease on PFTs), does not preclude that another abnormality (chronic thromboembolic disease on VQ scan and pulmonary angiogram) is contributing or predominant. Contingent tests are recommended to elucidate or confirm results of the pivotal tests, and need only be performed in the appropriate clinical context. The combination of pivotal and appropriate contingent tests contributes to assessment of the differential diagnoses in the right-hand column. It should be recognized that definitive diagnosis might require additional specific evaluations not necessarily included in this general guideline.

6 MWT = 6-minute walk test; ABGs = arterial blood gases; ANA = antinuclear antibody serology; CHD = congenital heart disease; CPET = cardiopulmonary exercise test; CT = computed tomography; CTD = connective tissue disease; CXR = chest X-ray; ECG = electrocardiogram; HIV = human immunodeficiency virus screening; HTN = hypertension; IPAH = idiopathic pulmonary arterial hypertension; LFT = liver function test; PE = pulmonary embolism; PFT = pulmonary function test; PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; RA = rheumatoid arthritis; RAE = right atrial enlargement; RHC = right heart catheterization; RVE = right ventricular enlargement; RVSP = right ventricular systolic pressure; SLE = systemic lupus erythematosus; TEE = transesophageal echocardiography; VHD = valvular heart disease; VQ scan = ventilation-perfusion scintigram.

Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension (1 of 2)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accented pulmonary component of S₂ (audible in &gt;90%)</td>
<td>High pulmonary pressure increases force of pulmonic valve closure</td>
</tr>
<tr>
<td>Early-systolic click</td>
<td>Sudden interruption of opening of pulmonary valve into high-pressure artery</td>
</tr>
<tr>
<td>Midsystolic ejection murmur</td>
<td>Turbulent transvalvular pulmonary outflow</td>
</tr>
<tr>
<td>Left parasternal lift</td>
<td>High right ventricular pressure and hypertrophy present</td>
</tr>
<tr>
<td>Right ventricular S₄ (in 38%)</td>
<td>High right ventricular pressure and hypertrophy present</td>
</tr>
<tr>
<td>Increased jugular “a” wave</td>
<td>Poor right ventricular compliance</td>
</tr>
</tbody>
</table>

Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension (2 of 2)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central cyanosis</td>
<td>Abnormal V/Q, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt</td>
</tr>
<tr>
<td>Clubbing</td>
<td>Coronary heart disease, pulmonary venopathy</td>
</tr>
<tr>
<td>Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop</td>
<td>Congenital or acquired heart or valvular disease</td>
</tr>
<tr>
<td>Rales, dullness, or decreased breath sounds</td>
<td>Pulmonary congestion or effusion or both</td>
</tr>
<tr>
<td>Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough</td>
<td>Pulmonary parenchymal disease</td>
</tr>
<tr>
<td>Obesity, kyphoscoliosis, enlarged tonsils</td>
<td>Possible substrate for disordered ventilation</td>
</tr>
<tr>
<td>Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash</td>
<td>Connective tissue disorder</td>
</tr>
<tr>
<td>Peripheral venous insufficiency or obstruction</td>
<td>Possible venous thrombosis</td>
</tr>
<tr>
<td>Venous stasis ulcers</td>
<td>Possible sickle cell disease</td>
</tr>
<tr>
<td>Pulmonary vascular bruits</td>
<td>Chronic thromboembolic PH</td>
</tr>
<tr>
<td>Splenomegaly, spider angioma, palmary erythema, icterus, caput medusa, ascites</td>
<td>Portal hypertension</td>
</tr>
</tbody>
</table>

Table 2a
Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension

PH = pulmonary hypertension.


Table 2b
Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension

PH = pulmonary hypertension.


symptoms, prior medical history, and other findings on the two-dimensional echocardiogram. In the absence of other potential etiologies of PH, such as left heart disease or hypoxic lung disease, an estimated RV systolic pressure >40 mm Hg generally warrants further evaluation in patients with unexplained dyspnea. Other echocardiographic findings that warrant further evaluation include right atrial and RV enlargement, and abnor-

valvular heart disease are easily assessed on echocardiogram. The presence of left atrial enlargement suggests chronically elevated left heart filling pressures.

In some instances, particularly in the assessment of CHD, transesophageal echocardiogram provides additional information. The role of exercise echocardiography is controversial at this time.

The most important echocardiographic prognostic indicators for PAH include the presence of a pericardial effusion and the severity of RV dysfunction. Estimated RV systolic pressure is less meaningful prognostically; in fact, this value may decrease as...
the disease progresses and the RV becomes more dysfunctional.

Ventilation Perfusion Scan
Patients with unexplained dyspnea and PH should be evaluated for CTEPH. The ventilation perfusion scan is considered the most sensitive study for this purpose. If one has a normal or very low probability ventilation perfusion scan, CTEPH can be excluded. Many patients with PAH have slightly heterogeneous perfusion but not segmental or larger defects.

Although spiral computed tomography is an excellent study to evaluate for acute pulmonary embolism, this modality may miss surgically accessible CTEPH.

If there is a concern of CTEPH after noninvasive imaging, one should proceed to pulmonary angiography. Pulmonary angiography must be performed with caution in patients with advanced hemodynamics. The use of nonionic and low-osmotic contrast using the slowest flow rate and the smallest volume possible is essential. Findings of CTEPH on pulmonary angiography include irregular outlines of contrast-filled arterial contours, pouches, webs, bands, and complete vascular occlusion.

Pulmonary Function Tests
Pulmonary function tests are useful to assess for obstructive or restrictive lung disease. If these disorders need further evaluation, an arterial blood gas or high-resolution computed tomography study might be appropriate. Patients with Group One PAH may have modest restriction and a mildly reduced diffusing capacity of carbon monoxide. A declining reduced diffusing capacity of carbon monoxide in a patient with scleroderma might precede the development of PAH.

Overnight Oximetry
In addition to the patient history, overnight oximetry may help identify patients with obstructive sleep apnea. Formal polysomnography may be indicated in patients with significant nocturnal desaturation. Obstructive sleep apnea may cause modest PH, mediated in part by hypoxic vasoconstriction.

Significant PAH (mPAP ≥35 mm Hg) is rarely attributable to sleep disordered breathing; however, untreated obstructive sleep apnea will limit the effectiveness of other treatment approaches and, therefore, should be conscientiously investigated and managed in all patients with PAH.

Laboratory Studies
Given the epidemiologic associations, laboratory studies to screen for CTDs, HIV, and liver disease are included in the diagnostic evaluation.

Functional Assessment
The six-minute walk test (6MWT) is an important functional test to quantify exercise ability. Despite its technical inelegance and limitations, the 6MWT, when performed appropriately in a standardized fashion, has proven to be a useful prognostic predictor and an important parameter to include in the clinical assessment of disease progression and treatment effect. The 6MWT has been the primary endpoint of nearly every clinical trial in PAH to date.

Cardiopulmonary exercise testing offers a more sophisticated means of assessing exercise capacity and gas exchange. Poor
prognostic indicators during cardiopulmonary exercise testing include peak systolic blood pressure of <120 mm Hg and peak oxygen uptake <10.4 mL/kg/min.

**Right Heart Catheterization**

Invasive hemodynamic assessment by RHC is pivotal in the evaluation of any patient with suspected PAH. RHC is typically performed after noninvasive testing for PH, as described previously. Some patients initially suspected of having PAH will not require RHC if an alternative diagnosis is established by noninvasive testing. However, all patients who are thought to have PAH after noninvasive evaluation should undergo RHC before the initiation of therapy. The utility of RHC depends on the accuracy and completeness of the data obtained. Essential measurements during RHC include the following:

- Oxygen saturations
  - Superior vena cava (SVC)
  - Inferior vena cava (IVC)
  - Pulmonary artery (PA)
  - Systemic arterial saturation, SA
- Right atrial pressure
- RV pressure
- Pulmonary artery pressure
- Left heart filling pressure (wedge pressure, left atrial pressure), cardiac output/cardiac index
- Pulmonary vascular resistance
- Systemic blood pressure
- Heart rate
- Response to acute vasodilators

Misinterpretation of the wedge pressure is a common pitfall in the invasive diagnosis of PH. The wedge pressure should be measured at end-expiration and in several different segments of the pulmonary vasculature. The LVEDP via left heart catheterization should be obtained if there is any doubt about the accuracy of the wedge pressure tracing or if the results are unexpected in a given patient. A fluid challenge may be necessary to elicit the presence of diastolic dysfunction.

Acute vasodilator testing should be performed in most patients with IPAH. Exceptions include patients who would not be candidates for long-term calcium channel blocker therapy, such as those patients with hemodynamic instability of overt right heart failure. Responders are rare among patients with associated PAH. The most common agents used for acute vasodilator testing are inhaled nitric oxide, intravenous (IV) epoprostenol, and IV adenosine. A positive acute response is defined as a decrease in mPAP by at least 10 mm Hg to an absolute mPAP of <40 mm Hg in the setting of an unchanged or increased cardiac output. Treatment of PAH has evolved considerably over the past decade, due in part to advances in knowledge of the disease and the availability of agents that target known derangements in the pathobiologic process. Numerous treatment algorithms have been published in recent years. The algorithm from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2009 Expert Consensus Document on Pulmonary Hypertension is reproduced in Figure 4. Treatment decisions are often made with the severity of illness in mind. Table 3 reviews factors that are known to influence the prognosis of patients with PAH. Current treatment goals include improvement of symptoms, exercise tolerance, RV function, and hemodynamics. Although clinicians strive to improve survival, clinical trials in PAH are often of insufficient size and duration to demonstrate a survival benefit. However, a recent meta-analysis of currently approved therapies suggested durable effects on outcomes.7

**General Measures**

Basic counseling and disease state education are important components in the care of PAH patients. Low-level, graded aerobic exercise, such as walking, is recommended. The benefits of intensive pulmonary rehabilitation have been demonstrated.8 Patients are advised against heavy physical exertion and isometric exercise, as these activities may evoke exertional syncope. Oxygen supplementation to keep saturation above 92% at rest and with exertion, sleep, or altitude is advisable. This may not be possible in patients with intracardiac shunting (including a PFO). A sodium-restricted diet (<2400 mg) is advised and is particularly important to manage volume status in those with RV failure. Routine immunizations, such as those against influenza and pneumococcal pneumonia, are advised.

The hemodynamic fluctuations of pregnancy, labor, delivery, and the postpartum period are potentially life-threatening in patients with PAH, with a maternal mortality rate of 30-50%.9 Current evidence-based clinical practice guidelines on medical therapy for pulmonary arterial hypertension recommend that pregnancy be avoided or terminated early in women with PAH.10 It is important to discuss effective methods of birth control with women of child-bearing potential diagnosed with PAH.

**Background Therapy**

Despite a paucity of data, diuretics and anticoagulants are often appropriate therapies in PAH patients. Anticoagulants have been studied in three uncontrolled observational series, one prospective and two retrospective, primarily in IPAH patients.11-13 An improvement in survival was observed in all three. Most guidelines recommend warfarin anticoagulation titrated to an INR of 1.5-2.5 in patients with IPAH. There is scant evidence on anticoagulation in patients with other forms of PAH; however, most experts recommend warfarin anticoagulation in those with more advanced disease (e.g., those on continuous IV therapy) in the absence of contraindications. Diuretics are indicated to manage RV volume overload. Occasionally, IV diuretics are required. Serum electrolytes and renal function should be monitored closely. Data are scarce regarding treatment with digoxin, although this agent is sometimes used in patients with right heart failure and a low cardiac output and in those with atrial arrhythmias.
Calcium Channel Blockers

Calcium channel blockers can be very effective therapies for those few patients with a very robust positive response to acute vaso-dilator testing, as discussed previously. Patients who meet these criteria may be treated with calcium channel blockers and should be monitored closely for both safety and efficacy of therapy. In patients who meet the definition of an acute positive response but do not improve to World Health Organization (WHO) functional class I or II while on calcium channel blockers, the patient should not be considered a chronic responder and an alternative PAH-specific therapy should be prescribed. Very few patients (<7%) with IPAH do well on calcium channel blockers over the long term. Long-acting nifedipine, diltiazem, or amlodipine are the most commonly used agents. Due to its potential for negative inotropic effects, verapamil should be avoided.

Prostanoids

Prostacyclin synthase is reduced in PAH, resulting in inadequate production of prostacyclin I2, a vasodilator with antiproliferative effects. Administering prostanoids has been a mainstay of PAH therapy for nearly two decades. A number of prostanoids are commercially available: epoprostenol (continuous IV), treprostinil (continuous subcutaneous, continuous IV, intermittent inhaled) and iloprost (intermittent inhaled). Prostanoids are complex therapies and are best administered by a center with expertise in the complicated delivery systems and long-term management of the adverse effects and dosing.

Epoprostenol was the first therapy approved by the Food and Drug Administration (FDA) for the indication of what was then termed PPH. Randomized, controlled clinical trials in PPH (now termed IPAH) demonstrated improvements in exercise tolerance as measured by the 6MWT, hemodynamics, quality of life, and survival over a 12-week period.14 Long-term observational series have also suggested improved survival with IV epoprostenol.15,16 In addition, IV epoprostenol has been evaluated in PAH related to the scleroderma spectrum of diseases. A 12-week randomized, controlled clinical trial in this population demonstrated improvements in 6MWT and hemodynamics.17 Observational series have also reported favorable effects of IV epoprostenol in patients with numerous forms of associated PAH.

Epoprostenol must be delivered by continuous IV infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. A thermostable formulation of epoprostenol, which does not require ice packs and can be mixed on a less frequent basis, was approved more recently. IV epoprostenol is commonly started in the hospital at a dose of 2 ng/kg/min and uptitrated based on symptoms of PAH and adverse effects of therapy.

Although dosing is highly individualized, the optimal dose for most adult patients tends to be in the range of 25-40 ng/kg/min. Common adverse effects include jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening.

Treprostinil is a prostanooid that is currently approved as a continuous subcutaneous infusion, continuous IV infusion, or an intermittent inhaled treatment. Treprostinil was first studied as a subcuta-
Background therapies include warfarin anticoagulation, which is recommended in all patients with IPAH without contraindication. Diuretics are used for management of right heart failure. Oxygen is recommended to maintain oxygen saturation >90%.

* Acute vasodilator testing should be performed in all IPAH patients who may be potential candidates for long-term therapy with calcium channel blockers (CCB). Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs, thus, the value of acute vasodilator testing in such patients should be individualized. IPAH patients in whom CCB therapy would not be considered, such as those with right heart failure or hemodynamic instability, should not undergo acute vasodilator testing.

* CCBs are indicated only for patients who have a positive acute vasodilator response and such patients need to be monitored closely for both safety and efficacy.

* For patients who did not have a positive acute vasodilatory testing and are considered lower risk based on clinical assessment (Table 3), oral therapy with ERA or PDE-5I would be first line of therapy recommended. If an oral regimen is not appropriate, other treatments should be considered based on patient’s profile and safety profile of each therapy.

* For patients who are considered high risk based on clinical assessment (Table 3), continuous treatment with intravenous prostacyclin (epoprostenol or treprostinil) would be the recommended first line of therapy. If a patient is not a candidate for continuous intravenous treatment, other therapies should be considered based on patient’s profile and safety profile of each treatment. Epoprostenol improves exercise capacity, hemodynamics, and survival in IPAH, and is the preferred treatment option for the most critically ill patients. Although epoprostenol is expensive and difficult to administer, this agent is the only therapy for PAH that has been shown to prolong survival. Treprostinil may be delivered via either continuous intravenous or subcutaneous infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device six times daily. The endothelin receptor antagonists are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored monthly for an indefinite period. Phosphodiesterase inhibitors also improve exercise capacity. Combination therapy should be considered when patients do not respond adequately to initial monotherapy (see Table 4).

* Timing for lung transplantation and/or atrial septostomy is challenging and is reserved for patients who progress despite optimal medical treatment.

neous infusion in a placebo-controlled, multicenter, randomized trial of 470 patients over 12 weeks. There was an improvement in 6MWT of 16 m, although this improvement was noted to be dose related. Adverse effects included pain and erythema at the site of the subcutaneous infusion in 85% of patients. Other common adverse effects included headache, diarrhea, rash, and nausea. Based on bioequivalence data, treprostinil is also FDA approved to be delivered on a continuous IV basis. Most recently, treprostinil has been approved for intermittent inhaled use. In a multicenter, randomized, placebo-controlled study of 235 patients with PAH who were still symptomatic despite therapy with either oral bosentan or sildenafil, the addition of inhaled treprostinil resulted in an improvement in the primary endpoint of 6 MWT. Common adverse effects included cough, headache, nausea, dizziness, and flushing.

Iloprost is an inhaled prostanoid that was studied in a 12-week, multicenter, randomized, placebo-controlled trial of 207 patients. This study demonstrated an improvement in a novel composite endpoint that included an improvement by at least one level of functional class, improvement in 6MWT by at least 10%, and the absence of clinical deterioration. Inhaled iloprost has also been studied in combination with bosentan in a multicenter, randomized, placebo-controlled trial. After 12 weeks, there were improvements in functional class and time to clinical worsening. The combination appeared to be safe. Common adverse effects of inhaled iloprost include cough, headache, flushing, and jaw pain.

**Endothelin Receptor Antagonists**

Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen that contributes to the pathogenesis of PAH. Two endothelin receptor antagonists, bosentan and ambrisentan, are currently available for the treatment of PAH.

Bosentan has been studied in multiple placebo-controlled trials in PAH. The initial multicenter, randomized, placebo-controlled trial in 32 patients with functional class III or IV PAH demonstrated improvements in six-minute walk distance (6MWD) and hemodynamics over a 12-week period. BREATH-E (Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Hypertension), a multicenter, randomized, placebo-controlled trial of 213 functional class III and IV PAH patients demonstrated an improvement in 6MWT and the composite endpoint of time to clinical worsening over 16 weeks.

More recently, bosentan has been evaluated in functional class II patients in a six-month multicenter, randomized, placebo-controlled trial. This study demonstrated an improvement in PVR and time to clinical worsening. The improvement in 6MWT was not statistically significant. Bosentan has been studied specifically in patients with congenital systemic to pulmonary shunts and Eisenmenger physiology. In this population, improvements in PVR, mPAP, and 6MWT were noted, and bosentan did not worsen oxygen saturation. Bosentan is currently used widely in patients with PAH. Close monitoring of both efficacy and safety is encouraged. The FDA requires that liver function tests be checked on a monthly basis and an algorithm for managing elevated liver function tests is available in the package insert. Other adverse effects include headache, anemia, and edema.

Ambrisentan has been studied in two phase III multicenter, randomized, placebo-controlled trials in 394 PAH patients and demonstrated an improvement in 6MWT and time to clinical worsening. The FDA no longer requires monthly liver function test monitoring in patients on ambrisentan, although many experts continue to check liver function tests periodically. Other adverse effects of ambrisentan include headache and lower extremity edema, which is more common in the population older than 65 years of age.

**Phosphodiesterase Inhibitors**

The reduction in nitric oxide synthase in PAH results in derangements of the cyclic guanosine monophosphate (cGMP) pathway. Phosphodiesterase-5 (PDE-5) inhibition has the potential to inhibit the hydrolysis of cGMP and has proven to be an effective therapy for PAH.

Sildenafil has been studied in a 12-week multicenter, randomized, placebo-controlled trial and was found to improve 6MWT and hemodynamics, but not the secondary endpoint of time to clinical worsening. More recently, tadalafil was studied in a 16-week, multicenter, randomized, placebo-controlled trial and demonstrated an improvement in the primary endpoint of 6MWT. The highest dose studied (40 mg) also resulted in an improvement in the secondary endpoint of time to clinical worsening. Tadalafil is approved at a dose of 40 mg once daily. The most common adverse effects of the PDE-5 inhibitors include headache, flushing, dyspepsia, myalgias, and epistaxis.

**Investigational Therapies**

Although current therapeutic approaches for PAH target three pathways, patient outcomes remain suboptimal, and active research continues to identify potential therapies for this disease. Agents currently undergoing multicenter, randomized, placebo-controlled trial include the following: macitentan (a tissue selective endothelin receptor antagonist), imatinib and nilotinib (tyrosine kinase inhibitors), riociguat (soluble guanylate cyclase stimulator), seleaxipag (prostacyclin receptor stimulator), and treprostinil (oral).

**Interventional Therapies**

Atrial septostomy creates a right-to-left interatrial shunt, decreases right heart filling pressures, improves RV function, and improves left heart filling. Several case series have reported hemodynamic and clinical improvements following this procedure. Although the created shunt decreases systemic arterial oxygen saturation, the goal is an improvement in systemic oxygen delivery based on the improved cardiac output. However, procedural mortality is high and is driven by the severity of PAH and right heart failure in patients undergoing this procedure.

Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure despite maximal medical therapy. The goals of this procedure are palliation and restoration, as well as maintenance of clinical stability until transplantation can be performed. Only experienced operators in centers with the resources to care for such critically ill patients
Chapter 12: Pulmonary Hypertension

The choice of therapy depends on many factors, most often relies on animal models, which may not accurately reflect human disease. To advance translational science, the Pulmonary Hypertension Breakthrough Initiative is a project that harvests explanted lungs from PAH patients at the time of lung transplantation. Making human tissue available for study has the potential to accelerate advances in both basic and translational sciences.

Patients with PAH have better quality of life and survival than they did 10 or 20 years ago, but their survival remains suboptimal, and more advances in medical therapies are needed. Fortunately, numerous therapies, including some with novel mechanisms of action, are currently being investigated. Data from important current registries continue to highlight important prognostic variables and may help guide appropriate treatment strategies.

The importance of the RV cannot be overstated. Imaging modalities of the RV are being refined, and it is likely that magnetic resonance imaging will play a crucial role. Patients do not die of high pulmonary artery pressures; they die of RV failure. Improving treatment of RV failure is a priority for the future.

Key Points

- PH is a common disorder with many potential etiologies.
- The most common type of PH observed by cardiologists is Group Two, or that owing to left heart disease. Treatment of the underlying disorder is the mainstay of therapy.
- PAH is defined as an mPAP ≥25 mm Hg and a left heart filling pressure (wedge, LVEDP) ≤15 mm Hg.
- Group One PAH may be idiopathic, heritable, or associated with other disorders such as connective tissue disease, CHD, portal hypertension, and HIV.
- The concern for PAH often starts with the echocardiogram. In addition to an elevated estimated pulmonary artery systolic pressure, right heart enlargement and dysfunction serve as clues to the diagnosis of PAH. However, the diagnosis requires confirmation through RHC.
- The diagnostic algorithm for PAH is thorough and methodical. Clinicians must remember to evaluate for chronic thromboembolic PH, as this disorder can be treated surgically.
- The RHC is the culmination of the diagnostic evaluation and must meticulously measure key hemodynamic parameters.
- A small proportion of patients (those who meet certain criteria at the time of acute vasodilator testing) respond to calcium channel blockers.
- Background therapy for PAH may include diuretics, and oxygen.
- Multiple therapies are now FDA approved for the treatment of PAH. They fall into three broad categories: prostanoids, endothelin receptor antagonists, and PDE-5 inhibitors.
- The choice of therapy depends on many factors, most importantly the severity of illness.

Prognosis

Recently, two large registries have increased understanding of the prognosis of patients with PAH in the era of PAH-specific therapies. The French registry demonstrated that the survival of PAH patients has improved compared with the predicted survival based on the NIH registry, although survival remains suboptimal with one-, two-, and three-year survival of 85.7%, 69.5%, and 54.9%, respectively, for incident cases. Key predictors of survival include: gender (males fare worse), functional class, exercise tolerance as measured by 6MWT, and hemodynamics, specifically right atrial pressure and cardiac output. Similarly, in REVEAL (a large US-based registry), important prognostic variables were described. Key predictors of outcome in this study included: etiology of PAH, functional class, gender, exercise tolerance, and hemodynamics that reflect RV function.

Longitudinal Assessment

Consensus recommendations on reassessment are provided in the 2009 ACCF/AHA Expert Consensus Document on Pulmonary Hypertension and rely on routine assessment of important prognostic indicators such as WHO functional class, 6MWD, and echocardiographic and hemodynamic parameters (Table 4). In most cases, goals of therapy include improving patients to functional class I or II status, with a 6MWD >400 m (considering demographic factors) and normal or near normal RV function, as assessed by echocardiography or invasive hemodynamics.

Future Directions

Although our understanding of the pathogenesis and treatment of PAH has advanced substantially over recent decades, much work remains to be done. The basic understanding of the pathobiology often relies on animal models, which may not accurately reflect
**Longitudinal Evaluation of Patients with Pulmonary Arterial Hypertension**

<table>
<thead>
<tr>
<th>Clinical Course</th>
<th>Stable; No Increase in Symptoms and/or Decompensation</th>
<th>Unstable; Increase in Symptoms and/or Decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>No evidence of right heart failure</td>
<td>Signs of right heart failure</td>
</tr>
<tr>
<td>Functional class</td>
<td><strong>I / II</strong></td>
<td><strong>IV</strong></td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;400 m</td>
<td>6MWD 300-400 m</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>RV size/function normal</td>
<td>RV enlargement/dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP normal</td>
<td>RAP high</td>
</tr>
<tr>
<td></td>
<td>CI normal</td>
<td>CI low</td>
</tr>
<tr>
<td>BNP</td>
<td>Near normal/remaining stable or decreasing</td>
<td>Elevated/increasing</td>
</tr>
<tr>
<td>Treatment</td>
<td>Oral therapy</td>
<td>Intravenous prostacyclin and/or combination treatment</td>
</tr>
<tr>
<td>Frequency of evaluation</td>
<td>Every 3-6 months</td>
<td>Every 1-3 months</td>
</tr>
<tr>
<td>FC assessment</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>6MWT</td>
<td>Every clinic visit</td>
<td>Every clinic visit</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Yearly or center dependent</td>
<td>Every 6-12 months or center dependent</td>
</tr>
<tr>
<td>BNP</td>
<td>Center dependent</td>
<td>Center dependent</td>
</tr>
<tr>
<td>RHC</td>
<td>Clinical deterioration and center dependent</td>
<td>Every 6-12 months or clinical deterioration</td>
</tr>
</tbody>
</table>

**Table 4**

**Longitudinal Evaluation of Patients With Pulmonary Arterial Hypertension**

* For patients in the high-risk category, consider referral to a PH specialty center for consideration for advanced therapies, clinical trials, and/or lung transplantation.

* The frequency of follow-up evaluation for patients in FC III and/or 6 MWD between 300-400 m would depend on composite of detailed assessments on other clinical and objective characteristics listed.

* For patients who remain stable on established therapy, follow-up assessments can be performed by referring physician(s) or PH specialty centers.

* Echocardiographic measurement of PASP is estimation only and it is strongly advised not to rely on its evaluation as the sole parameter to make therapeutic decisions.

* The utility of serial BNP levels to guide management in individual patients has not been established.

6MWD = 6-minute walk distance; 6 MWT = 6-minute walk test; BNP = brain natriuretic peptide; CI = cardiac index; FC = functional class; PAH = pulmonary arterial hypertension; PASP = pulmonary artery systolic pressure; RAP = right atrial pressure; RHC = right heart catheterization; RV = right ventricle.

Longitudinal assessment is critical to ensure that patients meet treatment goals that improve prognosis.

References

17. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intrave-