PULMONARY VASCULAR CHANGES IN HEART DISEASE

Robyn J. Barst, MD

Extracted from Chapter on Pulmonary Hypertension available in full on the website.

I. INTRODUCTION

Pulmonary hypertension is a common accompaniment of many cardiac and pulmonary disorders, for which the status of the pulmonary vascular bed is oftentimes the principal determinant of the clinical manifestations, course, and feasibility of surgical treatment. The prognosis for patients with pulmonary hypertension varies greatly, depending upon the cause of the pulmonary hypertension and its severity at the time of diagnosis. Although knowledge about the pulmonary circulation has advanced substantially, why one patient behaves differently from another with what appears to be the same degree of pulmonary hypertension remains unclear.

II. DEFINITION

The pulmonary circulation is a low resistance, highly distensible circulation. In normal individuals lying supine, systolic pressures are of the order of 15-25 mmHg; the corresponding diastolic pressures are 5-10 mmHg (Table 64-1). The mean driving pressure, i.e., the difference between the mean blood pressure in the pulmonary artery and in the left atrium, is about 10–12 mmHg, one-eighth of that in the systemic circulation. Since blood flow (cardiac output) is the same in both circulations in the absence of any systemic to pulmonary communications, the pulmonary vascular resistance is about one-eighth of systemic vascular resistance. The large aggregate cross-sectional area of the pulmonary circulation is responsible for this low resistance, which is reflected in the sparsity of muscle in the pulmonary resistance vessels, the large runoff of blood from the pulmonary arterial tree during each systole, the large capacity and expansibility of the pulmonary arterial tree, and the large number of minute vessels that are held in reserve. During exercise, pulmonary blood flow increases. Accompanying this increase in blood flow is a decrease in pulmonary vascular resistance brought about by recruiting new parts of the pulmonary vascular bed as well as by widening the calibers of those vessels that were already open. As a result of these accommodations, a considerable increase in pulmonary blood flow elicits only a moderate increase in pulmonary arterial pressure. For the adult at sea level, pulmonary arterial hypertension is said to exist when the mean pulmonary arterial pressure is greater than 25 mmHg at rest or greater than 30 mmHg during exercise. However, this level, which would represent a modest increase for adults at sea level, is normal for adults at high altitude.
III. CLASSIFICATION OF PULMONARY HYPERTENSION AND EPIDEMIOLOGY

Classification
Pulmonary hypertension was previously classified into two categories: primary pulmonary hypertension and secondary pulmonary hypertension, depending on the absence or presence of identifiable causes or risk factors. The diagnosis of primary pulmonary hypertension was one of exclusion, with ruling out all causes of pulmonary hypertension. In 2003, the Third World Symposium on Pulmonary Arterial Hypertension revised the existing 1998 Evian Classification (Table 64-2). The aim of this classification was to identify different groups with similar pathobiology, clinical characteristics and treatment modalities. This classification consists of five categories in which pulmonary hypertension disorders are grouped, according to therapeutic interventions aimed at treated the causes of: 1) pulmonary arterial hypertension, 2) pulmonary venous hypertension, 3) pulmonary hypertension associated with disorders of the respiratory system or hypoxia, 4) pulmonary hypertension due to thrombotic or embolic disease, and 5) pulmonary hypertension caused by diseases directly affecting the pulmonary vasculature. This classification is now widely accepted and used in clinical practice. Furthermore, this is the classification used by the US Food and Drug Administration and the European Agency for Drug Evaluation for the labeling of approved pulmonary hypertension medications.

Epidemiology
In adults, the most common cause of pulmonary hypertension is lung disease, especially chronic obstructive pulmonary disease (COPD). An estimated 30,000 persons die each year from COPD, many of whom have pulmonary hypertension and resulting right ventricular failure as a contributing cause of death. Patients with interstitial lung disease, cystic fibrosis, sleep apnea syndrome and lung disorders caused by occupational and other exposures, also commonly develop secondary pulmonary hypertension when they become chronically hypoxic. In the United States, about 200,000 patients die annually from acute pulmonary embolism, often with acute right ventricular failure owing to acute and severe pulmonary hypertension. Pulmonary hypertension is also seen in patients with chronic or recurrent pulmonary embolism, regardless of the source of the embolic material.

Estimates of the incidence of idiopathic pulmonary arterial hypertension (formerly termed primary pulmonary hypertension) range from 1 to 2 newly diagnosed cases per million people per year in the general population. The prevalence of pulmonary vascular disease in patients with other illnesses is not known, but it appears that 1% to 2% of patients with portal hypertension or HIV infection have pulmonary arterial hypertension. The incidence of pulmonary arterial hypertension in patients with collagen vascular disease ranges from 2% to 35% in patients with scleroderma and may reach 50% in patients with limited scleroderma (formerly termed the CREST variant). Pulmonary arterial hypertension has been reported to occur in 23% to 53% of patients with mixed connective tissue diseases and in 1% to 14% of cases of systemic lupus erythematosus, but it is rare in patients with rheumatoid arthritis, Sjogren’s syndrome, or dermatomyositis. Idiopathic pulmonary arterial hypertension has also been associated with autoimmune phenomena, including Raynaud’s syndrome, positive antinuclear antibodies, and autoimmune thyroid disorders. It is also estimated that the approximately 5% rate of increased pulmonary arterial reactivity in patients with mitral stenosis...
or left ventricular dysfunction may represent a genetic predisposition for pulmonary arterial hypertension.

Pulmonary vascular obstructive disease related to congenital systemic to pulmonary shunts, i.e., the Eisenmenger syndrome, develops after a period of decreased pulmonary vascular resistance and increased pulmonary flow. The high rates of pulmonary vascular obstructive disease in uncorrected congenital heart disease (Table 64-3) demonstrate that even if all other causes of death could be eliminated, approximately one-third of these patients would eventually die from pulmonary vascular disease. Why some patients develop irreversible pulmonary vascular obstructive disease in the first year of life and other patients remain “operable” from a pulmonary vascular disease standpoint into the second or third decade of life or later with the same congenital cardiac defect remains unknown. For example, the prevalence of the Eisenmenger syndrome among patients with a secundum atrial septal defect is 6% to 9% and is unrelated to the size of the defect. In contrast, a large ventricular septal defect or a large patent ductus arteriosus invariably leads to the Eisenmenger syndrome. Although secundum atrial septal defects are twice as common among females as among males, the Eisenmenger syndrome is still more prevalent among female patients with a secundum atrial septal defect (5:1 ratio in some series), a pattern reminiscent of what is observed with idiopathic pulmonary arterial hypertension (2:1). For other congenital heart defects, the risk of the Eisenmenger syndrome is not sex-related, raising the question of whether some Eisenmenger syndrome patients with an atrial septal defect do, in fact, have idiopathic pulmonary arterial hypertension.

**Risk Factors for Pulmonary Arterial Hypertension**

Pulmonary hypertension probably reflects an interaction between a genetic predisposition and exposures. Risk factors can be categorized based on the strength of the association with pulmonary arterial hypertension and a possible causal role (Table 64-4). The risk of pulmonary arterial hypertension related to the use of appetite suppressants, e.g., fenfluramine or dexfenfluramine, increased concomitantly with longer length of exposure.

**IV. PATHOLOGY, PATHOBIOLOGY and PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION**

**Pathology and Pathobiology**

The pathology of pulmonary vascular disease was first classified in the 1950s by Heath and Edwards (Table 64-5). Unfortunately, this pathologic classification does not correlate well with the pathobiology or clinical and hemodynamic findings of pulmonary hypertension. The vascular endothelium is an important source of locally active mediators that contribute to the control of vasomotor tone. Imbalances in the production or metabolism of vasoactive mediators of pulmonary vascular tone include increased thromboxane and endothelin, and decreased prostacyclin and nitric oxide. Thromboxane and endothelin are vasoconstrictors as well as mitogens; in contrast, prostacyclin and nitric oxide are vasodilators with antiproliferative effects. Vasoconstrictors may also serve as factors or cofactors that stimulate growth of smooth muscle or elaboration of matrix. It appears likely that endothelial injury results in the release of chemotactic agents leading to migration of smooth muscle cells into the vascular wall. This
endothelial injury, coupled with excessive release of vasoactive mediators locally, promotes a procoagulant state, leading to further vascular obstruction. The process is characterized, therefore, by an inexorable cycle of endothelial dysfunction leading to the release of vasoconstrictive and vasoproliferative substances, ultimately progressing to vascular remodeling and progressive vascular obstruction and obliteration. In addition, defects in the potassium channel pulmonary resistance smooth muscles may also be involved in the initiation and/or progression of pulmonary hypertension.

**Pathophysiology**

Whether the pulmonary hypertension is due to increased flow or increased resistance depends upon the cause of the pulmonary hypertension (Table 64-2). The pulmonary artery wedge pressure will be elevated in patients with pulmonary venous hypertension but normal in other patients with pulmonary hypertension unless there is incidental, coexisting left heart disease. In patients with pulmonary venous hypertension, e.g., mitral stenosis or left ventricular dysfunction, the same elevation of pulmonary venous pressure may result in very different pulmonary artery pressures because of individual differences in pulmonary arterial vasoreactivity.

Pulmonary hypertension can be classified according to the site of increased pulmonary vascular resistance. In patients with pre-capillary pulmonary hypertension, the abnormalities occur in the pulmonary arteries or arterioles. In passive pulmonary hypertension, the increase in pulmonary artery pressure is caused by an increase in pulmonary venous pressure, owing to disease of the pulmonary veins or, more commonly, increased left atrial pressures due to diseases of the mitral valve, left ventricle (systolic or diastolic) or aortic valve. In passive pulmonary hypertension, the increase in pulmonary arterial blood pressure is a direct reflection of the increase in pulmonary venous pressures.

In reactive pulmonary hypertension, increased pulmonary venous pressure leads to reactive pre-capillary pulmonary artery abnormalities that raise the pulmonary arterial pressure more than would be expected based on the pulmonary venous hypertension alone. This mixed picture, which was commonly seen with long-standing mitral valve disease during the rheumatic fever era, is less often seen today. The pulmonary hypertension related to connective tissue disease, drugs, toxins, as well as idiopathic pulmonary arterial hypertension and familial pulmonary arterial hypertension is pre-capillary. Similarly, in the Eisenmenger syndrome, high pulmonary blood flows cause pre-capillary pulmonary hypertension, which then progresses independent of flow via a reactive phase.

The normal pulmonary vascular bed has a remarkable capacity to dilate and recruit unused vasculature to accommodate increases in blood flow. In pulmonary hypertension, however, this capacity is lost, leading to increases in pulmonary artery pressure at rest and further elevations in pulmonary artery pressure with exercise. In response to this increased afterload, the right ventricle hypertrophies. Initially, the right ventricle is capable of sustaining normal cardiac output at rest, but the ability to increase cardiac output with exercise is impaired. As pulmonary vascular disease progresses, the right ventricle fails, and resting cardiac output decreases. As right ventricular dysfunction progresses, right ventricular diastolic pressure increases, and evidence of right ventricular failure, the most ominous sign of pulmonary hypertension, becomes manifest (Figure 64-3). Although the left ventricle is not directly affected by pulmonary
vascular disease, progressive right ventricular dilatation can impair left ventricular filling, leading to modestly increased left ventricular end-diastolic and pulmonary capillary wedge pressures. Dyspnea, the most frequent presenting complaint in patients with pulmonary hypertension, is due to impaired oxygen delivery during physical activity as a result of an inability to increase cardiac output in the presence of increased oxygen demands. Chest pain most often results from right ventricular ischemia as coronary blood flow is impaired in the setting of increased right ventricular mass and elevated systolic and diastolic pressures; however, left main coronary artery compression by an enlarged main pulmonary artery can cause left ventricular ischemia. Syncope, which is often exertional or post-exertional, implies a severely restricted cardiac output and diminished cerebral blood flow, which may be exacerbated by peripheral vasodilatation during physical exertion.

The two most frequent mechanisms of death are progressive right ventricular failure and sudden death, the latter being more common in patients who have the Eisenmenger syndrome. Pneumonia may cause alveolar hypoxia, which worsens pulmonary vasoconstriction with a resultant inability to maintain adequate cardiac output, followed by cardiogenic shock and death. Arterial hypoxemia and acidosis can precipitate life-threatening arrhythmias. Other causes of sudden death include bradyarrhythmias and tachyarrhythmias, acute pulmonary embolus, massive pulmonary hemorrhage, and sudden right ventricular ischemia. In patients with right-to-left cardiac shunts, complications can result from brain abscess, bacterial endocarditis, volume changes associated with pregnancy, ill-advised attempts at surgical repair in patients with the Eisenmenger syndrome, and, rarely, as a complication of cardiac catheterization.

V. CLINICAL MANIFESTATIONS

Symptoms

With mild pulmonary hypertension, the earliest complaints are often fatigue and vague chest discomfort. These symptoms are often ignored unless the patient has another underlying condition, such as COPD, interstitial lung disease, alveolar hypoventilation, or sleep apnea (Table 64-2). Nevertheless, the clinical picture still is generally dominated by any associated disorders until dyspnea and tachypnea are present.

When the pulmonary hypertension is advanced, the clinical manifestations include cyanosis, dyspnea on exertion, hemoptysis, atypical chest pain or angina pectoris, syncope, heart failure, arrhythmias, cerebral vascular accidents from paradoxical emboli, and gout. Dyspnea, the most common symptom of idiopathic pulmonary arterial hypertension, is also the most frequent symptom of the Eisenmenger syndrome. Syncope is an exceedingly rare symptom in unoperated patients with the Eisenmenger syndrome because of the ability to decompress the right heart via an open atrial septal defect, ventricular septal defect, or patent ductus arteriosus. In contrast, patients with idiopathic pulmonary arterial hypertension with an intact atrial septum, (i.e., without a patent foramen ovale) and patients with elevated pulmonary vascular resistance after complete surgical repair of congenital shunts may present with syncope. Angina, a common symptom that is often underappreciated, most often results from right ventricular ischemia (although left ventricular ischemia can also occur, as discussed above). Edema is generally a
reflection of right ventricular failure and is more likely to be associated with advanced pulmonary vascular disease.

**Physical Examination**
Each underlying or associated condition (Table 64-2) affects the clinical presentation. For example, COPD is usually associated with hyperinflation of the lungs, and this hyperinflation often shifts the position of the heart so that heart sounds are more difficult to hear. With interstitial lung disease, tachypnea invariably occurs. Nevertheless, certain physical findings (e.g., an increased intensity of P2, a palpable P2, a right-sided third heart sound, and, as the pulmonary hypertension progresses, murmurs of pulmonary and tricuspid insufficiency) typically develop. Ultimately, the neck veins are distended and the liver is pulsatile, and the patient may develop peripheral edema, pleural effusions, and ascites. In patients with pulmonary venous hypertension, the presentation is frequently overshadowed by signs of left-sided heart disease, e.g., mitral stenosis, systemic hypertension, or heart failure. In idiopathic pulmonary arterial hypertension, there is no evidence of underlying pulmonary or cardiac disease. The cardiac examination will show right ventricular overload as for any cause of pulmonary hypertension (see above).

Physical examination in a patient with the Eisenmenger syndrome demonstrates central cyanosis, clubbing of the digits, right ventricular lift, palpable P2, increased intensity of P2 (frequently with a single loud second heart sound), a pulmonic ejection sound associated with a dilated pulmonary trunk, and a diastolic murmur of pulmonary insufficiency. In the presence of heart failure, patients develop edema, ascites, and hepatosplenomegaly. In patients who have undergone corrective surgery for congenital heart disease when the pulmonary vascular resistance was already elevated, the physical examination is similar to that seen with idiopathic pulmonary arterial hypertension, i.e., an increase in the pulmonic component of the second heart sound, a right-sided fourth heart sound, and tricuspid regurgitation; a right ventricular third heart sound and pulmonary insufficiency generally reflect advanced disease. Peripheral cyanosis and edema are common. Clubbing, which is common with the Eisenmenger syndrome, is typically not seen in idiopathic pulmonary arterial hypertension or in patients who have undergone repair of the congenital heart defect(s) after pulmonary vascular resistance was already increased.

VI. **DIAGNOSIS AND DIFFERENTIAL ASSESSMENT**

**Detection**

Using current medical technology, a correct diagnosis and assessment of the severity of the pulmonary hypertension in a given individual can be made with a high level of confidence. Once pulmonary hypertension is suspected, an electrocardiogram (ECG) and chest radiograph should be performed. Although the ECG may be unremarkable, it more frequently shows right axis deviation and right ventricular hypertrophy with secondary T-wave changes, however, the ECG changes often do not parallel the severity of the pulmonary hypertension. The chest radiograph demonstrates a large right ventricle, dilated hilar pulmonary arteries, and variably oligemic peripheral lung fields depending upon the amount of pulmonary blood flow.
If the ECG and chest radiograph are either nondiagnostic or consistent with pulmonary hypertension, the evaluation continues with an echocardiogram to exclude congenital heart disease, myocardial dysfunction, and/or valvular disease. The classic echocardiographic appearance of a patient with idiopathic pulmonary arterial hypertension shows right ventricular and right atrial enlargement with normal or reduced left ventricular size (Figure 64-4). Pulmonic and tricuspid insufficiency are also often easily detected with Doppler interrogation. Right ventricular pressure overload in advanced disease reverses the normal interventricular septal curvature. Underfilling of the left ventricle, manifested by reduced dimensions, is a reflection of the severity of the pulmonary vascular disease. Doppler ultrasound is useful to estimate the pulmonary artery systolic pressure noninvasively as the sum of systemic venous pressure plus four times the tricuspid regurgitation velocity squared. Transesophageal echocardiography can provide a more precise assessment of intracardiac defects, including the detection of a patent foramen ovale. Saline contrast echocardiography can also assess the integrity of the atrial septum as well as the resting cardiac output (based on the rate of saline clearance).

**Characterization: Essential and Contingent Tests**

The echocardiogram is the key to detecting congenital or acquired heart disease as the cause of pulmonary hypertension. Pulmonary function tests and cardiopulmonary exercise tests help evaluate patients with uncertain causes of dyspnea. When a cardiac cause is not found, the evaluation should follow a systematic approach (Figure 64-5). Based on the results of the sequentially performed tests, underlying causes and/or related conditions can be diagnosed (Table 64-2).

Magnetic resonance imaging and computed scanning can help assess anatomy in patients with cardiac defects, and a high resolution CT is very useful for the evaluation of patients with suspected interstitial lung disease. Exercise testing is useful for the initial assessment of functional capacity before initiating treatment, as well as serially to assess the response to therapy.

The prevalence of pulmonary arterial hypertension in the setting of sleep disordered breathing is quite low; and the severity of the pulmonary hypertension is most often mild. And although obesity and recent weight gain are associated with sleep disordered breathing, they are not necessary for it to be present. Pulmonary hypertension in sleep disordered breathing is most strongly associated with other risk factors such as left-sided heart disease, parenchymal lung disease, nocturnal desaturation and obesity. Limited data suggest that sleep disordered breathing is uncommon in patients with idiopathic pulmonary arterial hypertension. However, an assessment of sleep disordered breathing is recommended in the evaluation of patients with pulmonary arterial hypertension. In contrast, routine evaluation for the presence of pulmonary arterial hypertension is not recommended in the management of patients with obstructive sleep apnea. Screening overnight oximetry will exclude significant obstructive sleep apnea/hypopnea. Nevertheless, when clinical findings such as history of habitual loud snoring, poor quality or restless sleep, or excessive daytime somnolence suggest the presence of sleep disordered breathing, particularly in obese individuals with systemic hypertension, an overnight sleep study that measures sleep EEG, electromyography in selected muscle groups, eye movements,
oral/nasal air flow, ECG, respiratory effort, and oxygen saturation is indicated. For those patients with documented obstructive sleep apnea and pulmonary arterial hypertension, treatment of obstructive sleep apnea with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize, particularly when pulmonary arterial hypertension is severe. In general, patients with obstructive sleep apnea and pulmonary arterial hypertension are older, heavier, and have worse lung function compared to patients with obstructive sleep apnea without pulmonary arterial hypertension. In the setting of sleep disordered breathing, the stimulus for pulmonary hypertension is thought to be hypoxic pulmonary vasoconstriction.

Ventilation-perfusion lung scanning and spiral CT are useful screening tests for chronic thromboembolic disease, although pulmonary angiography remains the gold standard for this assessment. In chronic thromboembolic pulmonary hypertension, the clots are incorporated into the wall of the pulmonary arteries and become endothelialized; therefore, pulmonary angiography may underestimate the extent of the obstruction or be difficult to interpret. Angioscopy and/or MRI may be useful in selected cases. It is extremely important to diagnose chronic thromboembolic disease since thromboendarterectomy provides a clinical, hemodynamic, and survival benefit in patients with chronic thromboembolic pulmonary arterial hypertension.

Abnormalities of pulmonary function testing may be present in patients with idiopathic pulmonary arterial hypertension or the Eisenmenger syndrome, particularly in more advanced stages of the disease, owing to derangements in either the mechanical or gas exchanging properties of the lung. Severe hypoxemia can occur in idiopathic pulmonary arterial hypertension due to right to left shunting via a patent foramen ovale or in the Eisenmenger syndrome, due to right to left shunting via unrepaired systemic to pulmonary communications.

For all patients in whom pulmonary hypertension is still suspected after performing a chest radiograph, ECG, and echocardiogram, right heart cardiac catheterization is recommended to confirm the diagnosis and measure intracardiac, systemic, and pulmonic pressures, as well as cardiac output. Furthermore, acute testing with a short-acting vasodilator (at the time of right heart catheterization) to determine the degree of pulmonary vasoreactivity is recommended for all patients who have documented pulmonary hypertension and who are being considered for medical therapy. Unfortunately, no hemodynamic or demographic variables predict whether a patient will respond to acute vasodilator testing. Testing with the following vasodilators is recommended: intravenous epoprostenol sodium (dose range 2 to 12 ng/kg/min, half-life 2-3 minutes); inhaled nitric oxide (dose range 10 to 80 ppm, half-life 15 to 30 seconds); inhaled iloprost (aerosolized dose range 14-17 mcg, half-life 20-30 minutes); and/or intravenous adenosine (dose range 50 to 200 ng/kg/min, half-life 5 to 10 seconds). Patients who may benefit from chronic treatment with chronic calcium channel blockers can be identified by an acute vasodilator challenge; a positive response is defined as a decrease in mean pulmonary artery pressure of $\geq 10 \text{ mmHg}$ to reach a $P_{\text{APm}} \leq 40 \text{ mmHg}$ with a normal or high cardiac output. Patients who do not respond to acute vasodilator challenge are unlikely to have clinical benefit from oral calcium channel blockers and may actually deteriorate with them.
**Screening High-Risk Patients**

Screening may lead to the early identification of pulmonary hypertension in asymptomatic or minimally symptomatic individuals with scleroderma, who have high prevalence of pulmonary hypertension, as compared with the much lower prevalence in patients with systemic lupus erythematosus, rheumatoid arthritis, and other connective tissue diseases. Screening is also recommended for first degree relatives of patients with documented idiopathic pulmonary arterial hypertension. A transthoracic echocardiogram is performed in all patients with portal hypertension when they are evaluated for liver transplantation. There is no definitive recommendation regarding routine screening for pulmonary hypertension in patients with pulmonary disease such as COPD unless there are also signs or symptoms suggestive of pulmonary hypertension.

**Incidental Discovery of Pulmonary Hypertension**

The clinical significance and natural history of asymptomatic or mild pulmonary arterial hypertension is unclear; thus, the implications for further assessment and/or treatment when discovered incidentally, as a result of screening or during evaluation of nonspecific symptoms, remain uncertain. Moreover, the criterion of clinically significant pulmonary hypertension when detected under these circumstances by Doppler echocardiography, which in itself is an isolated estimate of right ventricular systolic pressure, is not precisely defined. Commonly used definitions of pulmonary hypertension are pulmonary artery systolic pressure >35 mmHg or mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise. However, a pulmonary artery systolic pressure >40 mmHg is present in 6% of otherwise normal individuals older than 50 years and 5% with a body mass index >30 kg/m². In general, any degree of pulmonary hypertension should prompt an attempt to define or exclude possible causes, because it may be the first evidence of a modifiable substrate. However, the severity of pulmonary hypertension and the reliability of the measurement should temper the aggressiveness of the evaluation. Confirmation by right heart catheterization is warranted before embarking on extensive evaluation for an underlying cause or considerations of prognosis or treatment.

Although most studies report a high correlation (0.57-0.93) between transthoracic echocardiography and right heart catheterization measurements of pulmonary artery systolic pressure, underestimation as well as overestimation of pulmonary artery systolic pressure by Doppler echocardiography is not infrequent. Reported sensitivity of transthoracic echocardiographic estimated pulmonary artery systolic pressure for detecting pulmonary hypertension ranges from 0.79 to 1.0 and specificity from 0.60 to 0.98. However, these figures are strongly influenced by the value used to define pulmonary hypertension. The range of right ventricular systolic pressure among healthy controls has been well characterized. Among a broad population of male and female subjects ranging from 1 to 89 years of age, right ventricular systolic pressure was reported as 28±5 mmHg (range 15-57 mmHg). The right ventricular systolic pressure increases with age and body mass index. Athletically conditioned men also have higher resting right ventricular systolic pressure. Defining the normal distribution of right ventricular systolic pressure does not *ipso facto* define the point at which an elevated right ventricular systolic pressure is clinically important or predictive of future consequences. Mild pulmonary hypertension is defined as a pulmonary artery systolic pressure of approximately 36-
50 mmHg or a resting tricuspid regurgitant velocity of 2.8-3.4 m/sec. Possible explanations for mildly elevated pulmonary artery systolic pressure suggested by echocardiography include: 1) overestimation of the right ventricular systolic pressure in a patient with truly normal pulmonary pressure; 2) serendipitous observation of a rare transient pressure elevation in an otherwise healthy individual; 3) discovery of stable mild pulmonary hypertension, possibly of long duration; or 4) discovery of early progressive pulmonary hypertension in an individual with pulmonary arterial hypertension. In addition, pulmonary artery pressure differences may be observed in different populations and conditions, including age, level of conditioning, exercise or stress. No clear guidelines are available that delineate normal from pathologic in all circumstances.
EVIDENCE-BASED REFERENCES


SUGGESTED READINGS


Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004; 124 (1,Suppl). *Evidence-based guidelines created by an expert committee (representing multiple disciplines) at the request of the American College of Chest Physicians (ACCP).*
TABLE 64-1. Adult Values for Normal Pulmonary Hemodynamics at Sea Level (Rest and Mild Exercise) and at Elevated Altitude (Rest)

<table>
<thead>
<tr>
<th></th>
<th>Sea level Rest</th>
<th>Sea level Mild Exercise</th>
<th>Altitude (~15,000 ft) Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial pressure, (mean) in mmHg</td>
<td>20/10(15)</td>
<td>30/13(20)</td>
<td>38/14(26)</td>
</tr>
<tr>
<td>Cardiac output, in L/min</td>
<td>6.0</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Left atrial pressure (mean), mmHg</td>
<td>5.0</td>
<td>9.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, units</td>
<td>1.7</td>
<td>0.9</td>
<td>3.3</td>
</tr>
</tbody>
</table>
### Table 64-2. The 2003 Venice Classification

1. **Pulmonary Arterial Hypertension (PAH)**
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      1.3.1 Collagen vascular disease
      1.3.2 **Congenital systemic-to-pulmonary shunts**
      1.3.3 Portal hypertension
      1.3.4 HIV infection
      1.3.5 Drugs and toxins
      1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
   1.4. Associated with significant venous or capillary involvement
      1.4.1 Pulmonary veno-occlusive disease (PVOD)
      1.4.2 Pulmonary capillary hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn

2. **Pulmonary hypertension with left heart disease**
   2.1. **Left-sided atrial or ventricular heart disease**
   2.2. **Left-sided valvular heart disease**

3. Pulmonary Hypertension associated with lung diseases and/or hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)
<table>
<thead>
<tr>
<th>Lesion</th>
<th>%</th>
<th>Total no.</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>30</td>
<td>9000</td>
<td>3000</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>9</td>
<td>2700</td>
<td>900</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>7</td>
<td>2100</td>
<td>700</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>3</td>
<td>900</td>
<td>800</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>5</td>
<td>1500</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonic stenosis</td>
<td>7</td>
<td>2100</td>
<td>0</td>
</tr>
<tr>
<td>Coarctation</td>
<td>6</td>
<td>1800</td>
<td>0</td>
</tr>
<tr>
<td>Tetralogy</td>
<td>5</td>
<td>1500</td>
<td>200</td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
<td>5</td>
<td>1500</td>
<td>500</td>
</tr>
<tr>
<td>Truncus Arteriosus</td>
<td>1</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Hypoplastic right heart</td>
<td>2</td>
<td>600</td>
<td>50</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>1</td>
<td>300</td>
<td>0</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>0.2</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous connection</td>
<td>1</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Univentricular heart</td>
<td>0.3</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>17.5</td>
<td>5250</td>
<td>2625</td>
</tr>
</tbody>
</table>

| Total                                      | 100.0| 30,000   | 9525 (32%) |

Table 64-3. Risk Pulmonary Vascular Disease in Persons with Congenital Heart Disease*

*Assumptions: 3,000,000 live births per year; 1% incidence of congenital heart disease
### Table 64-4 - Risk Factors and Associated Conditions for Pulmonary Arterial Hypertension Identified During the Evian Meeting (1998) and Classified According to the Strength of Evidence

A. Drugs and Toxins
   1. Definite
      - Aminorex
      - Fenfluramine
      - Dexfenfluramine
      - Toxic rapeseed oil
   2. Very likely
      - Amphetamines
      - L-tryptophan
   3. Possible
      - Meta-amphetamines
      - Cocaine
      - Chemotherapeutic agents
   4. Unlikely
      - Antidepressants
      - Oral contraceptives
      - Estrogen therapy
      - Cigarette smoking

B. Demographic and Medical Conditions
   1. Definite
      - Gender
   2. Possible
      - Pregnancy
      - Systemic hypertension
   3. Unlikely
      - Obesity

C. Diseases
   1. Definite
      - HIV infection
   2. Very likely
      - Portal hypertension/liver disease
      - Collagen vascular diseases
      - Congenital systemic-pulmonary-cardiac shunts
   3. Possible
      - Thyroid disorders
Table 64-5. Heath-Edwards Classification: Pulmonary Vascular Disease

Grade 1 - Medial hypertrophy in the small pulmonary arteries.

Grade 2 - Concentric or eccentric cellular intimal proliferation and thickening within the smaller pulmonary arteries and arterioles.

Grade 3 - Relatively acellular intimal fibrosis with accumulation of concentric or eccentric masses of fibrous tissue leading to widespread occlusion of the smaller pulmonary arteries and arterioles.

Grade 4 - Progressive, generalized dilatation of the muscular arteries and the appearance of plexiform lesions, complex vascular structures composed of a network or plexus of proliferating endothelial tissue, frequently accompanied by thrombus, within a dilated thin-walled sac.

Grade 5 – Thinning and fibrosis of the media superimposed upon the formation of numerous complex dilatation lesions.

Grade 6 - Necrotizing arteritis within the media with surrounding areas of inflammatory reaction and granulation tissue.
Table 64-6.  World Health Organization Classification of Functional Status of Patients With Pulmonary Hypertension

A.  Class I – Patients with pulmonary hypertension but without resulting limitations of physical activity.  Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

B.  Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity.  They are comfortable at rest.  Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

C.  Class III - Patients with pulmonary hypertension resulting in marked limitation of physical activity.  They are comfortable at rest.  Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

D.  Class IV - Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms.  These patients manifest signs of right heart failure.  Dyspnea and/or fatigue may even be present at rest.  Discomfort is increased by any physical activity.

*modified after the New York Heart Association Functional Classification
Figure 64-5.

Symptom Evaluation | Screening | Incidental Finding

Detection

Physical Examination
Chest X-ray
Electrocardiogram
Echocardiogram

Suspect PH

Essential Testing
Pulmonary Function Testing
Overnight Oximetry
V/Q Lung Scan
CTD Screen
HIV
CBC with platelet count
LFTs
Antiphospholipid Antibodies
Assessment of exercise capacity
Confirmatory RHC with acute VD testing

Characterization

Contingent Testing
TEE
Spiral CT/EBCT/HRCT/
Pulmonary Angiography
Clotting studies
SaO₂, uric acid, BNP, troponin
Polysomnography
Lung Biopsy