Chapter 64

PULMONARY HYPERTENSION
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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. GENETIC BASIS OF PULMONARY HYPERTENSION**
Although the prevalence of familial pulmonary arterial hypertension is uncertain, it represents at least 6% of all cases and perhaps considerably more. Familial pulmonary arterial hypertension is inherited as an autosomal dominant disorder with reduced or incomplete penetrance. It is estimated that individuals in a family with familial pulmonary arterial hypertension have a 5% to 10% lifetime risk of developing familial pulmonary arterial hypertension.

Mutations in two receptors of the transforming growth factor family, i.e. bone morphogenetic protein receptor 2 and activin receptor-like kinase type 1, have been identified in familial pulmonary arterial hypertension indicating a critical role for transforming growth factor superfamily ligand-receptor interactions in vascular homeostasis and in embryologic development (Figure 64-1). Exonic mutations in BMPR2 are found in approximately 50% of patients with familial pulmonary arterial hypertension, and ALK-1 mutations in a minority of patients with hereditary hemorrhagic telangiectasia and coexistent pulmonary arterial hypertension. BMPR2 mutations are also seen in approximately 10% of patients with idiopathic pulmonary arterial hypertension. Mutations in BMPR2 confer a 15-20% chance of developing pulmonary arterial hypertension in a carrier’s lifetime. Hence, gene-gene or gene-environmental interactions must be involved to either promote or prevent the development of the pulmonary vascular disease in individuals who carry a mutation, as well as other patterns of susceptibility based on genetic makeup. BMPR2 mutations have also been identified in other pulmonary arterial hypertension cohorts including appetite suppressant pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts. To date, BMPR2 mutations have not been found in pulmonary arterial hypertension related to connective tissue disease, HIV, or portal hypertension.
V. 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 (Figure 64-2). 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.

VI. 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
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.
VII. 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 ECH changes often do not parallel the severity of the pulmonary hypertension (Figure 42-6b). 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 (Figure 49-6).

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 \( \geq 10 \) mmHg to reach a \( \text{PAPm} \leq 40 \) 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.

VIII. ASSESSMENT OF PULMONARY HYPERTENSION SEVERITY

Natural History

Idiopathic pulmonary arterial hypertension historically has exhibited a course of relentless deterioration and early death. Newer pharmacological and surgical treatments have demonstrably altered not only symptomatic status, but also the progression of the disease and duration of survival. Until the 1980s, the survival of patients with idiopathic pulmonary arterial hypertension who did not undergo heart-lung or lung transplantation was 68%-77% at one year, 40%-56% at three years, and 22%-38% at five years; patients presenting with more advanced symptoms had a shorter subsequent survival, with a median survival of 59 months for patients diagnosed in WHO Functional Class I or II (Table 64-6) compared with 32 months for Class III and 6 months for Class IV. Survival for several decades has been reported, as have rare cases of apparent regression of the disease.

Pulmonary arterial hypertension associated with HIV infection or connective tissue disease has an overall worse survival than idiopathic pulmonary arterial hypertension. In contrast, patients with pulmonary arterial hypertension and coexisting portal hypertension have a similar prognosis as idiopathic pulmonary arterial hypertension. However, the natural history of the Eisenmenger
syndrome is markedly better than for idiopathic pulmonary arterial hypertension, with an overall 75% five year survival, and a 40% 25 year survival (Figure 64-6).

Similarly, the natural history of patients who have only mild pulmonary hypertension owing to underlying pulmonary diseases, such as COPD, is also much better than for idiopathic pulmonary arterial hypertension. In most cases, it is the natural history of the COPD that determines the patient’s ultimate prognosis. In patients with pulmonary venous hypertension, the picture is often mixed and varies depending upon the severity of the pulmonary vasoreactivity (which determines the magnitude of the pulmonary arterial hypertension) as well as the degree of pulmonary venous hypertension with or without left sided heart failure. When pulmonary arterial hypertension is the predominant abnormality, the naturally history can still vary substantially owing to the wide range of biologic variability of progressive pulmonary vascular disease.

**Disease Severity**

After pulmonary arterial hypertension is diagnosed, in order to assess risk:benefit profiles for various therapeutic options accurately, precise assessment of prognosis as a function of disease severity is required. Various demographic and hemodynamic characteristics, including functional class, exercise capacity, acute pulmonary vasoreactivity, assessment of right ventricular function, neurohormonal levels (e.g. BNP, norepinephrine as well as endothelin-1), uric acid and troponin correlate with survival. In addition to evaluating these various parameters at the time of diagnosis prior to initiation of medical therapy, reevaluation of these parameters on
treatment is useful in predicting outcome with a given therapy. Some of these modalities may provide prognostic information similar to that derived from invasive tests, e.g. cardiac catheterization, and may prove more useful and convenient in assessing treatment efficacy. These tools may also increase predictive accuracy when used in combination. However, it is important to remember that these tests evaluated patients with idiopathic pulmonary arterial hypertension and not patients with pulmonary arterial hypertension related to connective tissue diseases, congenital systemic to pulmonary shunts, HIV infection or portal hypertension. Thus, these parameters must be applied cautiously to pulmonary arterial hypertension patients in whom comorbid factors might contribute to the overall outcome; e.g. patients with pulmonary arterial hypertension related to connective tissue disorders are known to have a worse prognosis than do idiopathic pulmonary arterial hypertension, whereas patients with pulmonary arterial hypertension related to congenital systemic to pulmonary shunts have a much more slowly progressive course than do idiopathic pulmonary arterial hypertension patients.

IX. **TREATMENT**

Treatment for pulmonary hypertension depends upon an accurate assessment of the cause of the pulmonary hypertension (Figure 64-5). Although there is no cure nor single therapeutic approach that is uniformly successful for pulmonary arterial hypertension, therapy has improved substantially (Figure 64-7).

**General Measures**
Important general measures for patients with all forms of pulmonary arterial hypertension include the avoidance of circumstances or substances that may aggravate the disease state. For example, exercise should be guided by symptoms, and exposure to high altitude may worsen pulmonary arterial hypertension by producing hypoxia-induced pulmonary vasoconstriction. Pregnancy, oral contraceptives, and appetite suppressants should be avoided. Phlebotomy with replacement of fluid, e.g., plasma or albumin, is helpful in patients with pulmonary vascular disease and cyanotic congenital heart disease in whom severe hypoxemia has evoked substantial polycythemic. Phlebotomy is recommended for symptoms of polycythemia, such as headache or blurry vision, or if the hematocrit is greater than 65%-70%. Caution is required to avoid depletion of iron stores and to avoid reduction in the circulating blood volume. Cerebrovascular events are more often related to iron-deficiency anemia; however, plasma exchange appears to relieve symptoms for patients with severe polycythemia.

**Treatment of Underlying Conditions**

Before initiating treatment for a patient’s pulmonary arterial hypertension, treatment should be started for any underlying or associated conditions. After these other disorders have been optimally treated, additional treatment for the pulmonary arterial hypertension itself should be considered.

**Conventional Medical Therapy**

**Anticoagulation**
Histologic data demonstrate thrombotic lesions in small pulmonary arteries in a significant percentage of patients with idiopathic pulmonary arterial hypertension, and limited clinical data support the chronic use of anticoagulation in idiopathic pulmonary arterial hypertension. Warfarin anticoagulation is recommended to achieve an INR of 1.5-2; however, certain clinical circumstances may require a higher INR, and a lower INR is often appropriate for patients at a higher risk for bleeding. Heparin subcutaneously (5,000-10,000 units twice daily) or low molecular weight heparin (1mg/kg subcutaneously twice daily) may be suitable alternatives in patients with adverse effects to warfarin. Patients with chronic thromboembolic disease are treated with higher doses of warfarin, i.e., to achieve an INR of 2.5-3.5. Whether chronic anticoagulation is useful in patients with other forms of pulmonary arterial hypertension remains unknown.

**Calcium Channel Blockers**

Approximately 8-10% of adult patients with idiopathic pulmonary arterial hypertension appear to have a favorable response with acute vasodilator testing (as defined above) and (in uncontrolled studies) respond to chronic oral calcium channel blockade, as documented by an improvement in symptoms, exercise tolerance, hemodynamics and survival. Although most studies have used calcium channel blockers at relatively high doses, e.g., long-acting nifedipine 120 mg to 240 mg daily or amlodipine 20-40 mg daily, the optimal dosing for patients with idiopathic pulmonary arterial hypertension is uncertain. Patients with no evidence of an acute hemodynamic response to these drugs are unlikely to benefit from chronic therapy. Furthermore, because of the frequent adverse effects, including systemic hypotension, pulmonary edema, right ventricular failure, and
death, calcium channel blockers should be used only in patients in whom acute effectiveness has been demonstrated.

**Inotropic Agents/Diuretics**

The efficacy and toxicity of cardiac glycosides in pulmonary arterial hypertension remains unknown. Diuretics can reduce the increased intravascular volume and hepatic congestion that occur in patients with right heart failure, although great care should be taken to avoid excessive diuresis that decreases cardiac output in patients who are highly dependent on preload.

**Supplemental Oxygen**

Supplemental low-flow oxygen alleviates the arterial hypoxemia and attenuates the pulmonary hypertension in patients with chronic pulmonary parenchymal disease. In contrast, most patients with the Eisenmenger syndrome derive little hemodynamic benefit from supplemental oxygen, although patients with the Eisenmenger syndrome as well as patients with other forms of pulmonary arterial hypertension, including idiopathic pulmonary arterial hypertension, may benefit from supplemental ambulatory oxygen if they have oxygen desaturation with activity. In addition, supplemental oxygen is often helpful for patients who have substantial right heart failure and who have a low cardiac output at rest.

**Targeted Medical Therapy**

**Prostaglandins**
Prostacyclin (epoprostenol) or prostacyclin analogue treatment is supported by the imbalance of thromboxane to prostacyclin and the demonstration of a reduction in prostacyclin synthase in the pulmonary arteries of patients with idiopathic pulmonary arterial hypertension. Continuous intravenous epoprostenol improves exercise endurance and hemodynamics in patients with WHO Functional Class III or IV idiopathic pulmonary arterial hypertension (Grade A)\(^1\) or pulmonary arterial hypertension related to connective tissue disease (Grade A)\(^2\); in addition, survival is improved with continuous intravenous epoprostenol in Functional Class III or IV idiopathic pulmonary arterial hypertension (Grade A)\(^1\). The starting dose is 1 to 2 ng/kg/min with incremental increases, especially during the first several months of initiation. A mean dose after one year is 20-40 ng/kg/min for most patients, although there appears to be significant variability of the optimal dose. Continuous intravenous epoprostenol has also been used to treat patients with pulmonary arterial hypertension related to congenital systemic to pulmonary shunts, portal hypertension, HIV infection, or drugs and toxins, with reported improvement in exercise capacity, hemodynamics, and possibly survival, in uncontrolled studies.

In an attempt to avoid intravenous therapy, prostacyclin analogues administered by continuous subcutaneous infusion (treprostinil) or by inhalation (iloprost; 6-9 inhalations per day; 2½-5 mg/dose), are prostaglandin alternatives (Grade A)\(^3\). Treprostinil is started at 1 ng/kg/min and increased to achieve an optimal dose; treprostinil is approximately 30-40% as potent as epoprostenol. Treprostinil can also be administered by continuous intravenous infusion; its stability at room temperature and longer t\(\frac{1}{2}\) ~4½ hours in pulmonary arterial hypertension
patients is preferred to continuous intravenous epoprostenol by some patients. Treprostinil administered by inhalation (4 inhalations per day) is in clinical development.

**Endothelin Receptor Antagonists**

Endothelin-1, one of the most potent vasoconstrictors identified to date, has been implicated in the pathobiology of pulmonary arterial hypertension. The ET_A/ET_B antagonist bosentan was the first approved oral therapy for pulmonary arterial hypertension (Grade A). Bosentan is initiated at 62.5 mg twice daily for 4 weeks followed by uptitration to 125 mg twice daily. More recently, the orally active selective ET_A receptor antagonist sitaxsentan (100 mg once daily) has been approved for the treatment of pulmonary arterial hypertension (Grade A), and ongoing clinical development continues with another selective ET_A receptor antagonist, i.e. ambrisentan. Adverse effects of endothelin receptor antagonists include acute liver toxicity with an increase in hepatic transaminase levels; in addition, sitaxsentan reduces the metabolism of warfarin, i.e. a lower dose of warfarin is needed to achieve a therapeutic International Normalized Ratio.

**Nitric Oxide and Phosphodiesterase Inhibitors**

Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells, which increases cyclic GMP and decreases intracellular calcium concentration, thereby leading to smooth muscle relaxation. When inhaled, the rapid combination of nitric oxide with hemoglobin inactivates any nitric oxide diffusing into the blood, preventing systemic vasodilatation. Nitric oxide is therefore a potent and selective pulmonary vasodilator when administered by inhalation.
Although there is considerable experience with the use of inhaled nitric oxide as a short-term treatment for pulmonary hypertension in a variety of clinical situations, its chronic administration is cumbersome.

The pulmonary vasodilator effects of nitric oxide are mediated through its second messenger, i.e. cyclic guanosine monophosphate, which is rapidly degraded by phosphodiesterases. Phosphodiesterase type 5 is the predominant cyclic guanosine monophosphate metabolizing phosphodiesterase isoform in the lung, and it has been shown to be upregulated in conditions associated with pulmonary hypertension. By selectively inhibiting phosphodiesterase type 5, sildenafil promotes the accumulation of intracellular cyclic guanosine monophosphate thereby enhancing nitric oxide mediated vasodilatation; it may also induce antiproliferative effects in the pulmonary vasculature. Sildenafil improves exercise endurance, hemodynamics and functional class in patients with WHO Functional Class II, III or IV pulmonary arterial hypertension (Grade A). The recommended starting dose is 20 mg orally three times a day with an increase to 40 mg and/or 80 mg orally three times daily if needed to achieve and/or maintain its efficacy. More recently, clinical development continues with the phosphodiesterase type 5 inhibitor tadalafil.

**Interventional Therapy**

*Congenital Heart Disease*

Most patients with pulmonary hypertension due to systemic to pulmonary shunts will have had surgical repair as infants or children to prevent the development of irreversible pulmonary
vascular disease. New approaches to evaluation and peri-operative or peri-interventional (via interventional cardiac catheterization) management now make repair of congenital heart defects possible in many patients who present later in life with elevated pulmonary vascular resistance. For example, inhaled nitric oxide, intravenous epoprostenol or inhaled iloprost can unmask reversible pulmonary vasoconstriction and determine the minimal pulmonary vascular resistance that can be achieved. Temporary balloon occlusion of congenital heart defects or a patent foramen ovale with subsequent re-measurement of pressures can predict post repair hemodynamics. In contrast, pulmonary hypertension due to pulmonary venous hypertension is reversible whenever the left sided obstructive lesion is relieved, although the pulmonary hypertension may take months to resolve.

These newer approaches to the evaluation of surgical operability or repair via an interventional cardiac catheterization in patients with congenital heart disease are also being applied to treating perioperative and postoperative acute pulmonary hypertensive crises in patients with pulmonary arterial hypertension undergoing non cardiac operations. If a patient with elevated pulmonary resistance is being considered for surgery, there is an increased risk of postoperative pulmonary hypertensive crises. Knowing if the pulmonary circulation will respond favorably to inhaled nitric oxide, intravenous epoprostenol, inhaled iloprost or intravenous sildenafil will help in the management of this potential life threatening periooperative complication.

**Atrial Septostomy**
The rationale for the creation of an atrial septostomy in pulmonary arterial hypertension is based on experimental and clinical observations suggesting that an intra-atrial defect, allowing right to left shunting, may be beneficial in the setting of severe pulmonary hypertension. This procedure, though still investigational, may help patients who have severe pulmonary hypertension, recurrent syncope, and/or right ventricular failure despite maximal medical therapy and who have an intact atrial septum or a restrictive patent foramen ovale. It is also used for temporary palliation as a bridge to transplantation, in which case the atrial septostomy can be closed at the time of transplantation.

Heart-Lung or Lung Transplantation

Since 1981, over 1800 patients have undergone either a single lung, double lung, or heart-lung transplantation for progressive pulmonary hypertension worldwide. The operative mortality ranges between 15%-30% and is affected by the primary diagnosis. The one-year survival is between 65%-75%, three-year survival between 45%-55%, five-year survival between 40%-45% and ten-year survival 20-25%. Timing a referral for transplantation depends upon the patient’s prognosis with optimal medical therapy, the anticipated waiting time for transplantation in the region, and the expected survival after transplantation.

Evidence-Based Treatment Algorithm

The treatment algorithm based on the evidence derived from clinical trials published through 2002 is depicted in Figure 64-7. This algorithm was agreed upon at the 2003 Third World
Symposium on Pulmonary Arterial Hypertension. Based on the controlled clinical trials performed in pulmonary arterial hypertension, an evidence-based treatment strategy was adopted with the abandonment of a clinical-based treatment strategy. The algorithm is restricted to WHO Functional Class III or IV because these patients represented the largest population included in the controlled clinical trials as of 2002. In addition, these treatments were primarily evaluated in patients with idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension related to connective tissue disease or anorexigen use, and therefore extrapolation of the therapeutic recommendations to other pulmonary arterial hypertension subgroups requires caution. Since 2002, sildenafil and sitaxsentan have been approved for the treatment of PAH, and treprostinil has been approved for continuous intravenous infusion, further improving therapeutic options (Figure 64-8).

X. FUTURE DIRECTIONS

Future progress is likely to focus on attempts to discover final common pathways for pulmonary hypertensive diseases, to develop molecular and physiologic tests to monitor and diagnose pulmonary vascular disease, and to test currently available therapies and develop new ones based on established pathobiologic mechanisms. Investigations are needed to further elucidate the genetic basis of pulmonary arterial hypertension, including genome scanning for major and minor genes, analysis of genetic profiles of patients for candidate genes likely to modify risk for disease (e.g. serotonin transporter alleles, nitric oxide synthase), proteomics, transgenic mice, and altered signal transduction. Advances in genetic testing, presymptomatic screening, and biomarkers should permit early detection of disease in those at risk for pulmonary arterial
hypertension. With the clinical development of therapeutic modalities with different mechanisms of action, considerable interest has developed for the use of combination therapy, similar to the strategies utilized in the treatment of systemic hypertension and many forms of cancer. Some agents, such as phosphodiesterase inhibitors, may enhance and prolong the effects of others, e.g. prostaglandins. Other combinations may approach the problem from different mechanistic angles, and thus have potentially additive and/or synergistic effects. In addition to increasing efficacy, combination therapy may also allow lower dosages of the various agents, thereby minimizing side effects and toxicity. However, due to possible drug-drug interactions with unexpected increases in toxicity, well controlled clinical trials with combination therapy are needed. Hopefully, further research in clinical drug development will lead to further improvements in the treatment of this very challenging disease.
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).
LEGENDS

**Figure 64-1.** Signaling pathways of the bone morphogenetic protein receptor Type II (BMPR II). In the extracellular space, the receptor ligands BMPs bind directly to the BMPR-II on the cell membrane. The bioavailability of BMPs is regulated by the presence of BMPR-II receptor antagonists such as noggins, chordins and DAN (Differential screening-selected gene Aberrative in Neuroblastoma). The binding of ligands to BMPR-II leads to the recruitment of BMPR-I to form a heteromeric receptor complex at the cell surface. This complex results in the phosphorylation and activation of the kinase domain of BMPR-I. The activated BMPR-I subsequently phosphorylates and activates cytoplasmic signaling proteins Smads (Smad 1, 5 and 8). Phosphorylated Smads bind to the common mediator Smad 4, and the resulting Smad complex moves from the cytoplasm into the nucleus and regulates gene transcription. Other downstream signaling pathways that can be activated following the engagement of BMPR-I and BMPR-II by BMPs include cell-type dependent activation of p38 mitogen activated protein kinase (p38 MAPK) and protein kinase A (PKA). In addition, the cytoplasmic tail of BMPR-II has been shown to interact with the LIM motif-containing protein kinase 1 (LIMK1) that is localized in the cytoskeleton. Germ-line mutations of the gene encoding BMPR-II underlie idiopathic pulmonary arterial hypertension (IPAH), which is characterized by the abnormal proliferation of pulmonary vascular cells. However, the specific cytoplasmic proteins and nuclear transcription factors that are involved in the development of PPH have not been identified.
**Figure 64-2.** Schematic View of Pulmonary Arterial Hypertension Pathobiology. Pulmonary arterial hypertension has a multifactorial pathobiology; it is unlikely that one factor or gene mutation will explain all causes of pulmonary arterial hypertension. Dysfunctional pulmonary artery endothelial cells have a decreased production of prostacyclin and nitric oxide, with an increased production of endothelin-1 promoting vasoconstriction and proliferation of pulmonary artery smooth muscle cells.

**Figure 64-3.** Schematic View of Pulmonary Arterial Hypertension Pathophysiology. CO = Cardiac output; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

**Figure 64-4.** An ECHO image from a patient with pulmonary arterial hypertension showing an enlarged right ventricle, flattened interventricular septum with a small left ventricle cavity.

**Figure 64-5.** Guidelines for evaluating pulmonary hypertension. Abbreviations: BNP = brain natriuretic peptide; CBC = complete blood count; CT = computed tomography; CTD = connective tissue disease; EBCT = electron beam computerized tomography; HIV = human immunodeficiency virus; HRCT = high-resolution computerized tomography; LFTs = liver function tests; PH = pulmonary hypertension; RHC = right heart catheterization; SaO₂ = systemic arterial oxygen saturation; TEE = transesophageal echocardiography; VD = vasodilator; V/Q = ventilation/perfusion.

**Figure 64-6.** Survival of patients with PAH based on etiology: CHD = congenital heart disease; CTD = connective tissue disease; HIV = human immunodeficiency virus related; IPAH =
idiopathic pulmonary arterial hypertension; Portopulm = portopulmonary hypertension.

Reprinted with permission from McLaughlin et al. Chest 2004;126:78S-92S.

Figure 64-7. Evidence-Based Treatment Algorithm derived from clinical trials published through 2002, based on the consensus from the 2003 Third World Symposium on Pulmonary Arterial Hypertension. Levels of evidence A, B, and C defined as: Level of Evidence A - data derived from multiple randomized clinical trials or meta-analyses; Level of Evidence B - data derived from a single randomized clinical trial or from multiple randomized clinical trials with heterogeneous results; Level of Evidence C - data derived from small nonrandomized studies and/or consensus opinion of experts; inh = inhaled; IV = continuous intravenous. (1) The algorithm is restricted to patients in New York Heart Association (NYHA) functional class III or IV because they represent the largest population included in controlled clinical trials. For NYHA functional class I or II, very few data are available. In addition, the different treatments have been evaluated mainly in sporadic idiopathic pulmonary arterial hypertension (IPAH) patients, and in pulmonary arterial hypertension (PAH) associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution. (2) Owing to the complexity and dangers of the acute vasoreactivity tests, and to the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. (3) The acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in individuals with IPAH and PAH associated to anorexigen use. (4) A positive acute response to vasodilators is defined as a drop in mean pulmonary artery pressure of at least 10 mm Hg to \( \leq 40 \) mm Hg, with an increase or unchanged cardiac output during acute challenge with inhaled nitric
oxide (NO), IV epoprostenol, or IV adenosine. (5) Sustained response to calcium channel blockers (CCBs) is defined as patients being in NYHA functional class I or II with near-normal hemodynamics after several months of treatment. (6) In patients in NYHA functional class III, first-line therapy may include oral endothelin receptor antagonists, chronic IV epoprostenol, or prostanoid analogues. Phosphodiesterase type 5 (PDE5) inhibitors should be considered in patients who have failed or are not candidates to other therapies. (7) Most experts consider that NYHA functional class IV patients in unstable condition should be treated with IV epoprostenol (survival improvement, worldwide experience, and rapidity of action). Reprinted with permission from JACC 2004; 43 (12;Suppl S):81S-88S

**Figure 64-8.** Evolving Evidence-Based Treatment Algorithm derived from clinical trials published through 2005. Levels of evidence A, B, and C defined as: Level of Evidence A - data derived from multiple randomized clinical trials or meta-analyses; Level of Evidence B - data derived from a single randomized clinical trial or from multiple randomized clinical trials with heterogeneous results; Level of Evidence C - data derived from small nonrandomized studies and/or consensus opinion of experts; inh = inhaled; IV = continuous intravenous. (1) Owing to the complexity and dangers of the acute vasoreactivity tests, and to the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. (2) The acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in individuals with IPAH and PAH associated to anorexigen use. (3) A positive acute response to vasodilators is defined as a drop in mean pulmonary artery pressure of at least 10 mm Hg to \( \leq 40 \) mm Hg, with an increase or unchanged cardiac output during acute challenge with inhaled nitric oxide (NO), IV
epoprostenol, or IV adenosine. (4) Sustained response to calcium channel blockers (CCBs) is defined as patients being in NYHA functional class I or II with near-normal hemodynamics after several months of treatment. (5) In patients in NYHA functional class III, first-line therapy may include oral endothelin receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, prostanoid analogues or chronic IV prostacyclin. (6) Most experts consider that NYHA functional class IV patients in unstable condition should be treated with chronic IV prostacyclin.
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 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>
<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>
<tr>
<td>Total</td>
<td>100.0</td>
<td>30,000</td>
<td>9525 (32%)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medial hypertrophy in the small pulmonary arteries.</td>
</tr>
<tr>
<td>2</td>
<td>Concentric or eccentric cellular intimal proliferation and thickening within the smaller pulmonary arteries and arterioles.</td>
</tr>
<tr>
<td>3</td>
<td>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.</td>
</tr>
<tr>
<td>4</td>
<td>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.</td>
</tr>
<tr>
<td>5</td>
<td>Thinning and fibrosis of the media superimposed upon the formation of numerous complex dilatation lesions.</td>
</tr>
<tr>
<td>6</td>
<td>Necrotizing arteritis within the media with surrounding areas of inflammatory reaction and granulation tissue.</td>
</tr>
</tbody>
</table>
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 64-1. (ppt slide)

Figure 64-2. (ppt slide)

Figure 64-3. (ppt slide)

Figure 64-4. (glossy photograph)
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
Figure 64-6. (ppt slide)

Figure 64-7. (ppt slide)

Figure 64-8. (ppt slide)
Signaling Pathways of BMPR-II

Antagonists (noggin, chordins, DAN) -> BMPs (BMP 4, BMP 7 in lung)

BMPR-I -> BMPR-II

LIMK1 -> Smad 1, Smad 5, Smad 8, Smad 4

p38 MAPK -> PKA

Proliferation of Pulmonary Vascular Cells

PPH

Genetic Predisposition + Vascular Injury

Endothelial Proliferation and Dysfunction

Coagulation Abnormalities -> Vasodilator/Vasoconstrictor Imbalance

Thrombosis in situ -> Vascular Smooth Muscle Hypertrophy

Vascular Smooth Muscle Hypertrophy -> Pulmonary Vasoconstriction

Plexogenic and Thrombotic Pulmonary Arteriopathy
Right Heart Failure/Death

Pre-symptomatic/Compensating
Symptomatic/Decompensating
Declining/Decompensated

Time (variable)

CO
PVR PAP

Symptom Threshold
Right Heart Failure/Death
**CHD**

**Portopulmonary**

**IPAH**

**CTD**

**HIV**

**Endothelin Receptor Antagonists**
- Bosentan (A)
- Prostanoid analogues
  - Iloprost inh (B)
  - Treprostinil SC (B)
  - Beraprost (B)
  - Epoprostenol IV (A)

**Oral CCB (C)**
- Continue CCB

**Sustained Response**
- Yes
- No

**PAH, NYHA Class III/IV(1)**

**Background Therapy (C)**
- (oral anticoagulants ± diuretics ± O₂)

**Expert Referral(2)**

**Acute Vasoreactivity Test(3)**
- Positive(4)
- Negative

**NYHA Class III(5)**

**Endothelin Receptor Antagonists**
- Bosentan (A)
- Prostanoid analogues
  - Iloprost inh (B), Treprostinil SC (B), Beraprost (B)
  - or
  - Epoprostenol IV(A)

**PDE-5 inhibitors**
- Sildenafil (B)

**NYHA Class IV(7)**

**Epoprostenol IV (A)**
- Bosentan (B)
- Treprostinil SC (B)
- Iloprostenol IV (C)

**Epoprostenol IV (A)**
- Bosentan (B)
- Treprostinil SC (B)
- Iloprostenol IV (C)

**Atrioseptostomy (C)**
- and/or
- Lung transplant (C)

**No improvement or deterioration:**
- (Combination therapy?)

**Background Therapy (C)**
- (oral anticoagulants ± diuretics ± O₂)
Endothelin Receptor Antagonists
- Bosentan (A)
- Sitaxsentan (A)

or

PDE-5 inhibitors
- Sildenafil (A)

or

Prostanoid analogues
- Iloprost inh (B)
- Treprostinil SC (B)
- Beraprost (B)

or

Continuous IV prostacyclin
- Epoprostenol IV (A)
- Treprostinil IV (C)
- Iloprost inh (B)
- Iloprost IV (C)

Sustained Response (NYHA I-II)
- Oral CCB (C)
- Continue CCB

Supportive Therapy and General Measures (C)
- Exercise limitation
- Birth control
- Psychological assistance
- Infection prevention

Acute Vasoreactivity Test
- Positive
- Negative

NYHA Class I-III

NYHA Class III

NYHA Class IV

Endothelin Receptor Antagonists
- Bosentan (A)
- Sitaxsentan (A)

or

PDE-5 inhibitors
- Sildenafil (A)

or

Prostanoid analogues
- Iloprost inh (A)
- Treprostinil SC (B)
- Beraprost (B)

or

Continuous IV prostacyclin
- Epoprostenol IV (A)
- Treprostinil IV (C)
- Iloprost IV (C)

No improvement or deterioration:
Combination therapy? (B)

BAS (C) and/or
Lung transplant (C)