greater than 30 mm Hg during exercise. The many causes of pulmonary hypertension are summarized in Table 12-3.

Patients with pulmonary hypertension not only have an elevated pulmonary arterial pressure but also a low cardiac output, causing symptoms of exertional dyspnea, fatigue, and syncope. Pulmonary capillary wedge pressure is usually normal (≤15 mm Hg) except in patients with pulmonary hypertension due to impaired left ventricular systolic or diastolic function or left-sided valvular heart disease.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is caused by a combination of pulmonary vasoconstriction, endothelial cell and/or smooth muscle proliferation, intimal fibrosis, and thrombosis in the pulmonary capillaries and arterioles. PAH is either idiopathic (primary pulmonary hypertension) or secondary to connective tissue disease, congenital heart disease, portal hypertension, human immunodeficiency virus (HIV) infection, or anorexigenic drugs or toxins. Connective tissue diseases, particularly scleroderma, are the most common secondary causes of PAH.

Patients with mild PAH can be asymptomatic, but patients with more advanced disease complain of dyspnea, chest pain, syncope, or presyncope. Physical findings include a left parasternal lift, loud pulmonary component of the second heart sound, murmur of tricuspid or pulmonic regurgitation, hepatomegaly, peripheral edema, or ascites. Associated electrocardiogram (ECG) abnormalities indicate right ventricular hypertrophy, right atrial enlargement, or right axis deviation. Echocardiography provides important information about the severity of the pulmonary hypertension (e.g., estimated pulmonary artery pressure, right ventricular dimensions and function) and its potential causes (e.g., left ventricular failure, valvular lesions, congenital heart disease with left-to-right shunt). Pulmonary function tests, ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scans, polysomnography or overnight oximetry, autoantibody tests, HIV serology, and liver function tests also should be performed to determine other potential causes. Right ventricular catheterization should be performed in all patients with suspected PAH. Under basal conditions in the catheterization laboratory, an elevated mean pulmonary artery pressure exceeding 25 mm Hg, a pulmonary capillary wedge pressure of less than 15 mm Hg, and a pulmonary vascular resistance exceeding 3 units confirm the diagnosis. Acute vasodilator drug challenge should be performed during right ventricular catheterization to guide appropriate treatment.

Without treatment, the prognosis of PAH is poor, with a median survival time of less than 3 years. Patients with severe symptoms should be treated with prostacyclin or epoprostenol (an intravenous prostacyclin analogue) because of their proven efficacy in improving exercise capacity, quality of life, and survival. Other prostacyclin analogues, such as treprostinil and iloprost, are also effective in reducing pulmonary artery pressure and improving exercise capacity. Other classes of drugs approved for treatment of PAH include endothelin-receptor blockers (bosentan or ambrisentan) and PDE5 inhibitors (sildenafil, tadalafil). Much higher daily doses of PDE5 inhibitors are needed to treat PAH than to treat erectile dysfunction or prostatism. Oral CCBs are indicated for the small subset of patients with mild to moderate symptoms who demonstrate significant reduction in pulmonary pressure with acute CCB challenge (decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute level of less than 40 mm Hg without a decrease in cardiac output). Supplemental home oxygen is indicated for all patients with hypoxemia. Travel to high elevations exacerbates hypoxia, and relocation to sea level improves symptoms. Oral anticoagulation is recommended for all patients with PAH. Diuretics should be prescribed for patients with peripheral edema or hepatic congestion. Lung transplantation is recommended only for patients in whom severe symptoms occur despite intensive medical therapy.

TABLE 12-3 CLASSIFICATION OF PULMONARY HYPERTENSION

CATEGORY	EXAMPLES
1. Pulmonary arterial hypertension (PAH)	
A. Primary or idiopathic PAH	Sporadic Familial
B. Secondary PAH	Connective tissue disease Congenital heart disease Portal hypertension Human immunodeficiency virus infection Drugs and toxins: anorexigens, cocaine
2. Pulmonary venous hypertension	Left ventricular heart failure Left ventricular valvular heart disease
3. Pulmonary hypertension associated with chronic respiratory disease or hypoxemia	Chronic obstructive pulmonary disease Obstructive sleep apnea
4. Pulmonary hypertension associated with chronic venous thromboembolism	Deep vein thrombosis
5. Pulmonary hypertension due to miscellaneous disorders directly affecting the pulmonary vasculature	Sarcoidosis, histiocytosis X, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

VENOUS THROMBOEMBOLIC DISEASE

The term *venous thromboembolism* (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). Among the adult population in the United States, the overall combined annual incidence is as high as 1 new case per 1000 persons. The incidence of VTE is higher in men than in women and higher in African Americans and whites than in Asians and Hispanics. More than 150 years ago, Rudolf Virchow recognized three predisposing factors: endothelial damage, venous stasis, and hypercoagulation (now known as Virchow's triad). Endothelial damage is common with surgery or trauma; venous stasis is common with prolonged bedrest or immobilization (e.g., leg cast); and hypercoagulation is common with cancer. Trousseau's syndrome consists of migratory thrombophlebitis with noninfectious vegetations on the heart valves (nonbacterial thrombotic endocarditis, formerly known as marantic endocarditis), typically in the setting of mucin-secreting adenocarcinoma. Trousseau, a pathologist, diagnosed his own pancreatic carcinoma on the basis of the association that now bears his name. Hypercoagulable states include hereditary diseases such as deficiencies in antithrombin III, protein C, or protein S; mutation in the factor V gene (factor V Leiden) or the factor II gene (prothrombin G20210A); and hyperhomocysteinemia. However, a thorough search for identifiable risk factors will remain negative in 25% to 50% of patients with VTE.