TABLE 18-1 WORLD HEALTH ORGANIZATION CLASSIFICATION OF PULMONARY HYPERTENSION

Group 1: pulmonary arterial hypertension (PAH)
- Idiopathic PAH
- Heritable PAH
  - Bone morphogenic protein receptor type II
  - ALK-1, endoglin , SMAD9, caveolin-1, KCNK3
  - Unknown
- Drug- and Toxin-Induced
- Associated with PAH:
  - Connective tissue disease
  - Human immunodeficiency virus infection
  - Portal hypertension
  - Congenital heart diseases
  - Schistosomiasis

Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Persistent pulmonary hypertension of the newborn

Group 2: pulmonary hypertension due to left heart disease
- Left ventricular systolic dysfunction
- Left ventricular diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Group 3: pulmonary hypertension due to lung diseases and/or hypoxia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental lung diseases

Group 4: chronic thromboembolic pulmonary hypertension

Group 5: pulmonary hypertension with unclear multifactorial mechanisms
- Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Modified from Simonneau G, Gatzoulis MA, Adatia L, et al: Updated clinical classification of pulmonary hypertension, J Am Coll Cardiol 62:D34–41, 2013.

estimate the level of pulmonary artery systolic pressure. Echocardiography also is useful for excluding group 2 pulmonary hypertension caused by heart diseases that increase pulmonary venous pressures (e.g., mitral valve stenosis).

Pulmonary function tests, lung imaging, and tests for conditions causing hypoxemia (e.g., obstructive sleep apnea) are important for excluding group 3 pulmonary hypertension. Acute pulmonary thromboembolism rarely causes pulmonary hypertension, but recurrent pulmonary emboli or nonresorbed clots that obstruct proximal pulmonary arteries can cause group 4 pulmonary hypertension. The diagnosis of group 4 disease requires a ventilation-perfusion ($\dot{V}/\dot{Q}$) scan, computed tomography (CT) angiography, or pulmonary arteriography.

Definitive diagnosis of PAH requires right heart catheterization and documentation of increased pulmonary arterial pressures and resistance with normal left-sided filling pressures as assessed by pulmonary capillary wedge pressure. Left-to-right intracardiac shunts can also cause pulmonary hypertension due to increased blood flow through the lungs. This can be diagnosed at the time of right heart catheterization by measuring the difference in oxygen content between blood from the superior vena cava and the main pulmonary artery. At the time of right heart catheterization, short-acting vasodilators are usually administered, and hemodynamic responses are recorded. These vasodilator trials are useful in predicting whether patients are likely to respond to calcium-channel blockers (a minority of patients).

Treatment

Modern treatment of PAH includes drugs with vasodilator activity such as calcium-channel blockers, prostacyclin, endothelin receptor antagonists, and phosphodiesterase inhibitors that increase vascular cyclic guanosine monophosphate (cGMP) levels. Continuous intravenous prostacyclin is the only therapy that has been shown to prolong survival and is the recommended treatment for patients with WHO class IV symptoms (level 1 evidence). However, because of the cost and technical challenges of intravenous prostacyclin, oral endothelin receptor antagonists or phosphodiesterase inhibitors, or inhaled or subcutaneous prostacyclin derivatives are preferred for patients with WHO class II or III symptoms.

Most studies of the effects of vasodilator drugs have used the 6-minute walk test as a surrogate for hemodynamic improvement and have demonstrated benefits for exercise tolerance and symptoms (level 1 evidence). Combination therapy may improve symptoms when one agent is not sufficient (level 2-1). In addition to relaxing vascular smooth muscle constriction, vasodilator drugs may stabilize or reverse vascular remodeling in PAH (level 3).

Other interventions include supplemental oxygen, anticoagulation (level 2-1 evidence), and judicious use of diuretic medications. Pulmonary rehabilitation also can improve exercise tolerance (level 1). Heart-lung, double-lung, or single-lung transplantations have been performed in these patients with some success, but the overall 5-year survival rate for PAH patients undergoing lung transplantation is only 50%.

SECONDARY PULMONARY HYPERTENSION

Pulmonary hypertension is associated with many disorders that increase pulmonary venous pressure (e.g., mitral valve stenosis, group 2 pulmonary hypertension) and diseases of the lungs associated with hypoxemia (e.g., sleep apnea, chronic obstructive pulmonary disease, group 3 pulmonary hypertension). These conditions have been called *secondary pulmonary hypertension.*

Vasoconstriction and vascular remodeling contribute to increased pulmonary vascular resistance in secondary pulmonary hypertension. For example, alveolar hypoxia causes intense pulmonary vasoconstriction. Long-standing hypoxia causes vascular remodeling that is similar to plexogenic pulmonary arteriopathy but does not include in situ thromboses or formation of plexiform lesions (E-Fig. 18-4).

Treatment of secondary pulmonary hypertension is directed at the underlying heart or lung disease. If the patient has hypoxia, home oxygen therapy should be used. It is not known whether vasodilator therapy is useful in group 2 or 3 diseases. Group 4 pulmonary hypertension caused by proximal, unresolved clot can be improved by pulmonary thromboembolectomy (level 1 evidence).