mitral valve disease, and heart failure with preserved ejection fraction (HFpEF). PH can develop as a result of all of these conditions. The hallmark of Group II PH (i.e., PH due to left heart disease) is elevated left atrial pressure with resulting pulmonary venous hypertension. In general, the transpulmonary gradient and PVR remain normal. Although this phenomenon is well described in both left-sided valvular disease and left-sided systolic heart failure, studies suggest that HFpEF may carry a higher overall risk of PH.

Whatever the cause of elevated left atrial pressure (i.e., systolic or diastolic heart failure or valvular disease), the increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure. The presence of PH portends a poor prognosis in all forms of heart failure. In particular, chronic pulmonary venous hypertension may lead to a reactive pulmonary arterial vasculopathy, seen as an elevated transpulmonary gradient (>12 mmHg) and elevated PVR (>3 Wood units). Pathologically, this process is marked by pulmonary arteriolar remodeling with intimal fibrosis and medial hyperplasia akin to that seen in PAH.

Pulmonary Hypertension Associated with Lung Disease Intrinsic lung disease is the second most common cause of PH, although its actual prevalence is difficult to ascertain. PH has been observed in both chronic obstructive lung disease and interstitial lung disease. It can also be seen in diseases with mixed obstructive/restrictive physiology: bronchiectasis, cystic fibrosis, mixed obstructive restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. As in patients with left heart disease, PH associated with chronic lung disease is usually modest; however, some of these patients appear to have PH "out of proportion" to their parenchymal lung disease, suggesting intrinsic pulmonary arterial disease. These patients typically have more severe PH, with results of pulmonary function tests demonstrating a very low DL_{CO}.

Although PH is described in most forms of interstitial lung disease, it has been most extensively studied in idiopathic pulmonary fibrosis; however, the individual studies have been small. Early echocardiographic data suggested that the prevalence of PH in interstitial lung diseases was high, but invasive hemodynamic monitoring suggests that the incidence is considerably lower than originally believed. The diagnosis of PH portends poor outcome in pulmonary fibrosis.

Also included in Group III PH is sleep-disordered breathing. Sleep apnea has long been associated with PH. However, PH associated with sleep-disordered breathing is generally mild.

Pulmonary Hypertension Associated with Chronic Thromboembolic Disease The development of PH after chronic thromboembolic obstruction of the pulmonary arteries is well described, but its incidence is not known. The incidence of PH after a single pulmonary embolic event is thought to be quite low and likely increases following recurrent embolism. The risk factors for developing CTEPH are unclear. Many patients have no history of clinical venous thromboembolism. The pathogenesis of CTEPH is poorly understood. Obstruction of the proximal pulmonary vasculature is important and often the dominant factor; however, additional pulmonary vascular remodeling occurs. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus.

OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

Sarcoidosis Patients with sarcoidosis can develop PH as a result of lung involvement. Consequently, patients with sarcoidosis who present with progressive dyspnea and PH require a thorough evaluation. Although the majority of sarcoidosis patients with PH generally do not respond to therapy for PAH, a subset of patients with sarcoidosis and severe PH do have a beneficial response to therapy.

Sickle Cell Disease Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease, including PH. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronic high CO, and chronic liver disease. The presence of PH in patients with sickle cell disease is rare.

Schistosomiasis Globally, schistosomiasis is one of the most common causes of PH. The development of PH occurs in the setting of hepatosplenic disease and portal hypertension. Studies suggest that inflammation from the infection triggers the pulmonary vascular changes that occur. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PH in these patients is unknown.

PHARMACOLOGIC TREATMENT OF PAH

PH was a consistently fatal condition with no effective medical treatment options before 1996; however, since that time, there has been an upsurge in the development of novel therapeutic agents for PAH. There are several approved agents for PAH, including prostacyclin and prostacyclin analogues, phosphodiesterase-5 inhibitors, a soluble guanylyl cyclase stimulator, and endothelin receptor antagonists, that have improved the outlook dramatically. Although there is no cure for PAH, current pharmacologic therapies improve morbidity and, in some cases, mortality.

PROSTANOIDS

In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A_2 production. Prostacyclin (PGI_2) activates cyclic adenosine monophosphate (cAMP)-dependent pathways that mediate vasodilation. PGI_2 also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of mediators is addressed by the exogenous administration of prostanoids as therapy in advanced PAH.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epoprostenol in WHO functional class 3 and 4 PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-minute walk distance (6MWD), and mortality. Treprostinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for continuous subcutaneous and intravenous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH.

Inhaled prostacyclins provide the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects (risk of infection and infusion site reactions) of infusion catheters. Both inhaled iloprost and treprostinil have been approved for patients with WHO class 3 and 4 PAH. The main advantage of treprostinil is less frequent administration. Inhaled formulations can be efficacious in moderately symptomatic patients with PAH and may be appropriate when used in combination with an oral medication. Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil) increase cyclic guanosine monophosphate (cGMP) levels and activate cGMP-dependent signaling pathways that also mediate vasodilation and platelet inhibition. Thus, the addition of a PDE5 inhibitor augments the pulmonary hemodynamic and functional capacity benefits of prostanoids in PAH.

Endothelin Receptor Antagonists Endothelin receptor antagonists (ERAs) target endothelin-1 (ET-1), a potent endogenous vasoconstrictor and vascular smooth muscle mitogen that is elevated in PAH patients. Endothelin levels are increased coincident with increased PVR and mPAP and decreased CO and 6MWD.

ERAs block the binding of ET-1 to either endothelin receptor A (ET-A) and/or B (ET-B). ET-A receptors found on pulmonary artery smooth muscle cells mediate vasoconstriction. In the normal pulmonary vasculature, ET-B receptors are found on endothelial cells and mediate vasodilation via production of prostacyclin and nitric oxide as well as ET-1 clearance. Three ERAs approved for use in the United States are bosentan and macitentan both, nonselective receptor antagonists, and ambrisentan, a selective ET-A receptor antagonist.

Studies have shown that both bosentan and macitentan improve hemodynamics and exercise capacity and delay clinical worsening.