

## Pulmonary Hypertension

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Pulmonary hypertension (PH) is a complex, multidisciplinary disorder, involving five distinct etiologic groups: 1) Pulmonary arterial hypertension (PAH), 2) PH owing to left heart disease, 3) PH owing to lung disease and/or hypoxemia, 4) chronic thromboembolic pulmonary hypertension (CTPH), and 5) PH with unclear multifactorial mechanisms. PH is defined as a resting mean pulmonary arterial pressure  $> 25$  mmHg. The subgroup of PH known as PAH adds the criterion that the pulmonary arterial wedge pressure must be  $< 15$  mmHg.

Due to the similar pathobiology and current management strategies, PAH has been the focus of the classification, and the nomenclature of the subgroups and associated conditions have evolved in time. At present, PAH includes the idiopathic (formerly known as PPH) and heritable forms of PAH. Idiopathic PAH corresponds to sporadic disease in which there is neither a family history of PAH nor identified risk factor. Familial PAH often results from a mutation in the bone morphogenetic protein receptor-2 (BMPR2) and is inherited as an autosomal dominant disease with incomplete penetrance and genetic anticipation. PAH is also associated with connective tissue disease, congenital heart disease, drugs and toxins, human immunodeficiency virus, portal hypertension, schistosomiasis, and some hemoglobinopathies. Persistent PH of the newborn, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are also included in the group of PAH.

PAH is characterized by increased pulmonary vascular resistance (PVR) and arterial pressure that eventually can lead to right heart failure and death. While previously considered a rare disease, recent evidence suggests that, as a group, the prevalence of PAH is about 15 per million. Despite advances in treatment, idiopathic PAH (IPAH) is still a disease with poor prognosis. Without treatment, the median survival in IPAH has been estimated in 2.8 years from diagnosis.

Increased PVR in IPAH is the result of vascular obstruction of the small pulmonary arterioles. Vasoconstriction, in situ thrombosis, and an abnormal proliferation of vascular cells (endothelial, smooth muscle, and fibroblasts) are the main factors involved in the pathophysiology of increased PVR. Multiple pathogenic pathways have been implicated in the development of PAH, including those at the molecular and genetic levels and in the smooth muscle, endothelial cells and adventitia. It is also recognized that PAH involves an imbalance of abnormal proliferation and apoptosis. Likewise, the role of inflammatory cell activation and that of the oxidative stress have been recently emphasized.

While pulmonary vascular thrombosis is widely accepted as the main pathophysiologic factor in patients with CTPH, the role of thrombotic arteriopathy in the pathophysiology of PAH and the use of anticoagulants in the treatment of PAH are controversial issues. It has been suggested that thrombotic arteriopathy is an epiphenomenon of the underlying pulmonary vascular disease. There is, however, evidence that thrombotic arteriopathy is an integral component of pulmonary vascular

remodeling, luminal narrowing, and increased PVR and contributes to the progression of IPAH.

The diagnosis and management of PAH has undergone significant change in the last few years. Among all the pathogenic factors, the imbalance in the vasoconstriction/vasodilator factors described in this condition (excess of endothelin-1, and deficit of prostacyclin and nitric oxide) has served as the rationale for current medical therapies. There is no question that with the contemporary use of prostanoids, endothelin-receptor antagonists, and phosphodiesterase-5 inhibitors, the exercise capacity, the quality of life, and possibly the survival of patients with PAH have improved significantly in recent years. It is also true, however, that a definitive cure for the disease does not exist.

There are many areas or important pathobiology pathways, with therapeutic potential, to be explored in future years. There is a need for well-designed clinical trials with appropriate end points that will enable reliable interpretation of the risk / benefit profile of all emerging therapies. Also, from the knowledge we have about the natural history of PAH, it has been increasingly recognized that we are making the diagnosis late in the course of the disease and thus, along with the development of new therapeutic options, an early and accurate diagnosis of PAH becomes increasingly important if we want to improve the prognosis of this very sick patient population in the upcoming years.