Group III Pulmonary Hypertension

Pulmonary Hypertension Associated with Lung Disease: Epidemiology, Pathophysiology, and Treatments

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KEYWORDS

• Pulmonary hypertension • Chronic obstructive pulmonary disease • Interstitial lung disease
• Obstructive sleep apnea • Endothelin receptor antagonist • Phosphodiesterase inhibitor
• Prostacyclin • Soluble guanylate cyclase stimulator

KEY POINTS

- Pulmonary hypertension occurs frequently in most chronic lung diseases, but is usually moderate with mean pulmonary artery pressure in the range of 20 to 30 mm Hg.
- The presence of even moderate pulmonary hypertension in chronic lung disease is associated with increased morbidity and mortality.
- The cause of pulmonary hypertension in chronic lung disease is multifactorial and includes loss of peripheral pulmonary vessels, chronic or recurrent hypoxia, and altered expression of vascular and inflammatory mediators.
- Management should be directed at treating the underlying lung disease because currently available medications for the treatment of pulmonary arterial hypertension have not been found to be effective for the treatment of pulmonary hypertension associated with chronic lung disease.
- Patients with severe pulmonary hypertension and mild to moderate lung disease may deserve consideration for enrollment in clinical trials or referral to centers experienced in the management of pulmonary arterial hypertension.

INTRODUCTION

Increased pulmonary arterial pressure (PAP) is a common feature of many chronic lung diseases and chronic lung disease is the second most common cause of pulmonary hypertension (PH).[1] PH caused by chronic lung disease is referred to as group 3 PH in the most recent classification scheme presented by the World Health Organization (WHO) meetings on PH (see Oudiz RJ: Classification of Pulmonary Hypertension, in this issue). Screening studies suggest that approximately a quarter of all patients with increased PAP have WHO group 3 PH.[1] The most common lung diseases in WHO group 3 PH are chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and obstructive sleep apnea (OSA). PH associated with pulmonary sarcoidosis

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and Langerhans histiocytosis X are classified as WHO group 5 PH (see Tannenbaum SK, Gomberg-Maitland M: Group 5 Pulmonary Hypertension: The Orphan's Orphan Disease, in this issue). The presence of PH in chronic lung disease is strongly associated with decreased survival, decreased functional capacity, and increased complications. However, it is unclear whether PH is the cause of worse outcome in these patients or simply a marker of more advanced lung disease.

Although treatment of the underlying lung condition remains the primary approach to managing PH associated with chronic lung disease, this is often easier said than done. PH often occurs in advanced lung diseases that are usually irreversible. When little else remains to be done for a patient's lung disease, health care providers often look to other associated conditions that might be addressed in order to improve the outcome of the patient. The large number of drugs that have been developed and approved for WHO group 1 pulmonary arterial hypertension (PAH) over the last 20 years has made it increasingly difficult to resist the temptation of using these medications to treat PH associated with chronic lung disease. Furthermore, the strong negative correlation between pulmonary artery (PA) pressure and survival in most lung diseases makes it seem reasonable that any success at treating PH in these patients should improve their outcomes. However, findings from a limited number of studies that have attempted to address this issue do not suggest that this is the case.

Two important questions need to be considered when treating PH associated with chronic lung disease: (1) are currently available medications able to improve pulmonary vascular resistance (PVR) in chronic lung disease, and (2) does improving pulmonary hemodynamics in chronic lung disease improve patient outcome? The latter question is particularly important because, unlike patients with idiopathic PAH, those with PH associated with lung disease may be more limited by impairments in ventilation than by cardiac output (CO).

This article reviews the pathophysiology of PH associated with lung disease and summarizes the clinical data that have been generated. Although there are currently no medical therapies that are approved or even recommended for the treatment of PH associated with chronic lung disease, the benefits and limitations of currently available therapies are discussed along with an approach to selecting patients and deciding under what conditions treatment of PH should be attempted.

EPIDEMIOLOGY

The pulmonary circulation is a low-pressure system that normally maintains a small pressure gradient between the pulmonary arterial and pulmonary venous circulations. In healthy adults, mean PAP (mPAP) is 14.0 $\pm$ 3.3 mm Hg[2,3] and right ventricular systolic pressures (RVSPs) are in the range of 24 to 30 mm Hg.[4] Therefore, mPAP of 21 mm Hg, which would result in an RVSP of 35 to 40 mm Hg, is about 2 standard deviations greater than the mean and would be considered to be abnormal. As a result, mPAP of 20 mm Hg and/or RVSP of 35 mm Hg have been used as cutoff values to define PH in many studies, particularly those examining PH in lung disease. However, PAP increases slowly with age and mPAP in patients with Group 1 PAH is well beyond 2 standard deviations from the mean, averaging 50 to 55 mm Hg in most registries.[4–7] As a result, the most widely accepted definition of PH is a mPAP greater than or equal to 25 mm Hg.[2]

In contrast with the near-systemic PAPs seen in patients with PAH, the increase in PAP in patients with chronic lung disease tends to be mild to moderate, with most studies reporting mPAP in the range of 25 to 35 mm Hg. Increase of mPAP to levels normally seen in PAH is rare. Most studies report that only about 3% to 4% of patients with chronic lung disease have mPAP greater than 40 mm Hg. This finding shows one of the marked differences between group 1 PAH and group 3 PH and points to important differences in the underlying pathophysiology and pulmonary vascular remodeling.

Prevalence of Pulmonary Hypertension in Patients with Chronic Obstructive Pulmonary Disease

The true incidence of PH in COPD has been difficult to establish, but most studies reported PH in 30% to 70% of patients.[8–10] This broad range in prevalence rates is attributable to several factors, including differences in the severity of COPD in the population studied, minor differences in the definition used for PH, and differences in the techniques used to assess PAP. Studies using transthoracic echocardiography (TTE) to measure PAP and defining PH as systolic PAP (sPAP) greater than 40 mm Hg report a prevalence of about 35% to 50%. However, TTE has considerable limitations in accurately measuring PAP in patients with chronic lung disease. In one often-cited study the correlation between sPAP estimated by TTE and measured by right heart catheterization (RHC) in patients with advanced lung disease was good (r = 0.69; P<.0001), but varied by