

Editorial

Pulmonary hypertension in chronic respiratory disorders: we need to learn more

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Pulmonary hypertension is a common complication of chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis and sleep apnea. It is estimated that the prevalence of pulmonary hypertension in patients hospitalized for respiratory disorders is 28%.⁽¹⁾ In patients with COPD or idiopathic pulmonary fibrosis who are referred for lung transplantation or lung volume reduction surgery, the prevalence of pulmonary hypertension - defined as mean pulmonary artery pressure (mPAP) >25 mmHg - approaches 30%.⁽²⁻⁴⁾ In general, the pulmonary hypertension seen in such patients tends to be mild, with an mPAP ranging from 25 to 35 mmHg. In the majority of cases, the severity of pulmonary hypertension is directly correlated with the severity of the respiratory disease and with the degree of hypoxemia. However, these correlations are weak, and some patients present severe pulmonary hypertension out of proportion to the severity of the lung disease. For instance, Thabut et al. studied 215 patients with advanced COPD and identified a subgroup of 16 patients that had severe pulmonary hypertension (mPAP, 39.8 ± 10.2 mmHg) and yet presented a more moderate reduction in forced expiratory volume in one second (FEV_1 ; $48.5 \pm 11.8\%$ of predicted).⁽⁵⁾ In a group of 28 patients with idiopathic pulmonary fibrosis, Leuchte et al. identified 6 patients with an mPAP > 35 mmHg.⁽⁶⁾

It seems clear that hypoxic vasoconstriction is not the sole mechanism associated with the pathogenesis of pulmonary hypertension in patients with chronic respiratory disorders. Individuals living at high altitude develop pulmonary hypertension and pulmonary artery medial hypertrophy that are reversible at sea level. In addition, chronic oxygen use does not reverse pulmonary hypertension in patients with COPD or pulmonary fibrosis, suggesting that remodeling of the pulmonary arterial circulation occurs in such patients. In contrast to that seen in individuals living at high altitude, pulmonary hypertension in patients with COPD or pulmonary fibrosis affects all layers of the arterial wall.⁽⁷⁾ These changes are more prominent in the intima, which is thickened by the presence of smooth muscle fibers, together with the deposition of collagen and elastin, in the extracellular space. Furthermore, in patients with pulmonary fibrosis, intimal lesions can lead to acellular fibrosis and cause luminal obstruction, which is more prominent within the fibroblast layer, where the vascular density is

extremely low.⁽⁸⁾ Although the pathobiological mechanisms involved are not well defined, these histological changes appear to be related to abnormalities in the same mediators implicated in the pathogenesis of idiopathic pulmonary hypertension. Such mediators include nitric oxide, endothelin and prostacyclins.

Pulmonary hypertension is associated with worse survival in patients with chronic respiratory disorders. In one cohort of patients with COPD, the 5-year survival rate was 36% for individuals with pulmonary hypertension and 62% for those without.⁽⁹⁾ In patients with severe pulmonary hypertension, median survival is 26 months.⁽²⁾ In a study using echocardiography to estimate pulmonary artery systolic pressure in patients with idiopathic pulmonary fibrosis, mean survival was found to be 0.7 years among those presenting pulmonary artery systolic pressure > 50 mmHg, compared with >4 years in those with pulmonary artery systolic pressure <50 mmHg.⁽¹⁰⁾ These findings were confirmed in a study in which pulmonary hypertension was defined as an mPAP >25 mmHg: in patients with pulmonary hypertension, the 1-year mortality rate was 28%, whereas it was 5.5% in those without pulmonary hypertension.⁽³⁾ Leuchte et al. evaluated prognostic factors in 176 patients with chronic lung diseases such as COPD, pulmonary fibrosis, cystic fibrosis, sarcoidosis and bronchiectasis.⁽¹¹⁾ In that study, elevated levels of brain natriuretic peptide, mPAP ≥ 35 mmHg, pulmonary vascular resistance ≥ 320 dynes.s.cm⁻⁵ and cardiac output ≤ 4.4 L/min were associated with an increase in mortality that was independent from pulmonary function test abnormalities. In this context, the study conducted by Rovedder et al. and published in this issue of the Brazilian Journal of Pulmonology provides further evidence that pulmonary hypertension occurs frequently in patients with cystic fibrosis.⁽¹²⁾ The authors employed echocardiography to identify pulmonary hypertension in 37 patients with cystic fibrosis, using tricuspid regurgitant jet velocity (TRV) to evaluate pulmonary artery systolic pressure. Using TRV cut-off points of 2.5 and 2.8 m/s, the prevalence of pulmonary hypertension was found to be 49% and 30%, respectively. The authors also demonstrated that, in patients with pulmonary hypertension, resting SpO₂, SpO₂ after exertion, forced vital capacity and FEV₁ were significantly lower, and that TRV correlated with various markers of lung disease severity. These significant findings confirm those of other studies

and suggest that, in patients with cystic fibrosis, pulmonary hypertension is linked to the severity of the lung disease. Unfortunately, the authors did not evaluate the functional consequences of pulmonary hypertension in this population. For example, it would have been interesting to investigate whether, among patients with similar lung function, pulmonary hypertension results in a decrease in the distance covered on the six-minute walk test.

Given the high prevalence of certain chronic lung diseases, such as COPD, respiratory disorders are certainly among the most common causes of pulmonary hypertension. In addition, pulmonary hypertension is at least a marker, and more likely a cause, of worse prognosis in this population. Nevertheless, little is known regarding the appropriate management of these patients. Although the treatment of lung diseases and the chronic use of oxygen, as well as lung transplantation, have been extensively studied, there are no robust data regarding the specific treatment of the accompanying pulmonary hypertension. Small uncontrolled studies of prostacyclins, bosentan, sildenafil and inhaled nitric oxide suggest that these agents have a beneficial effect and do not attenuate hypoxic pulmonary vasoconstriction, which could worsen systemic oxygenation. For example, acute sildenafil administration in patients with pulmonary fibrosis and an mPAP > 35 mmHg results in hemodynamic improvement without adverse effects on oxygenation.⁽¹³⁾ In two case series in patients with COPD and idiopathic pulmonary fibrosis, the use of sildenafil for 8-12 weeks resulted in improvements in hemodynamic parameters and functional capacity.^(14,15) We hope these preliminary results will lead other authors to carry out larger randomized and placebo-controlled studies in this patient population. We cannot currently recommend the treatment of pulmonary hypertension in patients with chronic lung diseases. However, it is this author's opinion that treatment of pulmonary hypertension should be considered for symptomatic patients presenting a moderate to severe increase in mPAP, especially for those in which the severity of the pulmonary hypertension appears to be out of proportion to the severity of the lung disease.

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