Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease: When Is It Out of Proportion?

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Patients with chronic obstructive pulmonary disease (COPD) often present with mild pulmonary hypertension (PH). This finding has been attributed to hypoxic pulmonary vasoconstriction. However, a small proportion of COPD patients will present with moderate or severe elevations in their pulmonary artery pressure (PAP), and these patients appear to have worsened symptoms and survival when compared to patients with milder elevations in PAP. The diagnosis of PH in COPD may be difficult, due to inaccuracies in the echocardiographic estimates of PAP in these patients. Additionally, many patients with COPD will also have comorbid conditions such as diastolic heart failure, systolic heart failure, or obstructive sleep apnea, which may cause increased pulmonary pressures through other mechanisms. Clinical trials investigating the effect of PH-specific therapy for patients with PH and COPD have been small, with mixed results. A careful evaluation for other causes of PH and hemodynamic evaluation will help guide medical therapy for this group of patients.

The diagnostic evaluation of a new patient with suspected pulmonary hypertension (PH) must be done methodically to ensure the correct diagnosis and treatment plan is assigned. An essential part of the evaluation of a patient with suspected PH is to correctly categorize their disease in the World Health Organization (WHO) classification system for PH. This system groups patients together on the basis of the underlying physiology of their pulmonary pressure elevation and possible response to therapy. Over the past 20 years, the characterization of patients with Group 1 pulmonary arterial hypertension (PAH) and development of therapy for those patients has progressed substantially. This allows for an increasingly data-driven approach to the treatment plan for these patients. However, the characterization of some of the other types of PH has not progressed as quickly. This leaves providers reaching for guidelines on the management of these patients who are also presenting with significant symptoms and morbidity. One of these more poorly characterized groups of patients is WHO Group 3: PH related to respiratory disease/hypoxia. In this article, we will review the current characterization of and data regarding a subgroup of these patients—those with chronic obstructive pulmonary disease (COPD) and PH.

PREVALENCE AND EPIDEMIOLOGY OF PH IN COPD

The prevalence of COPD in the US adult population is 6%, and it is estimated that at least 15 million Americans have a COPD diagnosis.[1] The true prevalence of PH in the COPD population is unknown, because it is difficult to diagnose. Echocardiography is unreliable in the COPD population, leaving one without a noninvasive way to accurately obtain this information in population-based studies.[2] However, information does exist regarding the prevalence of PH in patients with severe COPD who underwent right heart catheterization (RHC) as part of the evaluation for either lung volume reduction surgery or lung transplantation. Vizza et al described the hemodynamics of 156 patients referred for lung transplantation in the early 1990s. The mean pulmonary artery pressure (mPAP) of these patients was 25.6 mm Hg, consistent with mild PH.[3] Fifty-nine percent of these patients also had significant right ventricular dysfunction with a right ventricular ejection fraction <45%. Scharf et al reported RHC results in patients screened for the National Emphysema Treatment Trial (NETT). Of 120 patients who underwent RHC, 91% had mild PH with mPAP >20 mm Hg. However, only 5% had severe PH (mPAP >35).[4] Thabut et al reported a retrospective review of 215 patients who underwent RHC and were referred for lung volume reduction surgery or lung transplantation. These patients had severe COPD, with a mean FEV_1 of 23.9% of the predicted value. Most patients had mild PH with mPAP of 26.9 mm Hg (Figure 1). Pulmonary hypertension as defined by the traditional definition (mPAP >25 mm Hg) was present in 50.2% of the cohort. Severe PH (mPAP >45 mm Hg) was a

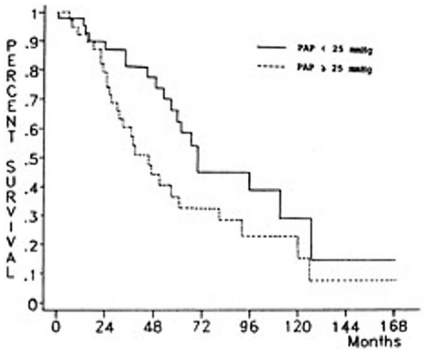

Figure 1: Pulmonary Artery Pressures in COPD Patients. Pulmonary artery pressures of patients with severe COPD, referred for lung volume reduction surgery or lung transplantation. Thabut et al. *Chest*. 2005;127(5): 1531-1536.

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rare event, occurring in only 3.7% of patients. Further, a subgroup of patients (7.4%) was identified by cluster analysis, with less impairment of their pulmonary function (FEV_1 48.5% predicted) but severe PH (average mPAP 39.8 mm Hg). It was postulated that this subgroup of patients may have PH out of proportion to their COPD and may benefit from pulmonary vasodilator therapy.[5] Lastly, Cuttica et al retrospectively reviewed RHC findings in 4930 COPD patients listed for lung transplantation between 1997 and 2006. In this group, 48% had mPAP ≥25 while 30% had both mPAP ≥25 and pulmonary artery occlusion pressure ≤15. Less than 1% of patients had mPAP >35.[6]

All of these patients were selected from a population referred for intervention (lung volume reduction or lung transplantation); therefore, an inherent selection bias exists. In 2005, Chaouat reported a retrospective review of 998 patients referred to their department for chronic respiratory failure management (not a surgery) and who underwent RHC as part of the evaluation. Only 27 patients had severe PH with mPAP >40 mm Hg. Of those 27, 16 had another identifiable risk factor for PH, while 11 had only COPD as an identifiable risk factor.[7]

Thus, in COPD patients with chronic respiratory failure or those referred for surgery mild PH is fairly common, but severe PH remains rare.

Pathophysiology

The pathophysiology of PH in patients with COPD is complex and likely involves the combination of hypoxic pulmonary vasoconstriction, vascular inflammation, and loss of alveolar capillary units. Hypoxic pulmonary vasoconstriction (discussed in detail in another article in this issue) is a well-described phenomenon that preserves ventilation/perfusion matching by constricting pulmonary blood vessels in areas of lung with localized hypoxia, therefore sending blood to healthier areas of lung. However, when local hypoxia becomes more widespread, this process can produce a sustained elevation in pulmonary vascular resistance. When this process becomes chronic, pulmonary vascular remodeling ensues.[8] Autopsy specimens from COPD patients reveal muscularization of the small pulmonary arteries, proliferation of the medial and intimal layers, and inflammatory cells in the vascular wall.[9] Additionally, a reduction in the total number of pulmonary vessels in patients with COPD has been noted on both pathology specimens and angiographic studies.[8]

Clinical Course

In most patients with COPD, the degree of PH is mild and its progression is slow. The natural history of this population was described by Weitzenblum and colleagues in 1979. They reported the hemodynamics of 84 patients with COPD and arterial hypoxemia. Patients underwent 2 RHCs at least 3 years apart, each measure taken at a time of disease stability. Hemodynamic measurement revealed that 34 of 84 patients had mPAP greater than 20 mm Hg at baseline, and at follow-up their mPAP had increased about 0.5 to 0.6 mm Hg. Only 28 of 84 patients increased their mPAP by 5 mm Hg or more, and those who did also exhibited more hypoxemia and hypercarbia than patients with more stable hemodynamics.[10]

Conversely, as described in the epidemiology section, a small percentage of patients with COPD exhibit moderate to severe PH at baseline.[5] These patients do not have the same disease stability as those patients with mild baseline disease. Oswald-Mammosser and colleagues examined a cohort of 82 patients with COPD requiring oxygen therapy and sought to describe prognostic indicators for this group. On final analysis, the 5-year survival of COPD patients with a baseline mPAP of 25 mm Hg or less was 62.2%, vs 36.6% for those patients with PH (Figure 2). Multivariate analysis revealed that PAP was a better prognostic indicator than FEV_1, or the degree of hypoxemia or hypercapnea.[11] In the previously referenced 2005 study by Chaouat et al, the 27 out of 998 (2.7%) COPD patients with severe PH (mPAP >40) had a significantly reduced survival when compared to the rest of the COPD cohort.[7] Therefore, while the presence of more severe PH is rare in patients with COPD, it is associated with increased mortality.

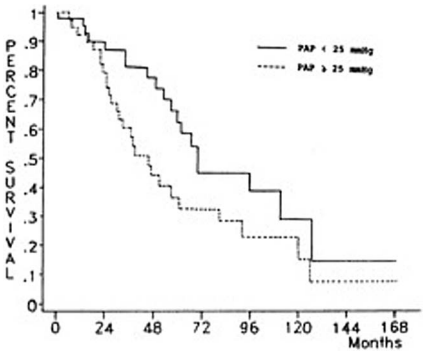

Figure 2: Survival in Patients With COPD and PH. Survival of patients with both COPD and PH, divided by degree of PH. Oswald-Mammosser et al. *Chest*. 1995;107(5):1193-1198.

PITFALLS IN THE DIAGNOSIS OF PH IN COPD PATIENTS

Because of the prognostic significance of PH in COPD patients, it seems clinically important to identify its presence; however, making the diagnosis can be a difficult endeavor. Echocardiography, the most common screening tool for PH in the general population, is less accurate in those with COPD. Arcasoy and colleagues compared the accuracy of echocardiographic estimates of PAP to RHC measurements in 374 lung transplant candidates, the majority of which had obstructive lung disease. Fifty-two percent of pressure estimates were inaccurate (varied by more than 10 mm Hg) and 48% of patients were misclassified as having PH by echocardiography when they did not. The sensitivity and specificity of echocardiography for the presence of PH in this population were 85% and 55%, respectively (Figure 3).[2] Therefore, if PH is suspected, RHC is required for confirmation and correct classification of the diagnosis. But, the RHC itself also contains diagnostic pitfalls in the COPD population. Patients with pulmonary parenchymal disease may exhibit significant negative swings in pleural pressure with inspiration, which may increase both the PAP and the left ventricular afterload. Therefore, in these patients in particular, it is important that all measurements be taken at end expiration.[12] Even at end expiration, hyperinflation with alveolar distension and increased intrathoracic

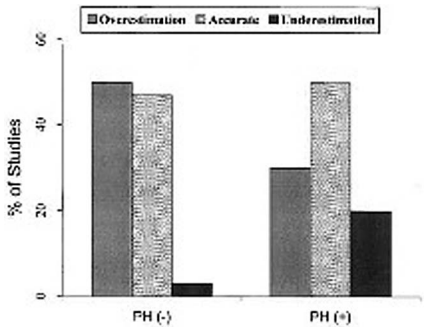

Figure 3: Echocardiographic Estimates of PAP in COPD Patients. The accuracy of echocardiographic estimates of PAP when compared to RHC. The PH-negative group includes those without PH on RHC and the PH-positive group shows elevations of PAP on RHC. Arcasoy et al. *Am J Respir Crit Care Med*. 2003;167(5):735-740.

pressure can contribute to elevation in mPAP and pulmonary vascular resistance. Finally, it is important that COPD patients have hemodynamics measured at their baseline lung function because PAP may rise up to 20% during a COPD exacerbation, only to fall again after resolution of the exacerbation.[10,13]

COMPLICATING PROBLEMS

The presence of concomitant conditions that may affect the PAP further complicates the diagnostic evaluation of PH in COPD patients. These comorbidities include sleep apnea, venous thromboembolism (VTE), systolic or diastolic left heart failure, and pulmonary fibrosis. Historically, it was thought that COPD patients exhibited higher rates of sleep apnea than the general population, with rates up to 15% quoted.[14] However, the population-based Sleep Heart Health Study, in which 1138 patients with mild COPD were studied, revealed that sleep apnea-hypopnea syndrome (SAHS) is present in approximately 5% of the general adult population, and its prevalence in the COPD population appears to be the same.[15] Patients with SAHS and COPD exhibit more significant hypoxemia than those with SAHS alone.[14] Further, patients with overlap syndrome not treated with CPAP therapy had a higher mortality and were more likely to be hospitalized for a COPD exacerbation than patients with COPD alone. Treatment with CPAP therapy, however, ameliorated this risk and these treated patients had no greater risk for hospitalization or mortality than those with COPD alone.[16,17] The investigation of and treatment for both SAHS and nighttime hypoxemia in patients with COPD will help eliminate reversible hypoxic pulmonary vasoconstriction as a cause of increased pulmonary pressures.

Patients with COPD may also be at increased risk for VTE and pulmonary emboli, which can be a cause of increased dyspnea, hypoxemia, and elevated PAP. Therefore, evaluation for VTE is recommended in patients with COPD and worsening dyspnea.[18,19]

Additionally, in an aging population, COPD and either systolic or diastolic left heart failure often overlap in the same patient and can contribute to dyspnea, increased pulmonary pressures, and morbidity.[20,21] A careful evaluation of left sided filling pressures during heart catheterization will help identify this confounder and direct management toward appropriate therapy.

Finally, patients with the combined pulmonary fibrosis emphysema syndrome (CPFE) may initially present with breathlessness and a diagnosis of COPD. This entity has no consensus definition, but this characterization has been proposed: a history of smoking, severe dyspnea, primarily upper lobe emphysema, primarily lower lobe pulmonary fibrosis, a severely reduced diffusing capacity for carbon monoxide and unexpectedly preserved spirometry values.[22] In some reports, these patients exhibit markedly increased rates of severe PH (50% to 90% of patients) and a very poor 5-year survival rate of 25%.[23-25] Specific treatment trials have not been done for this group. However, given the severity of the PH in these patients and data that suggest the PH may drive mortality, early referral for lung transplantation should be considered and future studies might address the role of PH-specific treatments for this group.

WHO GROUP 1 PAH AND COPD

COPD patients with more severe elevation in PH represent a unique group, and it is likely that conditions other than COPD may underlie PH in this setting. This is an important consideration, particularly in patients with PH and mild COPD. In the Registry to EValuate Early And Long-term PAH disease management (REVEAL), 17% of patients classified as having PAH (WHO Group 1) had COPD listed as a comorbid condition. These patients had mild COPD with a mean FEV_1 of 69% of predicted. Pulmonary hemodynamics and the distribution of PAH etiologies—idiopathic (50%), connective tissue disease (28%), congenital heart disease (11%), and portopulmonary hypertension (5%)—were similar for COPD patients and the overall registry population. When compared to patients without comorbid conditions, COPD patients had a greater incidence likelihood of New York Heart Association functional class III or IV (odds ratio 2.19, $P<0.001$), lower 6-minute walk distance (304.5 vs 400 m), and lower 3-year survival (64.7% vs 77.4%, $P<0.001$).[26]

TREATMENT

As the previously mentioned studies demonstrate, mild PH (mPAP <30) is relatively common in the COPD population and is thought to be related to hypoxic pulmonary vasoconstriction. Therefore, the mainstays of treatment for these patients remain long-term oxygen therapy, smoking cessation, inhaled bronchodilators, and inhaled corticosteroids. However, the debate about treatment of PH in COPD surrounds those patients with mPAP >35, or the so-called "PH out of proportion to COPD" patients. The argument for treatment centers on their increased symptomatology and poorer outcomes compared with patients with COPD and milder increases in pulmonary pressures. Data are confined to a few small trials and case reports, and no large trial has specifically enrolled this "out-of-proportion" group. Thus, the debate on treatment continues.

The phosphodiesterase type 5 inhibitor sildenafil has been investigated for this group of patients in a couple of small trials. Acutely, sildenafil caused hemodynamic improvements over 1 hour in patients with COPD and PH, but this improvement was accompanied by worsened hypoxemia. This hypoxemia is likely due to obliteration of hypoxic pulmonary vasoconstriction in more

diseased areas of lung with worsening of ventilation/perfusion mismatch.[27,28] Small trials of outpatient use of sildenafil in these patients have yielded conflicting results, with one trial showing an improvement in exercise capacity and hemodynamics and other trials reporting no improvement after 3 months of therapy.[29,30]

The endothelin receptor antagonist (ERA) bosentan was investigated in a small (30 patients), 12-week, placebo-controlled trial in subjects with COPD and PH. There was no improvement in exercise capacity or pulmonary pressures, and oxygenation and quality of life scores decreased on therapy.[31] Other small trials and case reports have shown improvement on ERA therapy.[32] A larger trial is needed to definitively elucidate the role of ERA therapy in patients with COPD and PH.

Inhaled prostacyclins are a theoretically attractive option for this group of patients, because the inhaled drug will likely be preferentially delivered to better-ventilated areas of lung, perhaps offering a less deleterious effect on ventilation perfusion matching. Inhaled iloprost was investigated in patients with COPD and echocardiographic evidence of PH. Treatment acutely improved gas exchange and walk distance.[33]

Treatment trials with other agents, such as tadalafil, sildenafil, udenafil, riociguat, inhaled nitric oxide, inhaled treprostinil, and inhaled iloprost, are ongoing. As these results become available, the effect of PH-specific therapy on COPD patients should become clearer. In the interim, the decision of when to consider treatment may hinge on the clinical assessment of whether or not COPD represents the cause of PH as opposed to a comorbidity seen in association with treatable WHO Group 1 PAH. In the absence of established guidelines, this requires consideration of COPD vs PH severity as well as assessment for other associated comorbidities.

CONCLUSION

Mild PH is relatively common in patients with COPD. However, a small subgroup of patients may present with COPD and moderate-severe elevations in their PAP. Whether the pathophysiology involved in this severe PH is different from those with milder PH is unclear. In this setting, a diligent search for other contributing conditions should be undertaken. Given the high prevalence of COPD, some patients will have more than one condition contributing to PH, and those with mild COPD and more severe PH might still be categorized into WHO Group 1. Patients with severe PH and COPD have increased morbidity and mortality when compared with the milder patients. This observation spurs clinicians to consider PH treatment for patients with COPD and PH. Currently, data confirming both the safety and efficacy of PH therapy for such patients is lacking and it is hoped that future studies will lead to identification of new, effective treatments as well as subgroups of patients with COPD-associated PH more likely to respond to therapy.

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