

# Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease: Diagnosis and Management



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Pulmonary hypertension (PH) related to chronic obstructive pulmonary disease (COPD) is part of Group III, as defined by the World Health Organization (WHO), which comprises the group of PH associated with lung disorders and hypoxemia, such as COPD, interstitial lung disease, sleep disordered breathing, and high altitude PH. Similar to other types of PH complicating various disorders, PH associated with COPD confers a poor prognosis. While PH associated with COPD has been a well-recognized entity, only recently has attention been focused toward understanding the epidemiology and characteristics of this form of PH. In this issue, we will examine characteristics of PH in COPD, describe similarities and differences with other forms of PH, and present current recommendations for diagnosis and management.

## Definition and Epidemiology of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Pulmonary hypertension is present in a wide range of patients with COPD. The exact incidence of clinically significant PH is difficult to estimate in COPD patients, as most reports are in patients with advanced disease. Up to 90% of COPD patients have exercise-induced PH. In contrast, resting PH is reported less frequently (5-30%).<sup>1,2</sup> Several recent large epidemiologic studies on severe COPD patients found an incidence of PH up to 91%, with most patients having mild to moderate PH (with mean pulmonary artery [PA] pressures between 20-35 mm Hg), while 1% to 5% had severe elevations of mean PA pressures above 35 mm Hg<sup>2</sup> or 40 mm Hg,<sup>3</sup> respectively. Chronic obstructive pulmonary disease is a leading cause of death, illness, and disability in the United States. In 2002, National Health Survey estimated that the US prevalence of COPD in people aged >25 is 12.1 million, but as many as 24 million may be affected. Therefore, the number of patients with severe PH from COPD may rise up to 121,000 to 600,000 in the US. Special attention to those patients is warranted, as they have an increased morbidity and mortality.

*Key Words*—Chronic obstructive pulmonary disease, pulmonary hypertension, “out of proportion” pulmonary hypertension.

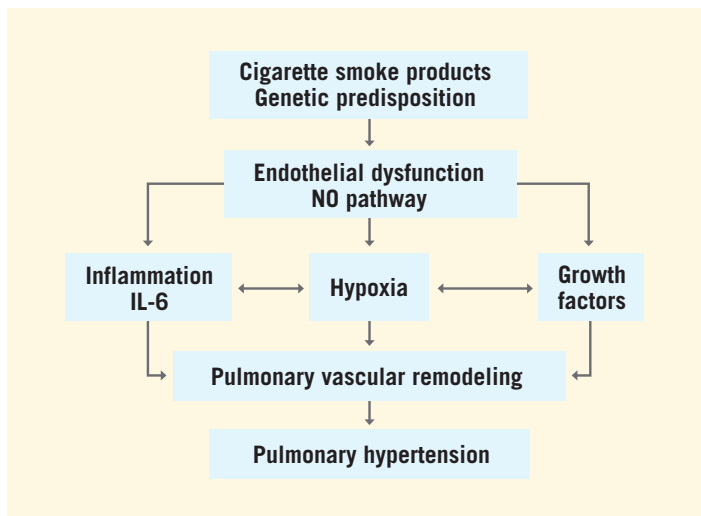
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## Pathophysiology of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Vascular abnormalities seen in COPD are of complex nature. Initial mechanisms are thought to involve hypoxic pulmonary vasoconstriction and release of proinflammatory mediators. Ultimately, there is structural damage with vascular remodeling and narrowing of the vascular lumen (**Figure 1**). Pathologic changes in pulmonary vessels of COPD patients with PH involve all layers: muscularization of pulmonary arterioles which normally lack a muscular layer, accompanied by involvement of postcapillary vessels and venules, intimal thickening of the muscular pulmonary arteries and pulmonary arterioles, suggesting endothelial cell dysfunction. Infiltration of the pulmonary vessel walls with inflammatory cells, especially lymphocytes, is another hallmark of this type of PH. Recent reports suggest that potential key regulators of endothelial damage in PH are related to COPD inflammatory mediators, such as IL-6.<sup>4</sup> The degree of pulmonary vessel remodeling does not correlate with the degree of either PH or obstruction and vascular changes that are encountered even in mild disease. These pathological features are distinct from the predominant medial hypertrophy that develops with chronic hypoxia at high altitude. While high altitude-induced PH is usually reversible after returning to normoxic conditions, PH and vascular remodeling of COPD patients are only partially reversible with oxygen treatment. In addition, PH associated with COPD is not characterized by the plexogenic arteriopathy seen in forms of pulmonary arterial hypertension (PAH) of WHO Group I (idiopathic, HIV-related, connective tissue disease-related, etc).

## Natural Progression of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Patients with COPD and PH have a 5-year survival of 20% to 36%, and it correlates with worsening PH and age, even in the era of long-term oxygen therapy.<sup>5</sup> The progression of PH is slow in COPD patients, and PA pressures may remain stable over periods of 3 to 10 years.<sup>6</sup> Pulmonary hypertension appears first during sleep and with exercise, and may progress over time to resting PH.<sup>7</sup> Initially, COPD patients become hypoxemic during sleep due to decreased intercostal muscle activity, decreased motor neuron input, increased airway resistance, and worsening V/Q mismatch,

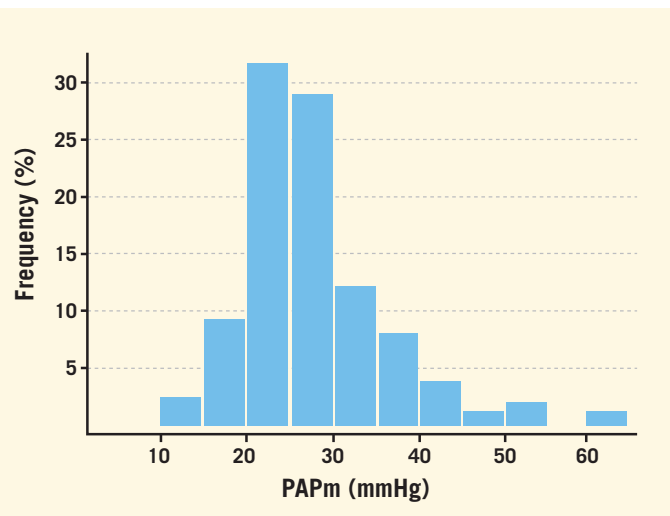


**Figure 1.** Diagram depicting possible pathophysiological mechanisms responsible for PH in COPD.

leading to nocturnal hypoventilation in these patients. Nocturnal desaturations during sleep coincide with rise in PA pressures. Diurnal hypoxemia develops later in the disease progression and is mainly due to V/Q mismatch which is caused by blood flow inequalities, tissue loss, and loss of distal vessels as a consequence of severe parenchymal destruction. Most patients with mild to moderate PH describe dyspnea on exertion and limitations in functional capacity. Interestingly, the PH does not correlate with the degree of obstructive ventilatory defect, but with degree of hypoxemia and the decrease in carbon monoxide diffusing capacity (DLCO). There are several key differences between PH related to COPD and PAH of Group I WHO that are worth mentioning: unlike patients with PAH whose limitation is due to inadequate increase in blood flow, symptoms of patients with PH and COPD seem to be mainly due to exhaustion of the ventilatory reserve,<sup>8</sup> although higher mean PA pressures contribute to lower 6-minute walk distances.<sup>9</sup> Pulmonary hypertension related to COPD is characterized by a relatively normal systolic right ventricular function (possibly diastolic dysfunction) and preserved cardiac output, while PAH patients in Group I are characterized by limitations in the right ventricular flow (cardiac output) and in advanced stages by a hypocontractile and dilated right ventricle. Although at risk for increased mortality, COPD patients with PH do not typically succumb to right ventricular failure.

### The Subgroup of “Out of Proportion Pulmonary Hypertension”

As mentioned previously, most COPD patients without other cardiopulmonary comorbidities who develop PH usually have mild to moderate elevations in PA pressures (mean PA pressures up to 35 mm Hg). Increasingly recognized is a subset of COPD patients who have severe elevations of PA pressures. In a cohort of COPD patients undergoing lung transplant evaluation or volume reduction surgery, 50% of patients had mean PA pressure elevations above 25 mm Hg, but a small percentage had severe PH (**Figure 2**).<sup>10</sup> These patients tend to have less obstruction, more severe hypoxemia, and a lower DLCO<sup>11</sup> and are referred to as “out of proportion PH.” There is poor understanding in pathophysiologic characteristics of this subset of patients, but there may be a preferential destruction of the pulmonary vasculature that accompanies the severely decreased DLCO and severe hypoxemia. A



**Figure 2.** In a cohort of 215 COPD patients undergoing evaluation for either lung transplantation or volume reduction surgery, 50.2% had PH at right heart catheterization; 13.5% had at least moderate PH (mean PA >35 mm Hg). Those with the most severe PH had lower oxygen levels but fairly modest obstruction (FEV1 = 45% predicted vs 24% for the overall group).<sup>10</sup>

genetic predisposition has been proposed to account for increased risk of “out of proportion PH,” although the data are conflicting. Serotonin transporter (5-HTT) gene polymorphism has initially been found to determine the severity of PH in hypoxemic patients with COPD in a European cohort.<sup>12</sup> The severity of PH in patients with COPD was directly related to 5-HTT gene polymorphism, as shown by the markedly higher PA pressures in patients carrying the LL genotype compared to those carrying the LS and SS genotypes. A multinational American-English cohort of COPD-PH patients failed to replicate the French findings.<sup>13</sup> It is unclear whether the differences reported are due to population differences, or to sample size and statistics. Another possible association reported was the association of a single nucleotide polymorphism in the surfactant protein B in patients with PH and COPD.<sup>14</sup> Another recent study in 148 patients with COPD found that patients with PH had elevated IL-6 levels, and the IL-6 GG genotype was more common than CG or CC genotypes in PH patients (adjusted odds ratio, 4.32; 95% confidence interval, 1.96 to 9.54).<sup>4</sup> Whether patients with “out of proportion PH” have a higher likelihood to respond to therapies proven to be beneficial in PAH WHO Group I remains to be proven.

### Clinical Presentation and Diagnosis of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Patients with PH and COPD present with dyspnea and hypoxemia out of proportion to the degree of obstruction. While Doppler echocardiography is the best screening tool for PH, it is associated with a poor sensitivity and specificity in patients with advanced lung disease. The ability of determining a tricuspid jet in these patients for estimations of peak PA pressures is lower than in patients without lung disease, ranging from 24% to 77%.<sup>15-17</sup> In a cohort of patients with end stage lung disease including COPD undergoing evaluation for lung transplant, estimations of systolic PA pressures were possible only in 44% of the patients and obtained values were accurate in only 48%.<sup>18</sup> To make matters more complex, there are no biomarkers available for clinical screening for PH in the setting of COPD. New reports suggest that brain na-

triuretic peptide (BNP) and its precursor NT-pro-BNP are elevated when PH is severe and during exacerbation of COPD (when PH is worse), but they lack specificity and may also be elevated in the presence of left heart disease, mainly diastolic dysfunction seen quite commonly in COPD patients (left ventricular diastolic dysfunction was reported in up to 32% of patients with COPD exacerbation).<sup>19</sup> Therefore, similar to PH of other etiologies, right heart catheterization is the only test to confirm the diagnosis and determine the degree of severity. We recommend that patients with COPD who develop signs of right heart failure, have right ventricular dilatation on echocardiogram, have dyspnea not fully explained by the degree of obstruction, and/or develop hypoxemia and a low DLCO out of proportion for their obstruction, undergo a right heart catheterization to determine the degree and severity of PH and establish whether underlying diastolic left ventricular dysfunction is also present. An elevation in precapillary wedge pressure may be indeed due to left ventricular diastolic dysfunction, but may also be related to thoracic hyperinflation.<sup>20</sup> The complexity of hemodynamic data makes these patients good candidates for referral to a PH center, in order to be evaluated on an individual basis, and possibly be offered enrollment in clinical trials.

Lastly, an important consideration must be given to pulmonary embolism (PE) that may present as episodes of unexplained COPD exacerbation. Recent prospective studies suggest that patients with COPD admitted with an episode of unexplained exacerbation of COPD have a 25% prevalence of acute PE.<sup>21</sup> In addition, *post mortem* studies indicate that up to 30% of patients dying with COPD have had pulmonary embolic events.<sup>22</sup> Therefore, an important aspect in PH-COPD workup is evaluation for PE. In the workup of these patients, similar to any patient with suspected PH, we recommend doing a combination of V/Q scan, which is more sensitive at diagnosing chronic PEs but may be confounded by the underlying V/Q mismatch of the obstructive disease, and a computed tomography pulmonary angiogram, which is sensitive in diagnosing proximal PEs but may miss distal emboli.

### Management of Pulmonary Hypertension Due to Chronic Obstructive Pulmonary Disease

To date, the only specific treatment proven to have an impact on survival in hypoxemic COPD patients is long-term oxygen therapy, which ameliorates the degree of PH and improves survival.<sup>23</sup> Unfortunately, long-term oxygen therapy has been associated with minor improvements in pulmonary hemodynamics and even in patients treated with long-term oxygen therapy survival does not approach that of COPD patients without PH.<sup>5</sup> This lack of improvement solely with oxygen therapy suggests an intricate physiological mechanism resulting in complex structural damage. The major question remains whether COPD patients with any degree of PH, or even only those with “out of proportion PH” may benefit from PAH-specific therapy, such as phosphodiesterase 5 (PDE5) inhibitors, prostacyclins, or endothelin receptor blockers. Because these patients have been consistently excluded from randomized clinical trials testing specific PH therapies, only scattered data are available.

#### Nitric oxide pathway

Dysfunction of endothelial nitric oxide (NO) release has been documented in patients with COPD.<sup>24</sup> Some studies showed a beneficial effect on PA pressures and oxygenation with short-term inhaled NO,<sup>25-27</sup> others showed a worsening of V/Q mismatching

and oxygenation with inhaled NO.<sup>28</sup> Special attention was given to PDE5 inhibitors as agents that enhance the NO pathway. Holverda et al showed that a single dose of sildenafil attenuates the increase in mean PA pressures during submaximal exercise in a small group of COPD patients with mild resting or exercise-induced PH, but the improvement in pulmonary hemodynamics was not accompanied by an increased stroke volume or cardiac output.<sup>29</sup> A more recent study evaluated 20 patients with COPD and PH before and after 1 dose of sildenafil (20 mg or 40 mg).<sup>30</sup> Sildenafil in both doses improved baseline and exercise hemodynamics by decreasing PA pressures, but it affected the V/Q mismatch at rest (but not with exercise). Six patients with COPD and PH were treated with sildenafil 50 mg twice daily; after 3 months, pulmonary hemodynamics and functional capacity improved (mean PA pressure decreased from  $30.2 \pm 5.5$  to  $24.6 \pm 4.2$  mm Hg, pulmonary vascular resistance declined from  $401 \pm 108$  to  $264 \pm 52$  dyne $\cdot$ s<sup>-1</sup> $\cdot$ cm<sup>-5</sup> and the 6-minute walk distance increased from  $351 \pm 49$  to  $433 \pm 52$  m).<sup>31</sup> The few data on PDE5 inhibitors in this form of PH suggest that, if this treatment is considered, caution should be exerted to avoid worsening hypoxemia.

#### Endothelin receptor antagonists

Endothelin receptor antagonists are beneficial in PAH of Group I WHO classification, but preliminary data suggest no benefit in COPD patients with PH. In a small randomized trial in patients with COPD and mild PH, bosentan treatment was associated with a significant deterioration in oxygenation and lack of improvement in exercise capacity, peak oxygen uptake, and health-related quality of life.<sup>32</sup>

#### Prostacyclins

A placebo-controlled trial of 16 COPD patients in severe acute respiratory failure and mild PH showed that intravenous epoprostenol treatment was associated with a transient improvement in pulmonary pressures, but also with a significant decrease in oxygenation, rendering intravenous prostacyclins as nonselective vasodilators.<sup>33</sup> Inhaled prostacyclins, on the other hand, have the potential to act preferentially in ventilated regions of the lung, avoiding nonselective vasodilation and worsening V/Q mismatch. An acute vasodilator study of 10 COPD patients with PH (based on echocardiography), inhaled iloprost was associated with improvement in V/Q matching.<sup>34</sup> Although there are currently 2 inhaled prostacyclin analogues approved by the FDA for PAH of Group I WHO, their long-term efficacy in PH due to COPD has not been established.

#### New compounds

Cicletanine is an antihypertensive compound that is believed to act via NO and prostacyclin pathways and is currently being tested in a phase II clinical trial in patients with PAH. In a double-blind controlled study of 25 COPD patients with PH, 11 of whom were assigned to active therapy, cicletanine significantly decreased mean PA pressures and total pulmonary resistance in the treated group at 3 and 12 months, without any significant desaturations, suggesting a preferential pulmonary activity.<sup>35</sup>

#### Pulmonary rehabilitation

Chronic obstructive pulmonary disease is a systemic disorder, affecting not only the lungs, but also skeletal muscles. The role of pulmonary rehabilitation is well established in COPD.<sup>36,37</sup> Similarly, patients with PAH on medical therapy showed improvements



in exercise capacity after pulmonary rehabilitation was instituted.<sup>38</sup> Although no studies have specifically addressed the COPD population with PH, we believe that supervised pulmonary rehabilitation is beneficial in this population.

## Conclusions

Pulmonary hypertension in the setting of COPD is a common occurrence, associated with poor survival. It manifests initially during sleep and with exercise, and in later stages it occurs at rest. In most cases PH is mild to moderate. There is a subpopulation of patients with COPD with moderate obstruction, severe hypoxemia, and a low DLCO who have significant PH and are recently termed “out of proportion PH.” Workup of patients with COPD and PH should include a screening echocardiogram and evaluation for PE. In patients with suspected “out of proportion PH,” consideration for referral to a PH center and a right heart catheterization should be performed to further determine the diagnosis and severity of PH and possible treatment or enrollment in clinical trials. Decision of whether PH-specific therapy needs to be implemented should be done carefully and with the knowledge that worsening hypoxemia may occur. A concerted effort from PH physicians to study and find adequate treatment for patients with COPD and PH is acutely needed.

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