Pulmonary Hypertension in COPD: Epidemiology, Significance, and Management: Pulmonary Vascular Disease: The Global Perspective

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Pulmonary Hypertension in COPD: Epidemiology, Significance, and Management

Pulmonary Vascular Disease: The Global Perspective

Omar A. Minai, MD, FCCP; Ari Chaouat, MD; and Serge Adnot, MD

Pulmonary hypertension (PH) associated with parenchymal lung diseases is one of the most common forms of PH. Studies in patients with advanced COPD and hypoxemia have shown a very high prevalence of PH; however, prevalence in mild and moderate COPD is not known. Typical hemodynamic abnormalities include mild-to-moderate elevations in pulmonary artery pressure (PAP) and pulmonary vascular resistance with a preserved cardiac output. A small proportion (≤5%) of patients may have significant elevations in PAP (mean PAP >35-40 mm Hg) in the presence of mild airflow limitation and are believed to have disproportionate PH. COPD-associated PH has significant clinical implications because it can produce functional limitation and has a negative impact on prognosis. Doppler echocardiography is the best noninvasive test, but noninvasive methods used for diagnosis are prone to error and cannot be relied on when making or refuting the diagnosis of PH. All patients require right-sided heart catheterization if treatment with PH-specific medications is contemplated. The most important steps in managing these patients are: (1) confirm the diagnosis; (2) optimize COPD management; (3) rule out comorbidities; (4) assess and treat hypoxemia; and (5) enroll the patient in pulmonary rehabilitation, if indicated. In patients with PH and advanced airflow limitation, lung transplantation offers the best opportunity for long-term benefit. The role of PH-specific medications remains poorly defined and requires further study but may be considered in patients with disproportionate PH.

Abbreviations: BNP = brain natriuretic peptide; DE = echocardiography with Doppler imaging; LTOT = long-term oxygen therapy; LV = left ventricular; mPAP = mean pulmonary artery pressure; PAP = pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right-sided heart catheterization; RV = right ventricular

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strategies in COPD-associated PH; this review focuses on hemodynamic characteristics, clinical impact, and treatment of patients with this condition.

**Epidemiology and Hemodynamic Characteristics**

**Pulmonary Hemodynamics in COPD**

The literature on the prevalence of PH in COPD is confounded by several limiting factors. Estimates of the prevalence of PH in patients with COPD vary widely (Table 1) based on the definition of PH, the physiologic characteristics of the underlying lung disease, and the methods used to determine pulmonary pressures. The true prevalence of PH in patients with mild or moderate COPD is not known because of the absence of large-scale epidemiologic studies. Most studies have reported a prevalence of PH in COPD to be between 30% and 70% (Table 1). Relative to other forms of PH, COPD tends to produce relatively modest hemodynamic alterations at rest. Severe PH (defined as mean pulmonary artery pressure [mPAP] > 40 mm Hg) is uncommon (<5%) and typically is associated with less severe respiratory function compromise (Table 2). This “severe” PH is “disproportionate” to the degree of airflow limitation. Patients with this condition are important to identify because they may be expected to have significant clinical compromise from the PH. Stevens et al reported that five of 600 (0.8%) patients with COPD had severely elevated pulmonary pressures and pulmonary vascular resistance (PVR). Thabut et al found that 21 of 215 (13%) patients with advanced COPD had an mPAP > 35 mm Hg and that eight (3.7%) had an mPAP > 45 mm Hg. In a retrospective study of 998 patients with COPD, Chaouat et al reported that 16 of 27 (60%) patients with severe PH (mPAP, ≥ 40 mm Hg) had a comorbid condition that explained the PH. The 11 of 998 (1.1%) remaining patients without an obvious comorbidity explaining the presence of PH had less severe airflow limitation, more severe hypoxemia, hypocapnia, and a decreased diffusing capacity of the lung for carbon monoxide. Severe cardiac dysfunction, however (defined as mean right atrial pressure > 8 and cardiac index < 2 L/min/m²), was present in only four of 11 (36%) patients. Severe PH is uncommon in patients with COPD, and if found, treatable comorbid conditions, such as pulmonary embolism and left-sided cardiac disease, should be sought.

**Pathophysiology**

The pathophysiology underlying development of PH in COPD is poorly understood and is likely multifactorial (Fig 1). Factors such as an increase in PVR, an increase in pulmonary capillary wedge pressure (due to left ventricular [LV] dysfunction or severe airway obstruction with wide intrathoracic pressure swings), and destruction of lung parenchyma leading to loss of part of the pulmonary vascular bed may play a role.

A consistent finding in patients with COPD is the close relationship between severity of hypoxemia and pulmonary artery pressure (PAP) or PVR, supporting a major role for alveolar hypoxia. Alveolar hypoxia causes constriction of resistance pulmonary arteries, and sustained alveolar hypoxia induces pulmonary vascular remodeling. The failure of oxygen therapy to reverse PH points to structural changes in pulmonary vessels as a major factor. Pathologic studies of lung specimens from patients with COPD have shown extensive pulmonary vascular remodeling with prominent intimal thickening, medial hypertrophy, and muscularization of small arterioles. Chronic alveolar hypoxia may play an important mechanistic role; however, pulmonary vascular remodeling has been observed in lung specimens from patients with mild-to-moderate COPD without chronic hypoxemia. Recent studies also have suggested a role for inflammation and genetic predisposition in the pathogenesis of COPD-associated PH. The risk of PH may depend on both a gene involved in pulmonary vascular remodeling and a gene encoding a multifunctional cytokine involved in the inflammatory response. In short, both alveolar hypoxia and inflammation may contribute to pulmonary vascular remodeling, the extent or consequences of which may depend on individual genetic susceptibility.

**Significance of PH in COPD**

Several lines of evidence indicate that PH associated with COPD has significant clinical implications, as follows: (1) PH can occur in a significant proportion of patients with advanced COPD; (2) severe PH can occur in COPD; (3) COPD-associated PH can progress over time; (4) COPD-associated PH is a multifactorial process and not just hypoxic pulmonary vasoconstriction; (5) right ventricular (RV) hypertrophy and dysfunction may occur in COPD; (6) a significant proportion of patients with COPD can have PH with exercise; (7) COPD-associated PH can produce functional limitation; and (8) PH is associated with reduced survival in COPD. The PH associated with hypoxia is characterized by more robust medial hypertrophy than intimal proliferation and is potentially reversible with restoration of normoxia. Pulmonary vascular changes in COPD are more typical of those seen in the hypoxia model; however, intimal changes also have been described. Studies have reported a rate of rise in mPAP of 0.5 to 1.5 mm Hg/y in patients with COPD. Patients with a more significant rise in mPAP over time typically are those with rapidly worsening hypoxemia.
Table 1—Resting Hemodynamics in Patients With COPD Undergoing RHC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No.</th>
<th>FEV₁, % Predicted</th>
<th>PaO₂ mm Hg</th>
<th>PH, mPAP in mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PH Characteristics and Prevalence</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burrows et al⁶</td>
<td>E + CB</td>
<td>50</td>
<td>37 ± 8.7</td>
<td>88.5 ± 8.6⁺</td>
<td>NA</td>
<td>26 ± 11.8</td>
<td>cardiac index, 2.5 ± 0.7; mPAP &gt; 26 in 20%</td>
<td>Survival inversely related to PVR; E, lower CO and normal PAP; CB, higher PAP and CO</td>
</tr>
<tr>
<td>Weitzenblum et al⁷</td>
<td>CB + E</td>
<td>175</td>
<td>40 ± 11</td>
<td>63 ± 11; &lt; 60 in 41%</td>
<td>&gt; 20</td>
<td>19.8 ± 7.6</td>
<td>mPAP &gt; 20 in 62 (35%)</td>
<td>FEV₁, hypoxia, hypercapnia, age, and PH were predictors of survival</td>
</tr>
<tr>
<td>Weitzenblum et al⁸</td>
<td>CB + E</td>
<td>93</td>
<td>1.29</td>
<td>65</td>
<td>&gt; 20</td>
<td>20.6</td>
<td>mPAP &gt; 20 in 32 (34%), &gt; 30 in 5 (5.3%), &gt; 40 in 1 (1%)</td>
<td>RVEDP &gt; 8 in 8; increase in mPAP at a rate of 0.65 mm Hg/y</td>
</tr>
<tr>
<td>Oswald-Mammosser et al⁹</td>
<td>COPD</td>
<td>63</td>
<td>NA</td>
<td>NA</td>
<td>&gt; 20</td>
<td>NA</td>
<td>mPAP &gt; 20 in 41 (65%)</td>
<td>mPAP &gt; 30 in 15 (24%); reliable TTE in 82%</td>
</tr>
<tr>
<td>Skwarski et al¹⁰</td>
<td>COPD</td>
<td>179</td>
<td>0.7</td>
<td>54</td>
<td>NA</td>
<td>30 ± 11</td>
<td>NA</td>
<td>mPAP increased during episode of exacerbation more prominently in those with elevated RVEDP at baseline</td>
</tr>
<tr>
<td>Oswald-Mammosser et al¹¹</td>
<td>E, all hypoxemic; 50% hypercapnic</td>
<td>84</td>
<td>0.85</td>
<td>52 ± 5</td>
<td>&gt; 20</td>
<td>27 ± 8.9</td>
<td>mPAP &gt; 20 in 65 (77%) and &gt; 30 in 31 (37%)</td>
<td>NA</td>
</tr>
<tr>
<td>Vizza et al¹³</td>
<td>E</td>
<td>168</td>
<td>20 ± 6</td>
<td>59 ± 12</td>
<td>NA</td>
<td>20 ± 6</td>
<td>NA</td>
<td>RVSP estimation possible in 26%</td>
</tr>
<tr>
<td>Bach et al¹⁴</td>
<td>E (LVRS evaluation)</td>
<td>64</td>
<td>19 ± 7</td>
<td>60 ± 11</td>
<td>NA</td>
<td>19 ± 7</td>
<td>NA</td>
<td>RVEF &lt; 45% in 59%</td>
</tr>
<tr>
<td>Scharf et al¹⁵</td>
<td>E (LVRS evaluation)</td>
<td>92</td>
<td>27 ± 7</td>
<td>66 ± 10</td>
<td>NA</td>
<td>≥ 35</td>
<td>NA</td>
<td>5.4%</td>
</tr>
<tr>
<td>Doi et al¹⁶</td>
<td>E</td>
<td>53</td>
<td>40 ± 16</td>
<td>71 ± 9</td>
<td>&gt; 20</td>
<td>19 ± 4</td>
<td>mPAP &gt; 20 in 91% and &gt; 35 in 6 (5%)</td>
<td>mPAP correlated inversely with PaO₂</td>
</tr>
<tr>
<td>Cottin et al¹⁷</td>
<td>COPD + ILD</td>
<td>61</td>
<td>80 ± 21</td>
<td>8.4 ± 1.9⁺</td>
<td>RVSP, ≥ 45</td>
<td>RVSP, 52 ± 20</td>
<td>RVSP, 52 ± 20</td>
<td>Median survival, 6.1 y</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. A1-ATD = α-1 antitrypsin deficiency; CB = chronic bronchitis; CO = cardiac output; E = emphysema; ILD = interstitial lung disease; LVRS = lung volume reduction surgery; mPAP = mean pulmonary artery pressure; NA = not applicable; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHA = right-side heart abnormalities; RHC = right-sided heart catheterization; RVEDP = right ventricular end-diastolic pressure; RVEF = right ventricular ejection factor; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

*Arterial oxygen saturation.
⁺FEV₁ measured in liters.
²PH is defined as the presence of right-sided heart abnormalities.
⁻BVSP measured by TTE.
⁴Pa.
A disproportionate increase in pulmonary pressures may occur with exercise (exercise-induced PH) related to increased flow, hypoxia, and intrathoracic pressure swings in COPD patients even with normal resting pulmonary hemodynamics and may be a marker of increased risk of subsequent development of resting PH. A recent retrospective study of 362 patients with advanced COPD found that high resting mPAP was associated with a short 6-min walk distance.

Table 2—Resting Hemodynamics in Patients With COPD and Severe PH

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>No.</th>
<th>FEV₁, % Predicted</th>
<th>PaO₂, mm Hg</th>
<th>Definition of Severe PH, mPAP in mm Hg</th>
<th>mPAP, mm Hg</th>
<th>PH Characteristics</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens et al⁶⁶</td>
<td>COPD with severe PH</td>
<td>5</td>
<td>2.0 (1.7-2.4)¹</td>
<td>Median, 38</td>
<td>&gt; 40</td>
<td>59 ± 7</td>
<td>1 of 5 (20%) vasoresponsive</td>
<td>4 of 5 (80%) with DLCO, &lt; 35% predicted</td>
</tr>
<tr>
<td>Scharf et al⁶⁵</td>
<td>E (LVRS, evaluation)</td>
<td>120</td>
<td>27 ± 7</td>
<td>Median, 66</td>
<td>&gt; 35</td>
<td>26 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thabut et al⁶⁵</td>
<td>E (LVRS or LT evaluation)</td>
<td>215</td>
<td>Overall, 27 ± 8; LT, 18 ± 9.6; IVRS, 27 ± 12.9</td>
<td>LT, 55 ± 12; IVRS, 66 ± 12.5</td>
<td>&gt; 25</td>
<td>Overall, 27 ± 8; LT, 28 ± 7; IVRS, 25 ± 8</td>
<td>mPAP, &gt; 25 mm Hg in 50%; &gt; 35-45 mm Hg in 10%; &gt; 45 mm Hg in 3.7%</td>
<td>Patients with severe PH had less severe obstruction and lower PaO₂.</td>
</tr>
<tr>
<td>Chaouat et al⁶⁵</td>
<td>Severe COPD</td>
<td>11</td>
<td>Median, 50</td>
<td>Median, 66</td>
<td>&gt; 40</td>
<td>NA</td>
<td>Patients with severe PH had more dyspnea and hypoxia than controls</td>
<td>16 of 27 (59%) patients with severe PH had comorbidities</td>
</tr>
</tbody>
</table>

Values given are mean ± SD unless otherwise noted. DLCO = diffusing capacity of the lung for carbon monoxide; LT = lung transplantation. See Table 1 legend for expansion of other abbreviations. *FEV₁ in liters.
Several additional mechanisms may contribute to RV dysfunction, including (1) RV ischemia due to a decreased RV perfusion pressure in the presence of increased RV oxygen demand and (2) decreased RV preload due to decreased venous return associated with hyperinflation. The less negative intrathoracic pressure and the low elastic recoil of the lungs in effect compress the ventricles into each other, preventing RV relaxation and reducing RV end-diastolic volume.

RV output and function invariably have an impact on LV function. RV output determines LV preload because of the serial linkage through the pulmonary vasculature. In view of their anatomic proximity, the common interventricular wall, and being bound by a common pericardial sac, acute elevations in RV afterload can cause significant geometric changes in the LV at end systole. It is unclear whether similar interactions of comparable clinical significance occur in patients with COPD-associated PH, where elevations in RV load are not nearly as the same and are much more gradual. RV hypertrophy or increased RV end-diastolic volume may cause the interventricular septum to encroach on the left ventricle, resulting in decreased LV diastolic compliance. However, it has been suggested that LV output may not be compromised because more complete emptying of the left ventricle with preserved LV output is ensured.

Impact of COPD-Associated PH on Survival

Cor pulmonale was identified to be a common cause of mortality in early studies in patients with COPD. Zielinski et al found that 13% of all COPD deaths in their study population (N = 215) were related to cor pulmonale with edema. Since that publication, several studies have shown that patients with COPD and PH have a reduced survival compared with those patients without PH (Fig 2). A study of 50 patients with COPD found that survival was inversely related to PVR and that none of the patients with a PVR > 550 dynes/s/cm were alive after 3 years of follow-up. Weitzenblum et al showed a 72% 4-year survival in patients with normal pulmonary pressure and a 49% survival rate in patients with an mPAP > 20 mm Hg. Other investigators have shown that ECG signs of right atrial enlargement or RV hypertrophy, degree of elevation of mPAP, RV ejection fraction measured by radionuclide ventriculography, and transthoracic echocardiographical evidence of RV dysfunction also predict survival in this population.

Diagnosis

It is unclear whether screening for PH is feasible in patients with COPD and, if so, which population should
### Table 3—Exercise and Pulmonary Hemodynamics in COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>COPD Characteristics</th>
<th>Hemodynamics Characteristics</th>
<th>Result of Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>population</td>
<td>No.</td>
<td>FEV1, % predicted</td>
<td>PaO2, mm Hg</td>
</tr>
<tr>
<td>Hickam and Cargill 10</td>
<td>E</td>
<td>5</td>
<td>Advanced</td>
</tr>
<tr>
<td>Horsfield et al 17</td>
<td>CB</td>
<td>17</td>
<td>0.93 (0.37-1.82)</td>
</tr>
<tr>
<td>Burrows et al 6 15</td>
<td>E + CB</td>
<td>50</td>
<td>37 ± 8.7</td>
</tr>
<tr>
<td>Timms et al 21</td>
<td>COPD</td>
<td>203</td>
<td>33 ± 14</td>
</tr>
<tr>
<td>Biernacki et al 16</td>
<td>COPD</td>
<td>100</td>
<td>0.71 ± 0.35</td>
</tr>
<tr>
<td>Fletcher et al 20</td>
<td>COPD with and without nocturnal desaturation</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Oswald-Mannosser et al 23</td>
<td>E</td>
<td>151</td>
<td>38 ± 12</td>
</tr>
<tr>
<td>Kessler et al 14</td>
<td>COPD</td>
<td>64</td>
<td>39 ± 20</td>
</tr>
<tr>
<td>Fujimoto et al 12</td>
<td>COPD with mild hypoxia</td>
<td>75</td>
<td>Mild, &gt; 50% moderate, &gt; 35-&lt; 50%; severe, ≤ 35%</td>
</tr>
<tr>
<td>Christensen et al 20</td>
<td>COPD with mild or no hypoxia</td>
<td>17</td>
<td>35 ± 10</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. EIPH = exercise-induced pulmonary hypertension; RA = room air. See Table 1 legend for expansion of other abbreviations.

*FEV1 in liters.

Arterial oxygen saturation.

kPa.
be screened. As discussed, patients with advanced compromise in pulmonary function often have PH, but the prevalence, etiology, and significance of PH in patients with mild COPD is unclear (Table 4).

PH should be suspected in patients with COPD and declining functional capacity or increasing shortness of breath in the presence of stable airflow obstruction and the lack of an alternative explanation (eg, other comorbidities). A high prevalence of PH has been described in patients with COPD who have concurrent interstitial lung disease\(^3\) or obstructive sleep apnea. Pedal edema in COPD is a complex process, and even though it should prompt a search for PH, its mere presence is not diagnostic of PH.\(^{11}\) ECG has a low sensitivity for use in the diagnosis of PH and does not correlate with PH severity. Given the loose correlation between measures of airflow limitation and hypoxemia\(^7,14,15\) and PH, any single measure is unlikely to be useful in screening for PH, and more attention should be paid to developing a prediction model incorporating multiple variables of both. Similar to ECG, chest radiography has a good specificity but low sensitivity for the presence of PH and cannot be used to estimate disease severity. Enlargement of the main pulmonary artery (\(\geq 29\) mm on CT scan) has been shown to have a sensitivity of 87%, a specificity of 89%, and a positive predictive value of 97%.\(^5,6\) Studies in patients with COPD have shown elevated brain natriuretic peptide (BNP) levels in those with PH\(^6,7\) and indicate that BNP levels may provide prognostic information\(^2,7\); however, BNP cannot be used as a reliable indicator of the presence or absence of PH.

Echocardiography with Doppler imaging (DE) can provide an estimated RV systolic pressure, which is believed to reflect pulmonary artery systolic pressure in the absence of RV outflow tract obstruction. However, DE has low sensitivity, specificity, and predictive values in patients with COPD\(^{5,8}\) largely because of technical difficulties in obtaining good windows. Overall, the success rate for DE in estimating RV systolic pressure in patients with COPD ranges between 26% and 66%.\(^14,5,9\)

In view of the limitations described here for the various noninvasive modalities in making the diagnosis of PH, all patients with COPD suspected of having PH should undergo right-sided heart catheterization (RHC) prior to initiation of PH-specific therapy. RHC allows for direct, accurate measurement of cardiac and pulmonary pressures, initial assessment of response to therapeutic interventions, and accurate

Table 4—Characteristics of PH in Patients With Stable COPD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mild-to-Moderate COPD</th>
<th>Severe COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Less common; frequency unknown</td>
<td>More common; frequency 30%-50%</td>
</tr>
<tr>
<td>Role of COPD in pathogenesis of PH</td>
<td>Less likely to be due to underlying lung disease and possible role of smoke exposure and genetics</td>
<td>More likely to be due to underlying lung disease and possible role of smoke exposure, hypertension, and vascular destruction</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Other causes of PH, such as cardiac disease or PE, more likely than PAH</td>
<td>Other causes of PH, such as cardiac disease or PE, more likely than PAH</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Precapillary PH (ie, elevated PAP and PVR, low CO, normal PCWP)</td>
<td>Mild PH with RV diastolic dysfunction (ie, elevated RAP, mildly elevated PAP and PVR, normal CO and PCWP)</td>
</tr>
<tr>
<td>Disproportionate PH</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>DLCO</td>
<td>Low out of proportion to degree of airflow obstruction</td>
<td>Low usually in proportion to degree of airflow obstruction</td>
</tr>
<tr>
<td>Significance of PH, if present</td>
<td>Likely to be a significant contributor to functional limitation and survival</td>
<td>Known to be a significant contributor to functional limitation and survival and primary driver of long-term outcomes likely to be underlying lung disease</td>
</tr>
</tbody>
</table>

PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PE = pulmonary embolism; RAP = right atrial pressure.

See Table 1 legend for expansion of other abbreviations.
estimation of left-sided filling pressures. Currently, RHC is recommended in COPD for accurate characterization of the presence, severity, and characteristics of PH when it is suspected and PH-specific treatment is contemplated; during preoperative evaluation of patients with COPD where the presence of PH may have an impact on candidacy for surgery or selection of type of surgery; or in perioperative management (eg, lung volume reduction surgery or lung transplantation).

**TREATMENT**

Investigators have attempted to study the role of various treatment modalities in patients with COPD, given its frequency and profound impact on both functional capacity and survival (Table 5). The goals of treatment remain alleviation of clinical symptoms, improvement in hemodynamics and RV performance, and improved functional parameters and survival. It is important to first rule out treatable comorbid conditions, such as pulmonary embolism, left-sided cardiac disease, and obstructive sleep apnea, among others. Table 6 summarizes the treatment recommendations for patients with COPD-associated PH.

**Optimization of therapy** is an important element in treating patients with COPD to improve ventilatory mechanics and reduce hyperinflation. Adverse effects of smoking on the natural history of lung function have been described extensively, and studies have suggested that tobacco smoke exposure may play an important role in the development of pulmonary vasculopathy; therefore, smoking cessation should be an integral part of any treatment plan in patients with COPD. Pulmonary rehabilitation has been shown to improve functional capacity in treated patients with pulmonary arterial hypertension and inpatients with COPD. It is likely that patients with COPD-associated PH would benefit from pulmonary rehabilitation once their COPD regimen has been optimized. Rehabilitation should be initiated at a center with experience in treating patients with advanced COPD and with pulmonary vascular disease.

**Oxygen Supplementation**

Current guidelines in patients with COPD recommend the use of oxygen when PaO₂ is < 55 mm Hg or is between 56 mm Hg and 59 mm Hg in patients with evidence of polycythemia or cor pulmonale. This recommendation largely is based on studies showing that long-term use of supplemental oxygen is associated with improved survival in patients with COPD. The potential beneficial impact of oxygen supplementation on pulmonary hemodynamics also has been studied.

Acute administration of oxygen provides little hemodynamic benefit in patients with stable COPD at rest or during an exacerbation episode. Interestingly, acute oxygen-induced reversibility of PH may predict long-term response to oxygen supplementation. Oxygen supplementation can modestly increase exercise tolerance, decrease PAP and PVR, and improve RV function in patients with COPD.

**Long-Term Oxygen Supplementation in Patients With Resting or Exertional Hypoxemia:** To date, long-term oxygen therapy (LTOT) is the only modality, to our knowledge, that has been shown to slow down and partially reverse the progression of PH in patients with COPD. Several trials have been conducted on the use of LTOT in patients with COPD, showing improved survival in those using oxygen more regularly. In the Medical Research Council trial (N = 87), mortality rate at 5 years was 67% in the no-oxygen group and 45% in the oxygen-treated group (15 h/day). In patients alive at 500 days who received repeat RHC, mPAP increased in the no-oxygen group (n = 21) at an average rate of 2.7 mm Hg/y and remained unchanged in the oxygen-treated group (n = 21). In the Nocturnal Oxygen Therapy Trial (N = 200), the mortality rate after 1 year was 11.9% in the continuous oxygen therapy group (averaging

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**Table 5—Summary of Techniques From the Literature Previously Used in Patients With COPD-Associated PH**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize COPD management</td>
<td>Smoking cessation, bronchodilator therapy, pulmonary rehabilitation</td>
</tr>
<tr>
<td>Workup for comorbidities contributing to PH (eg, PE, CAD, CCF, valvular disease)</td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>Short term and long term</td>
</tr>
<tr>
<td>Nonspecific vasodilators</td>
<td>Calcium channel antagonists, angiotensin-converting enzyme inhibitors, urapidil</td>
</tr>
<tr>
<td>PH-specific therapy</td>
<td>Inhaled nitric oxide, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogs</td>
</tr>
<tr>
<td>Surgical options</td>
<td>LVRS, LT</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CCF = congestive cardiac failure. See Table 1, 3, and 4 legends for expansion of abbreviations.

As detailed in the text, many of these techniques have not proven to be useful in patients with COPD-associated PH.
hemodynamic measurement at baseline and 6 months

group (averaging 12 h/day). In patients undergoing
17 h/day) and 20.6% in the nocturnal oxygen therapy
group. Curiously, the survival benefit only was seen
in patients with a low PVR, whereas there was no
difference in structural pulmonary vascular abnormali-
ties between patients receiving LTOT and those not
receiving LTOT.

Several mechanisms can be hypothesized to explain
this potential beneficial effect of LTOT. The most
obvious include relief of hypoxic pulmonary vasocon-
striction, causing a reduction in PVR and mPAP with
decreased RV strain, and improved performance with
increased oxygen supply to vital organs. Even though
LTOT resulted in a slight improvement in pulmonary
hemodynamics and survival, it remains unclear whether
the two are linked. The modest improvement in hemo-
dynamics and the lack of survival benefit in patients
with elevated PVR in the Nocturnal Oxygen Therapy
Trial indicate that the hemodynamic improvement is
unlikely to be the only factor. Additional evidence
comes from autopsy studies that show no significant
difference in structural pulmonary vascular abnormali-
ties between patients receiving LTOT and those not
receiving LTOT.

Current evidence seems to indicate that LTOT has
the potential to stabilize pulmonary hemodynamics
in patients with COPD requiring LTOT. However, pul-
monary hemodynamics do not return to normal, and
the structural changes are not reversed. Until further
evidence becomes available, continuous oxygen appears
to be the prudent option because patients appeared to
obtain the most benefit from this therapy.

**LTOT in Patients With Isolated Sleep-Related Hypoxemia:** With lower baseline oxygenation and
abnormal respiratory mechanics in patients with severe airflow limitation, alterations in ventilatory
control and respiratory muscle function that normally
occur during sleep can have profound effects and
contribute to the development of sleep abnormali-
ties. Episodes of nocturnal oxygen desaturation may
be seen in nonrapid eye movement sleep, are more
pronounced during rapid eye movement sleep, and
can develop despite an awake PaO₂ of >60 mm Hg.
Although predictors for the development of noctur-
nal oxygen desaturation have been identified, its
effect on pulmonary hemodynamics and overall sur-
vival are still uncertain. In addition, the associated
PH itself may exacerbate the sleep-related oxygen
desaturation. It has been hypothesized that noctur-
nal oxygen desaturation in these patients may lead to
fixed daytime PH. This hypothesis remains unpro-
ven, and thus the role and potential benefits of oxygen
supplementation in these patients remain unclear. In
a small study, Fletcher et al noted no difference in sur-
vival in patients with COPD with nocturnal oxygen
desaturation and an awake PaO₂ of >60 mm Hg who
were randomized to nocturnal oxygen at 3 L/min or a
sham control for 36 months. An improvement in pul-
monary hemodynamics was noted in the oxygen ther-
apy group (decrease in mPAP by 3.7 mm Hg) compared
with the control group (increase in mPAP by 3.9 mm
Hg) (P < .02). Chaouat et al reported similar results
with regard to survival in patients with mild-to-
moderate hypoxemia (PaO₂, 56-69 mm Hg) who were
randomized to nocturnal oxygen therapy (n = 24 study
completers) vs control (n = 22 study completers) and
followed for up to 60 months. There was no difference
in survival; and moreover, there was no difference in

### Table 6—Recommendations Regarding Management of COPD-Associated PH

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Mild-to-Moderate COPD</th>
<th>Severe COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimizing COPD management</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rule out comorbidities</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Confirm diagnosis</td>
<td>RHC</td>
<td>RHC</td>
</tr>
<tr>
<td>Oxygen</td>
<td>If needed; look for exertional and nocturnal hypoxia</td>
<td>If needed; look for exertional and nocturnal hypoxia</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>If needed</td>
<td>Yes</td>
</tr>
<tr>
<td>PH-specific therapy</td>
<td>Consider in the context of a clinical trial; potential functional and survival benefits are not known</td>
<td>Consider in the context of a clinical trial; may provide short-term functional benefit; survival benefit not known</td>
</tr>
<tr>
<td>LVRS</td>
<td>Contraindicated†</td>
<td>Contraindicated†</td>
</tr>
<tr>
<td>LT</td>
<td>Consider if disease progressing despite above</td>
<td>Yes, most likely to provide long-term benefit</td>
</tr>
</tbody>
</table>

See Table 1 and 2 legends for expansion of abbreviations.

†In patients with significant PH.
developing a need for conventional LTOT or in the degree of change in pulmonary hemodynamics.

In view of this evidence, the role for nocturnal oxygen supplementation is unclear in patients with isolated nocturnal oxygen desaturation with adequate daytime and exertional oxygen saturation. However, these patients should be evaluated for concomitant obstructive sleep apnea (overlap syndrome) as well as for the presence of PH. A large study on the role of oxygen therapy in patients with COPD, the Long-Term Oxygen Treatment Trial, is ongoing in North America and funded by the National Heart, Lung, and Blood Institute and the Centers for Medicare & Medicaid Services to shed light on this issue.

**PH-Specific Therapy**

The role and indications for PH-specific therapy in patients with COPD remain poorly defined, largely owing to a paucity of evidence. PH-specific therapy should be considered when (1) PH persists despite the steps previously outlined and (2) when PH is believed to be disproportionate to the degree of airflow limitation. Most PH-specific medications have vasodilatory and antiproliferative effects that help to unload the right ventricle in patients with pulmonary arterial hypertension. Enthusiasm for their use has been tempered by the realization that these medications may have limited value in patients with COPD-associated PH where the RV function may be preserved; the afterload may be only mildly increased; and the RV diastolic function and solute and water retention, along with airflow limitation and hypoxia, may be the primary factors.

**Vasodilators:** Several vasodilators, such as calcium blockers, angiotensin-converting enzyme inhibitors, nitrates, and hydralazine, have been used in an attempt to reduce PAP and PVR. Despite encouraging short-term effects in patients with COPD, the benefits unfortunately have not been sustained. In addition, these agents are not selective to the lung vasculature and have detrimental effects, including worsening of ventilation-perfusion matching, significant negative inotropic effects, and systemic hypotension. These agents currently are not recommended for use in treating COPD-associated PH.

**Vasoactive Agents:** In view of the negative impact of PH on clinical parameters in COPD, several investigators have attempted to study the impact of these medications in patients with COPD-associated PH. Unfortunately, these studies comprise case series or single-center investigations with poorly defined inclusion criteria or very small samples of patients with PH. Nitric oxide has been shown to improve ventilation-perfusion matching and stabilize PaO₂ in patients with COPD-associated PH during exercise. Studies also have shown short- and long-term improvement in oxygenation and hemodynamics in patients with COPD-associated PH receiving oxygen therapy and nitric oxide. This combination is somewhat cumbersome as an option for long-term use and requires further study. A single-center, 12-week, randomized study of bosentan in 30 patients with severe COPD (only six of whom had resting PH by echocardiography) showed no significant functional benefit. In fact, arterial oxygenation and quality of life declined in patients taking bosentan compared with those taking placebo. Small case series have alluded to the potential benefit of using sildenafil in patients with PH associated with parenchymal lung disease, including COPD. Holverda et al reported acute effects of sildenafil in 15 patients with severe COPD (five with resting PH and six with exercising PH) and found that regardless of mPAP at rest, sildenafil attenuated the increase in mPAP during submaximal exercise. However, this attenuated increase was accompanied by neither enhanced stroke volume and cardiac output nor improved maximal exercise capacity. The same group reported results of a 12-week prospective study of sildenafil in 15 patients with severe COPD (nine of whom had PH) and found no significant improvement in stroke volume or exercise capacity. Prostaglandins E1 and I2 have pronounced vasodilator effects on the pulmonary circulation. Prostaglandin analogs have been shown to decrease mPAP and PVR and to increase cardiac output and oxygen delivery in patients with COPD. However, there is a concern that parenteral prostanooid analogs may worsen ventilation-perfusion mismatch and hypoxia in these patients, especially if given to those in an acutely decompensated state. The role for inhaled prostanooid analogs remains to be defined. Despite these limitations, a recent survey of practicing pulmonologists in the United States found that a significant proportion prescribe these medications to patients with PH occurring in association with parenchymal lung disease.

Given the evidence outlining a potential role for inflammation in COPD-associated PH, medications with antiinflammatory properties theoretically may play a role. Several properties of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors could potentially be beneficial in these patients, including a protective effect on lung parenchyma from adverse effects of cigarette smoke and antiinflammatory, antithrombogenic, and antioxidant effects. In a 6-month randomized placebo-controlled prospective study of pravastatin in 53 patients with PH associated...
with COPD, Lee et al. reported a significant improvement in exercise time, echocardiographically derived RV systolic pressure, and Borg scores.

**Surgical Intervention**

Despite the theoretical implications of hyperinflation as a potential factor in exercise-induced worsening of pulmonary hemodynamics in patients with COPD, lung volume reduction surgery did not have an impact on hemodynamics. Lung transplantation is the best long-term option in patients with PH in the setting of advanced COPD.

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**References**


