REVIEW ARTICLE

Pulmonary Hypertension in COPD: A Review and Consideration of the Role of Arterial Vasodilators

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ABSTRACT

The possibility that pulmonary hypertension (PH) may develop in patients with chronic obstructive pulmonary disease (COPD) is well established, but prevalence data vary. The current World Health Organization clinical classification includes COPD in diagnostic group III: PH associated with disorders of the respiratory system or hypoxemia. The National Institute of Health defines PH as a mean pulmonary artery pressure of greater than 25 mmHg. Approximately 10% of the patients seen over the last decade in the PH Clinic at Mayo Clinic in Jacksonville, Florida, have PH due to COPD. The pathophysiology is likely complex and involves hypoxic pulmonary vasoconstriction. Ultimately, chronic hypoxia results in vascular remodeling with narrowing of the vascular lumen. The right heart is forced to generate increased driving pressures to overcome the increased vascular resistance. As the disease progresses, cor pulmonale may develop. The mortality in this setting is increased with five-year survival of 20% to 36% and seems to correlate with worsening PH and age. Fortunately, the PH in most cases is mild and occurs primarily in those with severe hypoxemia. Only 1% to 4% of patients have PH seemingly out of proportion to the severity of the COPD. This disproportionate subgroup may represent an important phenotype that requires a different therapeutic approach. Although supplemental oxygen remains the primary treatment for all PH in association with chronic hypoxia, pulmonary arterial vasodilators may have a therapeutic role in this subgroup. Vasodilators may worsen gas exchange, however, and to date, have no proven benefit. Rigorous future study will be required to determine whether there is a role for using pulmonary arterial vasodilators in this setting.

INTRODUCTION

The possibility that pulmonary hypertension (PH) may develop in patients with chronic obstructive pulmonary disease (COPD) is well established (1). The current World Health Organization (WHO) clinical classification includes COPD in diagnostic group III: PH associated with disorders of the respiratory system or hypoxemia (Table 1) (2). It is defined by the National Institute of Health as a mean pulmonary artery pressure (MPAP) of greater than 25 mmHg (3). An arbitrary severity scheme based on the MPAP is as follows: mild, 26 to 34 mmHg; moderate, 35 to 44 mmHg; and severe, 45 mmHg or more. (1) PH in COPD patients is generally mild and occurs primarily in those with severe hypoxemia. Disproportionate PH in patients with COPD seems best defined as at least moderate elevation in the MPAP (≥ 40 mmHg) particularly with evidence of right ventricular (RV) dysfunction or failure despite only mild to moderate reductions in the forced expiratory volume in 1 second (FEV1 ≥ 50% predicted) (1, 4, 5). A small fraction of patients have PH seemingly out of proportion to the severity of the COPD and serve as the primary focus of this discussion.
The exact incidence or prevalence of PH in COPD is unknown. An older study from the Strasbourg, France, group demonstrated PH in 62 of 175 patients (35%) with moderate to severe COPD using a low threshold of a MPAP greater than 20 mmHg. More recent data better characterize the prevalence in various subgroups of COPD. In a COPD population reviewed either for lung transplant or volume-reduction surgery, approximately half had PH (4). The PH was generally mild with an average MPAP of 27, plus or minus 8 mmHg.

Severe PH was present in only 4% of study subjects. Chaouat and colleagues (5) showed that only 27 of 998 COPD patients had a MPAP of 40 mmHg or more. Only 11 (1%) had PH without any other identifiable cause other than COPD. Extrapolation to known epidemiological data for COPD in the United States provides for an interesting analysis. Assuming that 1% of the 500,000 patients hospitalized for COPD have moderate to severe PH (mean MPAP of 40 mmHg or greater), then the general prevalence of significant PH in patients with COPD is markedly higher than the prevalence of idiopathic pulmonary arterial hypertension. Those patients with severe PH seem to have less severe obstruction as indicated by a forced expiratory volume in one second (FEV1) of approximately 50% predicted (5). Instead, the severe PH patients had more hypoxemia and a severe reduction in diffusing capacity.

Although autopsy series introduce a significant selection bias, 40% of COPD patients examined at autopsy have evidence of right ventricular hypertrophy, presumably on the basis of PH (6). The far end of the spectrum of disease prevalence is 90% reported in 120 patients (MPAP > 20 mmHg) evaluated for inclusion in the National Emphysema Treatment Trial (NETT) (7), 60% of whom also had elevated left heart pressures. This study overestimates the prevalence by using a MPAP that is lower than the standard definition recommended by the American College of Chest Physicians evidence-based guidelines which is a MPAP > 25 mmHg (8). In addition, those patients with elevated pulmonary artery occlusion pressures would be classified as pulmonary venous hypertension (2). Examination of a referral PH population provides yet another perspective. In our PH clinic at the Mayo Clinic in Jacksonville, Florida, 10% (58 of 578) of patients referred for PH between 1998 and 2008 have COPD as the primary or contributing cause. The referrals have been more prevalent over the last 3 years but this may reflect more screening in patients with COPD rather than increasing incidence.

The natural history of PH in the setting of COPD is also not well characterized. One longitudinal study suggested that exercise-induced PH may precede a persistent state even at rest (9). Another study of patients undergoing sequential right heart catheterizations demonstrated progression over time, albeit at a slow pace of 0.5 mmHg per year (10). Despite the mild levels and slow progression of PH in most patients with COPD, Chaouat’s study (5) confirms older data that suggest a more dramatic impact on survival (11, 12). Five-year survivals range from less than 20% to 36% (Chaouat less than 20%, Oswald 36%). The French group demonstrated that survival was correlated with both worsening PH and increasing age.

Furthermore, it has been demonstrated that PH is a predictive factor for COPD exacerbations (11). It may be difficult to sort out the independent impact of cardiovascular and pulmonary disease when they coexist. According to a 2005 Agency for Healthcare Research and Quality report, hospitalizations involving pulmonary heart disease (inclusive of, but not limited to, cor pulmonale) have risen 51% since 1997 (13). Although generally a secondary diagnosis, length of stay and hospital costs for pulmonary heart disease are higher compared to patients with similar primary diagnosis without pulmonary heart disease. Overall, the estimated cost is $5.6 billion, or 1.8% of the total cost for all hospital stays.

Pathobiology

Normally, the pulmonary circulation offers low resistance that can accommodate significant increases in cardiac output with little increased pulmonary arterial pressure (14). Pulmonary vessels have approximately one-tenth of the resistance and one-fourth of the arterial pressure compared to systemic circulation (15). Key features that provide for these differences include: thinner, more compliant arteries; dynamic vasoconstriction adjusting the vessel caliber; and an expandable alveolar-capillary surface area. Substantive alterations to the vasculature and milieu are necessary to produce PH.

A variety of pathophysiological processes have been implicated for COPD associated PH. For example, hypoxia produces vasoconstriction to maintain appropriate ventilation to perfusion balance (16, 17). The hypoxic pulmonary vasoconstrictive response is primarily mediated through altered levels of vasoconstrictors (18). Chronic hypoxia produces vascular remodeling involving altered cellular function including fibroblasts,
endothelial cells, and vascular smooth muscle cells (19). The remodeling may involve all three vascular layers: intimal fibrosis, medial smooth muscle hypertrophy, and adventitial alteration in the collagen matrix. Advanced pulmonary arterial pathology (e.g., plexogenic lesions) are indicative of severe idiopathic pulmonary arterial hypertension but are not generally seen in COPD PH. Nonetheless, the vascular remodeling that occurs is sufficient to reduce vascular compliance.

It is generally thought that the vascular remodeling described above explains the persistent PH in COPD. The lack of reversibility in response to oxygen or inhaled nitric oxide supports that contention. The mechanisms by which the remodeling occurs are unknown. Indeed, the correlation between PH and indicators of disease severity such as FEV₁ and PaO₂ is weak. Levels of vasoconstrictors such as endothelin-1, serotonin, and angiotensin II are generally elevated, and levels of endogenous vasodilators are correspondingly decreased. Endothelial cell dysfunction likely contributes to the imbalance of vascular mediators. As a result, there may be decreased production of nitric oxide and prostacyclin as well as decreased clearance of endothelin-1 (20, 21). In addition, angiotensin II, endothelin-1, and serotonin stimulate vascular smooth cell growth and proliferation, exacerbating the vascular remodeling.

Genetic polymorphisms may also play a role. Such links have been demonstrated with the nitric oxide synthase gene and the serotonin transporter LL genotype. The latter may be relevant to the potential role of serotonin and its transporter in vascular smooth muscle hyperplasia. One study demonstrated the correlation of the LL genotype with higher pulmonary artery pressures (22).

While the majority of patients with PH in association with COPD have mildly elevated MPAP, a small percentage have moderate to severe PH. Experts have speculated on the cause of PH disproportionate to the severity of the COPD. One author (23) believed that the two most likely explanations were either: (1) A hypersensitive hypoxic pulmonary vasoconstriction response perhaps due to genetic predisposition (22); or (2) Coexistent COPD and pulmonary arterial vasculopathy.

Other areas of active research include direct toxicity of cigarette smoke on the pulmonary circulation (24–26), ongoing inflammation involving cytokines, and the roles of chronic hypoxemia (27, 28) and polycythemia (29). All potentially cause or facilitate vascular remodeling. Mechanical factors may also play a role. Hyperinflation may lead to increased pulmonary vascular resistance (30). Diastolic dysfunction may elevate the left atrial filling pressure, thereby contributing to an elevated mean pulmonary artery pressure (7). Reduced capillary volume from emphysema may be contributory; however, PH does not seem to be related to total alveolar surface area or lung density.

Patients with COPD PH have exaggerated increases in transpulmonary pressures gradient (MPAP minus the left atrial pressure) with exercise (9). The increase in pulmonary pressure is greater than that predicted by Ohm’s law. The physiologic variant of that law used to calculate pulmonary vascular resistance (PVR) is: PVR = (MPAP – pulmonary artery occlusion pressure ÷ cardiac output) (31). The abnormal response suggests vasoconstriction with exercise. Certainly, the hypoxic pulmonary vasoconstriction response may be enhanced by a variety of factors in response to exercise: low mixed venous saturation, increased sympathetic tone, and respiratory acidosis. In addition, dynamic hyperinflation may occur with exercise raising intrathoracic pressure and right ventricular afterload. An exaggerated elevation in MPAP may also represent a phenotypic subgroup worthy of further study (32).

In patients with severe disease, progressive pulmonary arteriopathy increases resistance to flow requiring higher upstream driving pressures to be generated by the right ventricle. Ultimately, this results in right ventricle hypertrophy. As the disease worsens, the right ventricle is ill equipped to compensate, thus enlargement and hypokinesis ensue (33). Exacerbations of COPD may result in worsening PH and peripheral edema (34). Generally, the PH returns to baseline after the patient recovers from the acute exacerbation. Although fluid retention and peripheral edema may signal right ventricular failure, hypoxia and hypercapnea can independently produce sodium and water reabsorption via the renin-angiotensin-aldosterone system (35).

**Diagnosis**

Clinical manifestations are nonspecific but include decreased functional status and increased dyspnea and fluid retention. Despite the nonspecific nature of PH symptoms, the clinician should be alert to COPD patients who have symptoms seemingly disproportionate to the severity of the airway obstruction. Physical examination may be challenging if the chest is hyper-expanded and the heart rotated (36), but an accentuated second heart sound or new systolic murmur of tricuspid regurgitation (increased with inspiration) may be clues. Other features include facial plethora, clubbing, prominent jugular venous pressure, and right ventricular lift and gallop. Hepatic congestion, ascites, and peripheral edema may indicate decompensated right heart failure.

Plain chest radiographs may show enlarged hila, prominent pulmonary arteries, or peripheral vascular pruning; however, the sensitivity may be reduced in chronic lung disease. Nonetheless, one study demonstrated a 98% sensitivity of a combination of enlarged right and left descending pulmonary arteries (37). The electrocardiogram is quite specific and may demonstrate a pulmonary disease pattern: right axis deviation, prominent P wave in right-sidled leads (“P pulmonale”), and prominent S waves in leads I, II, and III. In addition, the patient has a worse prognosis if one or more of the following are present: rightward axis, right atrial enlargement, right ventricular hypertrophy, abnormal (inverted, biphasic, or flattened) precordial T waves, or right bundle branch block (38, 39). Chest CT may demonstrate an enlarged main pulmonary artery (greater than 29 mm) but this finding is not useful as a screen for chronic thromboembolic disease. Brain natriuretic peptide may be modestly elevated in most cases (40). The diffusion capacity for carbon monoxide may be the only pulmonary function variable that reliably correlates with PH (7).

If clinical presentation suggests the possibility of PH, an echocardiogram is a useful first test, but echocardiography may
be less reliable in COPD patients than in patients without chronic lung disease (41, 42). Fisher and colleagues (42) demonstrated a lower accuracy in 63 patients with severe COPD with a positive predictive value of 68% and negative predictive value of 67%. Although the reliability is reduced in advanced lung disease, echocardiography remains helpful. For example, the absence of any right heart enlargement or dysfunction and the presence of another explanation for dyspnea such as severe left-heart disease probably exclude PH as the cause of the symptoms. The reasons for the reduced accuracy in estimating right-heart pressures are likely mostly technical, such as hyperinflation. Nonetheless, advances in echocardiographic techniques continue, and in our lab we obtain reproducible results (43).

The gold standard for diagnosis of PH remains right heart catheterization (RHC). In addition, RHC provides other useful diagnostic and prognostic information. Left-to-right shunting that may be overlooked by contrast saline echocardiography can be diagnosed by measuring oxygen saturations in the vena cava, right heart chambers, and pulmonary artery. Left-sided pressures can be estimated with a pulmonary artery occlusion (wedge) pressure. If elevated, then the PH may be primarily pulmonary venous hypertension and unrelated to the COPD. In addition, conditions may coexist (7). The baseline pulmonary artery and right-heart pressures, as well as acute response to pulmonary arterial vasodilators, provide reliable prognostic information and guidance regarding therapeutic decisions in WHO diagnostic group I pulmonary arterial hypertension (Table 1) (44). The role of acute vasoreactivity testing has not been studied in COPD. Indeed, it is unclear that calcium channel blockers are of use in patients with PAH associated with COPD which would be the main reason to look for acute vasoreactivity. Nonetheless, acute vasoreactivity is done in other conditions associated with PAH. Fortunately, RHC is not required in most cases of mild COPD PH.

Exercise testing may help tease out the cause of the dyspnea. Ventilatory limitation may produce a different pattern than primary pulmonary vascular disease. Occasionally, exercise stress during a pulmonary artery catheterization is warranted. As noted above, those COPD patients with an exaggerated elevation in MPAP in response to exercise may represent a phenotypically important group (32).

Coexisting disease should be excluded where indicated. Particular focus should be on treatable co-morbidities. A common example would be sleep-disordered breathing. In patients with a high pretest probability (obese, snorer, excessively somnolent, and witnessed apneas), an overnight polysomnogram should be performed. In other cases, screening overnight oximetry may be more appropriate. We have demonstrated an increased prevalence of thyroid disease in all WHO diagnostic subgroups (45). Exclusion of human immunodeficiency and collagen vascular disease in appropriate patients is recommended. Chronic thromboembolic disease is often subclinical until manifested as pulmonary hypertension. Chest CT angiography may be falsely negative. In contrast to acute pulmonary embolism in COPD patients, a lung perfusion scan is the best screen for chronic thromboembolic disease causing PH (46). A formal pulmonary angiogram may be required to confirm the diagnosis.

Noninvasive assessments of right ventricular size and function may provide useful information to the clinician. Echocardiography is the most common methodology. Right ventricular size by magnetic resonance imaging correlates with mean pulmonary artery pressure and pulmonary vascular resistance (47). Right ventriculography has also been used. Chest CT seems to be less reliable.

**Treatment**

Oxygen should be considered the primary treatment of COPD PH in the setting of hypoxemia. The goal for oxygen saturation is 90% or greater (PaO2 of 60 torr) for hypoxic COPD patients with PH or cor pulmonale. Supplemental oxygen may blunt exercise-induced PH and slow disease progression (48–53). Daily use of oxygen therapy for 17 hours or more may result in decreased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), but the hemodynamics rarely normalize (48). One study demonstrated that acute response to oxygen predicted better long-term survival (54); however, the pulmonary vascular response may also be less in more advanced stages of disease. Not all studies show hemodynamic benefit with oxygen therapy (29). Furthermore, it is unknown whether the improved survival on oxygen is related to the potential beneficial impact on pulmonary vascular hemodynamics (48).

A discussion of treatment of PH in patients with COPD necessarily includes smoking cessation, bronchodilators, diuretics, and digoxin. Other than smoking cessation and inhaled bronchodilators, most supportive therapies have significant drawbacks. Diuretics may reduce pre-load and improve right ventricular function but have a number of practical limitations. Side effects include electrolyte abnormalities, metabolic alkalosis, and pre-renal insufficiency. Diuresis may also aggravate pre-existing polycythemia, which theoretically increases blood viscosity and vascular resistance. Excessive diuresis may actually decrease right ventricular function and cause hemodynamic deterioration. Theophylline has been shown to decrease PAP and PVR, but decreased drug clearance in the setting of right ventricular dysfunction may increase the likelihood of toxic serum levels (55). Digoxin is not used routinely in severe COPD because of the lack of proven benefit and risk of toxicity. Routine treatment of COPD is generally sufficient even for most patients with PH as the PAP is only modestly elevated.

In contrast, a small percentage of COPD patients with PH have severe elevations in MPAP (5). In this small subgroup, it seems that the PH is out of proportion to the COPD. It has been postulated that there is a coexisting pulmonary arterial vasculopathy similar to that seen in pulmonary arterial hypertension (e.g., idiopathic) (5, 23, 26). Although specific pulmonary arterial vasodilator therapy has not generally been recommended (32, 34), one might consider such therapy in severe disease (26). The stance against use of vasodilators is based on failure to improve outcome with more traditional agents such as calcium channel blockers and only limited data in support of use of the
newer agents. There are a number of older reports of small series of patients treated with systemic vasodilators, usually calcium channel blockers or hydralazine (56–61).

Most studies showed modest acute hemodynamic improvement with more limited long-term benefits (62–64). Indeed, all systemic vasodilators potentially worsen gas exchange by altering the physiologic hypoxic pulmonary vasoconstrictive response that may be important in COPD patients (65). The phosphodiesterase-5 inhibitor sildenafil lowers PAP and seems to better tolerated in this regard (66). The results are limited by the small number (six) of patients studied.

Delivery of the pulmonary vasodilator via inhalation may reduce pulmonary artery pressure while avoiding ventilation perfusion mismatching. Theoretically, an inhaled vasodilator will distribute only to those well-ventilated areas so should not over-ride the hypoxic pulmonary vasoconstrictive response in poorly ventilated diseased segments. The specific vasodilator and dose may be relevant. In one study, inhaled nitric oxide (NO) worsened oxygenation (67), while in another, “pulsed” NO decreased MPAP and PVR while oxygenation was unchanged (68).

Overall, the available data is limited on the utility of pulmonary arterial vasodilators in COPD patients with PH. Certain FDA-approved drug classes have no published data. There are no large, placebo-controlled, randomized trials for WHO diagnostic group III. One recent prospective study of bosentan, an endothelin-receptor antagonist, in patients with severe COPD did not show benefit and slightly worsened gas exchange (69). The study included only patients with mild elevations in right ventricular systolic pressure by echocardiography; therefore, does not address the potential efficacy for COPD patients with disproportionate PH. In addition, some of the small case series advocating use of pulmonary arterial vasodilators have included patients with PH of mixed etiologies and severity which confounds interpretation (70).

Despite the limitations discussed above, some authors have advocated treatment of PH even in the setting of COPD (26, 71). It may be prudent to consider treatment of severe PH in COPD particularly if the PH appears to be the primary cause of the progressive symptoms or deterioration (1, 23, 31). One may choose to follow the American College of Chest Physician algorithm for treatment of pulmonary arterial hypertension with the exception of calcium channel blockers (44). McLaughlin and McGoon have also proposed a construct for evaluation of severity of disease to aid in decision making for patients with WHO functional class III (72). Careful selection of patients is necessary; therefore, an approach is outlined in Figure 1.

Using severity of symptoms and evaluation of functional status as well as right heart function, one can identify those patients with PH disproportionate to the COPD. The selection of phosphodiesterase-5 inhibitor (sildenafil) for those with less severe disease seems logical for several reasons: it exists as an oral preparation that is generally well tolerated (66); it has a less adverse effect on gas exchange (73); and it is relatively less costly (Table 2) (74). It is the author’s opinion that sildenafil is the drug of choice but this has not been proven; therefore, requires more study.

**Table 2.** Typical costs of pulmonary arterial vasodilators

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSE</th>
<th>COST($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td>Oral</td>
<td>5–10 mg qD</td>
<td>4728</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Oral</td>
<td>125 mg BID</td>
<td>4658</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Oral</td>
<td>20 mg TID</td>
<td>1063</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>IV</td>
<td>20 ng/kg/min</td>
<td>2763</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>IV or SQ</td>
<td>40 ng/kg/min</td>
<td>8135</td>
</tr>
<tr>
<td>Ilprost</td>
<td>Inhaled</td>
<td>5 mcg/inhalation, 6 inhales/day</td>
<td>7679</td>
</tr>
</tbody>
</table>

The other oral agents, such as the endothelin-receptor antagonists (bosentan or ambrisentan), are more costly, have less desirable side-effect profiles, and have not shown benefit in mild COPD (69) or pulmonary fibrosis (75). Those with frank right heart failure may be better served with prostacyclin therapy. Inhaled prostacyclin (ilocprost) may be the second-line choice because it is delivered to the better-ventilated lung segments, where theoretically it should provide benefit and not worsen ventilation-perfusion mismatching.

Frequent inhalations are required up to 6 to 9 times daily. It is intermediate in cost but does not require the necessary training and logistical support inherent with continuous infusion prostacyclins. Epoprostenol and treprostinil are prostacyclins that require continuous infusion and should be reserved for patients with severe right heart dysfunction. Both require daily preparation and continuous infusion pumps. Epoprostenol is only available as an intravenous preparation, whereas treprostinil can be infused subcutaneously. As one advances through...
the therapeutic options from oral to intravenous, the side effects and costs increase (Table 2).

While it may be reasonable, in the author’s opinion, to treat PH disproportionate to the severity of the COPD (1), the overwhelming majority of COPD patients with PH will only have mild elevation in right heart pressures. The increased availability of better tolerated therapies for PH seems to have resulted in more patients being screened and referred to our center for evaluation. The clinician may therefore be commonly confronted with the question of whether to treat mild PH in this setting. The answer is unknown; however, it is the opinion of the author that these mild cases should not be placed on pulmonary arterial vasodilator therapy.

The basis for this recommendation is the low likelihood of improving symptoms, functional status or survival versus the potential risk and expense of treatment. In summary, there is little published data particularly which represents randomized, placebo-controlled trials of pulmonary arterial vasodilators for PH in COPD patients. The available studies are discussed but the conclusions and recommendations should be interpreted with significant caution. Finally, it should be noted that are no trials that these mild cases should not be placed on pulmonary arterial vasodilator therapy.

Special considerations

Evaluation and treatment of coexisting conditions that either cause or worsen PH are advisable. Several such conditions were discussed in the diagnosis section. Sleep-disordered breathing deserves special note because occurrence with COPD may have specific impact on PH. Hypoventilation during sleep, especially rapid eye movement, may exacerbate gas exchange abnormalities associated with COPD. The resulting hypoxia and hypercapnea may produce or exacerbate PH (78, 79). Treatment with nocturnal oxygen and/or nasal continuous positive airway pressure as appropriate to the diagnosis may be beneficial (80). Acute pulmonary embolism should also be considered as an important association particularly as a potential cause of unexplained acute exacerbation of COPD (81).

CONCLUSIONS

PH may develop in patients with COPD and is classified as WHO diagnostic group III: PH associated with disorders of the respiratory system or hypoxemia. The exact prevalence is unclear and depends on the population studied. The pathophysiology is likely complex and involves vascular remodeling due to, at least in part, hypoxic pulmonary vasoconstriction. As the disease progresses, cor pulmonale may develop, thereby increasing the mortality. Fortunately, the PH in most cases is mild and occurs primarily in those with hypoxemia. Only a small fraction of patients has PH seemingly disproportionate to the severity of the COPD. This disproportionate subgroup may represent an important phenotype that requires a different therapeutic approach. Although supplemental oxygen remains the primary treatment for all PH in association with chronic hypoxia, pulmonary arterial vasodilators may have a therapeutic role in this disproportionate subgroup. Nevertheless, vasodilators may worsen gas exchange and to date, have no proven benefit. Rigorous future study will be required to determine the best therapeutic approach to PH in association with COPD.

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