Pulmonary Hypertension in Chronic Lung Diseases

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Chronic obstructive lung disease (COPD) and diffuse parenchymal lung diseases (DPLD), including idiopathic pulmonary fibrosis (IPF) and sarcoidosis, are associated with a high incidence of pulmonary hypertension (PH), which is linked with exercise limitation and a worse prognosis. Patients with combined pulmonary fibrosis and emphysema (CPFE) are particularly prone to the development of PH. Echocardiography and right heart catheterization are the principal modalities for the diagnosis of COPD and DPLD. For discrimination between group 1 PH patients with concomitant respiratory abnormalities and group 3 PH patients (PH caused by lung disease), patients should be transferred to a center with expertise in both PH and lung diseases for comprehensive evaluation. The task force encompassing the authors of this article provided criteria for this discrimination and suggested using the following definitions for group 3 patients, as exemplified for COPD, IPF, and CPFE: COPD/IPF/CPFE *without* PH (mean pulmonary artery pressure [mPAP] <25 mm Hg); COPD/IPF/CPFE *with* PH (mPAP ≥25 mm Hg); PH-COPD, PH-IPF, and PH-CPFE); COPD/IPF/CPFE *with* severe PH (mPAP ≥35 mm Hg or mPAP ≥25 mm Hg with low cardiac index [CI <2.0 l/min/m^2]; severe PH-COPD, severe PH-IPF, and severe PH-CPFE). The "severe PH group" includes only a minority of chronic lung disease patients who are suspected of having strong general vascular abnormalities (remodeling) accompanying the parenchymal disease and with evidence of an exhausted circulatory reserve rather than an exhausted ventilatory reserve underlying the limitation of exercise capacity. Exertional dyspnea disproportionate to pulmonary function tests, low carbon monoxide diffusion capacity, and rapid decline of arterial oxygenation upon exercise are typical clinical features of this subgroup with poor prognosis. Studies evaluating the effect of pulmonary arterial hypertension drugs currently not approved for group 3 PH patients should focus on this severe PH group, and for the time being, these patients should be transferred to expert centers for individualized patient care.   (J Am Coll Cardiol 2013;62:D109–16)
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Epidemiology and Clinical Relevance of Pulmonary Hypertension in Lung Disease

Chronic obstructive pulmonary disease. The prevalence of pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) depends on the severity of the disease and the definition of PH (see discussion in the following text). Several studies in patients with the previous GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage IV showed that up to 90% of these patients have a mean pulmonary artery pressure (mPAP) of >20 mm Hg, with most ranging between 20 and 35 mm Hg and ∼3% to 5% patients with mPAP >35 to 40 mm Hg (1,2). The morphological appearance of vascular lesions in COPD patients correlates with the severity of PH, which is similar to idiopathic pulmonary arterial hypertension (IPAH) in severe cases (3). Even under moderate exercise conditions, COPD patients typically show a rapid further rise in mPAP values, indicating loss of lung vascular distensibility and/or vessel recruitment capability (4). The rate of PH progression in COPD is normally slow (an increase of <1 mm Hg per year [5]). Nevertheless, the presence of (even moderate) PH is a strong predictor of mortality in COPD, with an inverse correlation between mPAP and/or pulmonary vascular resistance (PVR) values and survival (2,6,7). A 5-year survival rate of only 36% was reported for COPD patients with mPAP values >25 mm Hg, with pulmonary hemodynamics being a far stronger predictor of survival than the forced expiratory volume in 1 s (FEV1) or gas exchange variables (7). In addition, enlarged pulmonary artery diameter, as detected by computed tomography (CT) scan, predicts hospitalization caused by acute COPD exacerbation (8).

Idiopathic pulmonary fibrosis and diffuse parenchymal lung disease. In idiopathic pulmonary fibrosis (IPF), which has a survival range of only 2.5 to 3.5 years, mPAP values of >25 mm Hg were reported in 8.1% and 14.9% of patients, respectively, upon initial workup (9,10). Higher percentages are found in advanced (30% to 50%) and end-stage (>60%) IPF cases (11–13). Among these, a small percentage may present with mPAP values >40 mm Hg (∼9% [14]). There is only a poor or even no correlation between PH severity and lung function impairment (14) or high-resolution CT fibrosis score (15). Increased dyspnea, deterioration of gas exchange at rest, low capacity of lung to diffuse carbon monoxide (DLCO) values, rapid desaturation upon exercise, high brain natriuretic peptide (BNP) levels, gross right heart dilation on chest radiography, and limitation of exercise capacity caused by circulatory impairment have been linked to PH development in IPF (12,16,17). Doppler-defined PH (systolic PAP >50 mm Hg [16]) and even invasive mPAP values of >17 mm Hg (9) were associated with impaired survival in IPF, with mPAP and forced vital capacity (FVC) being independent predictors of survival (10). Rapid progression of PH was reported in late stage diffuse parenchymal lung disease (DPLD)/IPF patients (13). In some studies, the prognosis of PH in lung fibrosis is not linked to the mPAP values but to PVR (18) or cardiac index (CI), with CI values <2.4 l/min/m² being correlated with survival of only a few months (19).

Combined pulmonary fibrosis and emphysema and other lung diseases. Combined pulmonary fibrosis and emphysema (CPFE) patients are particularly prone to PH development, with estimates approaching 30% to 50% (19,20). Here, severe PH and markedly impaired DLCO may contrast with normal or mildly subnormal lung volumes and absence of airflow obstruction. PH apparently contributes to the functional profile of CPFE (severe dyspnea, severely impairment of gas transfer, and hypoxemia upon exercise) and is associated with poor survival (19–21). At right heart catheterization (RHC), PH was hemodynamically severe in approximately one-half of the patients (mPAP >35 mm Hg in 68%, >40 mm Hg in 48%), and the CI was the most accurate prognostic determinant (19).

Several case reports and published series suggest a role for PH, for example, in advanced sarcoidosis (22,23), severe kyphoscoliosis, obesity-hypoventilation syndrome (24), Langerhans cell histiocytosis (25,26), and to a lesser extent,

in advanced lymphangioleiomyomatosis (27). Moreover, the incidence of adult bronchopulmonary dysplasia (28) and cystic fibrosis (29) patients with PH is apparently increasing.

Assessment and definition of PH due to chronic lung diseases (group 3). Echocardiography is the initial modality for noninvasive diagnosis of PH in COPD and DPLD. Comparing echo cardiographic data with RHC in lung disease patients, positive predictive values of 32% and 68%, respectively, and negative predictive values of 93% and 67%, respectively, were reported (30,31). Plasma levels of BNP or the N-terminal prohormone of BNP are elevated in severe COPD- and DPLD-associated PH, but lack sensitivity in moderate PH and may be confounded by left heart abnormalities (32). Nevertheless, BNP levels they were found to be strongly predictive of mortality in a mixed DPLD population (33).

RHC, the gold standard for PH diagnosis, should be performed in patients with chronic lung disease when 1) evaluation for lung transplantation is deemed necessary; 2) clinical worsening and progressive exercise limitation is disproportionate to ventilatory impairment; 3) progressive gas exchange abnormalities are disproportionate to ventilatory impairment; 4) an accurate prognostic assessment is deemed to be critical; 5) severe PH is suspected by noninvasive measures and further therapy or inclusion in clinical trials or registries are being considered; and 6) there is suspicion of left ventricular systolic/diastolic dysfunction and categorization of the pulmonary artery occlusion pressure might alter management (adapted from Nathan and Cottin [34]). Inhalation of iloprost and NO have been shown to reduce mPAP and PVR in PH-IPF (35–37) and PH-COPD (38), but there are currently no valid data to support routine use of acute vasodilator testing in lung disease patients with PH.

Combining RHC with exercise testing in IPF, systolic PAP measured by echocardiography correlated with peak O_2 uptake, anaerobic threshold, peak O_2 pulse, and ventilatory equivalent for CO_2, suggesting that PH has a negative impact on exercise capacity (17). In COPD, exercise testing may discriminate between an exhausted breathing reserve caused by airflow limitation and an exhausted circulatory reserve caused by PH, as detailed in the following text (39).

Use of the term "in proportion" PH in lung disease is based on the assumption that the underlying parenchymal remodeling process with accompanying hypoxia causes some "natural" loss of overall vascular cross-sectional area and thus an increase in PVR. "Out of proportion" PH, in contrast, signals that the severity of PH is high in relation to the degree of lung parenchymal abnormalities. Such a constellation may reflect the fact that: 1) the chronic parenchymal disease is a trigger of a progressive vascular remodeling process, developing independently of lung function impairment; or 2) the PH appears "by chance" in a patient with lung disease at some stage but independently of this comorbidity background. However, given the fact that a loss of only >80% of normal lung structure will provoke PH,

virtually any PAP value of >25 mm Hg may be considered out of proportion.

Recommendations

It is suggested that the term "out of proportion" be abandoned and that the following definitions for COPD, IPF, and CPFE (measurements undertaken at rest with supplemental oxygen if needed) be used:

1. COPD/IPF/CPFE without PH (mPAP <25 mm Hg);
2. COPD/IPF/CPFE with PH (mPAP ≥25 mm Hg; PH-COPD, PH-IPF, and PH-CPFE); and
3. COPD/IPF/CPFE with severe PH (mPAP ≥35 mm Hg or mPAP ≥25 mm Hg with low CI (<2.0 l/min/m^2); severe PH-COPD, severe PH-IPF, and severe PH-CPFE).

The choice of mPAP ≥35 mm Hg as a cutoff for severe PH is based on the following findings/assumptions, which should be further addressed and putatively revised in future studies:

1. The "severe PH group" includes only a minority of chronic lung disease patients suspected of having significant/severe vascular abnormalities (remodeling) accompanying the parenchymal disease (40). For COPD, this corresponds to ∼1% of the entire population included in the NETT (National Emphysema Treatment Trial) (41).

2. This degree of PH in COPD/IPF is assumed to cause circulatory impairment that substantially worsens the reduced exercise capacity caused by obstructive/restrictive ventilatory impairment. A recent study documented the fact that COPD patients with mPAP ≥40 mm Hg definitely showed an exhausted circulatory reserve at the end of exercise (documented by low mixed venous oxygen saturation and reduced slope of the cardiac output/oxygen consumption ratio), with breathing reserve maintained (documented by low arterial PaCo$_2$) (39). In contrast, COPD patients without PH and those with moderate PH (mPAP 31 mm Hg) are limited by ventilatory impairment (exhaustion of breathing reserve, arterial PaCo$_2$ increase at the end of exercise), with circulatory reserve maintained (39). Notably, although the FEV1 values were even higher in the COPD/mPAP ≥40 mm Hg group than in the COPD group without PH, the 6-min walk distance (6MWD) values were drastically lower in COPD with mPAP ≥40 mm Hg. In line with previous studies (1), these findings strongly support the view that circulatory impairment in COPD patients with severe PH markedly adds to the limitation in exercise capacity. Similarly, studies in IPF patients documented the fact that the development of PH, in particular with mPAP values ≥35 mm Hg, resulted in significantly lower values for capacity of lung to diffuse carbon monoxide and arterial oxygenation at rest, lower exercise capacity, and decline of arterial oxygenation upon exercise, independent of lung function tests (2,12,17).

Notably, IPAH patients may also display mild to moderate ventilatory impairment in the absence of any evidence of lung airway or parenchymal disease, mainly in the form of airway obstruction (42–45). In the largest of these studies (171 IPAH patients; mean age 45 years; mean PVR 1,371 dynes $\times$ s $\times$ cm^{-5}), the mean FEV1 was 83% of predicted value, and the FEV1/VC (Forced Expiratory Volume in 1 s/ Vital Capacity) ratio was 76%; in 22% of the total IPAH patients, the FEV1/VC ratio was below 70% (45). Against this background, randomized controlled trials in the field of PAH set exclusion criteria using pulmonary function testing in the following ranges: total lung capacity <60% to 70% of predicted values; FEV1 values <55% to 80% of predicted values; or FEV1/FVC ratio <50% to 70%.

Moreover, lung diseases (in particular COPD) are common conditions, and development of PAH in such patients may not necessarily be the result of these diseases (definition group 3 PH patients) but may be coincidental. When there is uncertainty in the classification of a patient with lung disease and PH to group 1 (PAH) or group 3 (PH caused by lung disease), the patient should be referred to centers with expertise. Some suggested criteria for discrimination between group 1 and group 3 are summarized in Table 1.

Treatment of PH Caused by Chronic Lung Disease (Group 3): Evidence for Appropriate Benefit/Risk Ratio of PAH-Focused Drugs?

The underlying lung disease should be treated according to current guidelines. Within these guidelines, none of the therapeutic measures focuses on the vascular component of the disease, with the exception of long-term oxygen treatment. In COPD patients with partial pressure of oxygen in arterial blood (PaO$_2$) values <60 mm Hg, long-term oxygen treatment improved life expectancy, which might be related to its retardation of PH development (46).

In DPLD, long-term oxygen treatment is usually recommended to maintain arterial oxygen saturation >90%; however, this recommendation is not supported by a controlled trial. As for PAH-focused drugs, the current state may be summarized in the following text.

Vasoactive therapy in lung fibrosis. Any vasodilator may worsen gas exchange in lung-diseased patients because of interference with hypoxic vasoconstriction, which diverts pulmonary blood flow from more seriously to less seriously affected lung segments. However, vasodilators may preferentially access the better ventilated and oxygenated areas of the fibrotic lung because of their mode of distribution (inhaled iloprost, treprostinil, or nitric oxide [35,37,47]) or may enhance normoxic vasodilation (the phosphodiesterase 5 inhibitor sildenafil [36,48]), which may be advantageous in this respect. Long-term studies using prostanoids in lung fibrosis-associated PH are missing, however. In IPF, the nonselective endothelin receptor antagonist (ERA) bosentan was well tolerated (49–51), but failed to improve the pre-defined endpoint "time to occurrence of lung fibrosis worsening" in a phase III trial (51). Negative trial results were also reported for the selective ERA ambrisentan (ARTEMIS-IPF [Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in Idiopathic Pulmonary Fibrosis]) and macitentan (MUSIC [Macitentan Use in an Idiopathic Pulmonary Fibrosis Clinical study]) in IPF. The ARTEMIS-IPF study was terminated because of an increased rate of disease progression and respiratory hospitalization (52). Within this entire IPF group, 11% of patients presented with PH (mPAP $\geq$25 mm Hg), which did not affect the endpoint estimates. Based on these results, the European Medicines Evaluation Agency recently contraindicated the use of ambrisentan in IPF patients, regardless of the presence of PH. No results are currently available from a bosentan trial particularly focusing on IPF-associated PH (B-PHIT [Bosentan in PH in Interstitial Lung Disease]; NCT00637065).

Table 1	**Differential Diagnosis Between Group 1 (PAH) and Group 3 (PH Due to Lung Disease) PH**	
Criteria Favoring Group 1 (PAH)	**Parameter**	**Criteria Favoring Group 3 (PH Due to Lung Disease)**
Normal or mildly impaired	Ventilatory function	Moderate to very severe impairment
FEV1 >60% predicted (COPD)		FEV1 <60% predicted (COPD)
FVC >70% predicted (IPF)		FVC <70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan*	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve		Features of exhausted ventilator reserve
Preserved breathing reserve		Reduced breathing reserve
Reduced oxygen pulse		Normal oxygen pulse
Low Co/Vo$_2$ slope		Normal Co/Vo$_2$ slope
Mixed venous oxygen saturation at lower limit		Mixed venous oxygen saturation above lower limit
No change or decrease in PaCo$_2$ during exercise		Increase in PaCo$_2$ during exercise

*As to CT diagnosis, parenchymal changes linked to PVOD are to be discriminated from those associated with DPLD.† Features of exhausted circulatory reserve are also noted in severe PH-COPD and severe PH-IPF, but are then accompanied by major lung function and CT abnormalities.

Co/Vo$_2$ = cardiac output/oxygen consumption ratio; COPD = chronic obstructive pulmonary disease; CT = computed tomography; DPLD = diffuse parenchymal lung disease; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; PaCo$_2$ = partial pressure of carbon dioxide in arterial blood; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease.

Table 2	Management of PH in the Setting of Chronic Lung Disease			
Underlying Lung Disease	mPAP <25 mm Hg at Rest	mPAP ≥25 and <35 mm Hg at Rest	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	No PH No PAH treatment recommended	PH classification uncertain No data currently support treatment with PAH-approved drugs	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
COPD with FEV1 <60% of predicted IPF with FVC <70% of predicted Combined pulmonary fibrosis and emphysema on CT	No PH No PAH treatment recommended	PH-COPD, PH-IPF, PH-CPFE No data currently support treatment with PAH-approved drugs	Severe PH-COPD, severe PH-IPF, severe PH-CPFE Refer to a center with expertise in both PH and chronic lung disease for individualized patient care because of poor prognosis; randomized controlled trials required

*Lower PA pressures may be clinically significant in COPD/DPLD patients with depressed cardiac index or right ventricular dysfunction.
CPFE = combined pulmonary fibrosis and emphysema; mPAP = mean pulmonary artery pressure; other abbreviations as in Table 1.

In a small open-label study in IPF patients with PH, sildenafil was noted to improve 6MWD (53). In a controlled trial of sildenafil in advanced IPF, the primary outcome variable (proportion of patients with 6MWD increase >20%) was not met, but arterial oxygenation, DLCO, dyspnea, and quality of life improved (STEP-IPF [Sildenafil Trial Of Exercise Performance In Idiopathic Pulmonary Fibrosis]) (48). A pre-specified analysis of the available echocardiographic data from this trial (119 of 180 patients) showed that sildenafil preserved the 6MWD and improved the St. George's Questionnaire score compared with placebo in the subgroup of 22 patients with right ventricular systolic dysfunction (54). Additional evidence is expected from trials focusing on the use of sildenafil in IPF patients with associated PH (NCT00625079; recruitment status currently unknown).

Pre-clinical and clinical findings support the view that both endothelin receptor antagonists and phosphodiesterase 5 inhibitors possess marked antiproliferative capacity in the pulmonary vasculature in addition to their vasodilatory effects (55). This field is currently extended by the use of direct stimulators and activators of the soluble guanylate cyclase, working even at sites with inactivated NO axis and exerting strong pulmonary vasodilatory and antiproliferative potency in experimental models of PH (56). Phase II and III trials in both PAH and chronic thromboembolic pulmonary hypertension (CTEPH) patients demonstrated the efficacy of the soluble guanylate cyclase stimulator riociguat in improved exercise capacity (primary outcome variable) and several secondary endpoints (57–60). A recent phase II trial missed the primary endpoint (reduction in PAP) but demonstrated the efficacy of riociguat in decreasing PVR but also systemic vascular resistance and in increasing cardiac output and 6MWD in PH-DPLD (61); a randomized controlled trial focusing on PH-DPLD is in preparation.

Occasional cases of improved hemodynamic data and, more rarely, clinical improvement with PH-specific therapy in CPFE patients have been reported (19,62). Randomized controlled trials are currently missing.

Vasoactive therapy in COPD. In COPD, pulmonary vasodilation without deterioration of gas exchange is more challenging than in lung fibrosis caused by the presence of low ventilation/perfusion ratio areas (63). Inhaled prostanoids may acutely reduce mPAP and PVR while largely maintaining gas exchange in PH-COPD (64); however, long-term clinical trials have not been reported. In COPD patients with mild PH, bosentan caused deterioration of gas exchange with lack of improvement in peak oxygen uptake, exercise capacity, and quality of life in a small randomized controlled trial (65). In 1 small trial, improved exercise capacity upon treatment of PH-COPD patients with bosentan was reported (66). Robust data for the effect of ERAs on pulmonary hemodynamics and exercise tolerance in PH-COPD are thus lacking.

Short-term administration of sildenafil in PH-COPD improved hemodynamics but deteriorated gas exchange (67). One month of sildenafil treatment in COPD patients without PH did not affect 6MWD and VO2 peak but worsened arterial oxygenation and quality of life (68,69). A recent randomized controlled trial of sildenafil added to pulmonary rehabilitation also failed to show improvement in exercise tolerance in COPD patients without severe PH (70). In contrast, 1 small randomized controlled trial reported a decrease in PAP, accompanied by an increase in 6MWD, upon long-term use of sildenafil in patients with severe PH-COPD (71). Thus, there is definitely a lack of evidence of a long-term beneficial effect of sildenafil in COPD patients in the absence of severe PH, whereas the impact of this agent on severe PH-COPD is still not settled.

When assessing the acute effects of riociguat in PH-COPD, improvement of pulmonary hemodynamics without major deterioration of gas exchange (multiple inert gas elimination technique technology) was noted (H.A. Ghofrani et al., nonpublished results, October 2013), thus warranting future studies in this indication.

Recommendations for COPD and Lung Fibrosis

Long-term randomized controlled trials focusing on patients with severe PH and chronic obstructive or restrictive lung diseases are needed. Only such an approach will provide reliable data for the use of PAH-approved drugs in these

patients. In such studies, obstructive and restrictive lung diseases should be investigated separately because of the major differences in underlying pathophysiology. Based on lung function testing, cardiopulmonary exercise testing, and clinical and CT evidence for lung airway or parenchymal disease and severity of PH, the following groups of PH patients are to be distinguished with respect to classification and therapy recommendations (Table 2):

1. Patients with milder forms of obstructive or restrictive lung disease and minor impairment of lung function testing, in whom CT analysis shows no gross parenchymal or airway abnormalities and who present with clinically relevant PH should be specified. Whether such patients have PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) is a diagnostic dilemma (see the previously mentioned conditions). Therefore, these patients should be referred to an expert unit, where a comprehensive diagnostic workup should be made, including high-resolution CT, hemodynamics, complete lung function testing, and detailed cardiopulmonary exercise testing. Chance association of PH is much less likely in IPF than in COPD.

2. Patients with more severe obstructive or restrictive lung disease (IPF with FVC <70% predicted; COPD with FEV1 <60% predicted) and accompanying less severe PH (mPAP ≥25 mm Hg and <35 mm Hg; PH-COPD, PH-IPF) and patients with combined pulmonary fibrosis and emphysema and accompanying PH (mPAP ≥25 mm Hg and <35 mm Hg; PH-CPFE; lung volumes may be preserved in these patients) should be classified. This group represents the majority of patients presenting with chronic lung disease and PH. Here, no data currently support therapy with PAH-approved drugs. Moreover, as the limitation in exercise capacity in these patients is largely based on ventilatory and not circulatory impairment, any benefit from PAH treatment is questionable. In addition, vasodilators may impair gas exchange, particularly in COPD. This does not exclude the fact that vascular changes may contribute to disease progression and may become a future therapeutic target from this angle, but controlled clinical trials addressing this topic are currently missing.

3. Patients with more severe obstructive or restrictive lung disease or a combination thereof and severe PH as defined in the previous text (mPAP ≥35 mm Hg; severe PH-COPD; severe PH-IPF; severe PH-CPFE) must be distinguished. These patients have a poor prognosis and should be referred to a center with expertise in both PH and chronic lung disease for individualized patient care. In some of these patients, a detailed analysis of hemodynamics may suggest that a low or low normal cardiac output (baseline conditions) and/or an inadequately increasing cardiac output upon exercise testing may substantially contribute to the limitation of peak oxygen uptake and, thus, physical activity and that the augmented right heart afterload is the main cause for the hemodynamic compromise. These patients should preferably be included in randomized controlled trials if available. In addition, for the time being, use of a PAH-approved drug on a compassionate treatment basis may be considered for this subpopulation, with thorough monitoring of gas exchange (PaO_2, $PaCO_2$) and inclusion in prospective registries. Gas exchange may be found to be deteriorated (caused by interference with the hypoxic vasoconstriction) or improved (caused by normoxic vasodilatation and higher central venous oxygen saturation upon drug-induced CI increase).

4. Patients with end-stage obstructive or restrictive lung diseases or a combination thereof should be included. In these patients, any use of PAH-approved drugs was hitherto largely discouraged because of limited life expectancy. However, the recent finding that bridging to transplantation may include the use of "awake extracorporeal membrane oxygenation" (extracorporeal membrane oxygenation) (72) and that long-term noninvasive (nocturnal) home mechanical ventilation may substantially prolong the life expectancy of these patients challenges this view. Controlled trials should address the question whether PAH-approved drugs may improve exercise capacity and quality of life, prolong time to clinical worsening, and improve survival or bridging to transplantation in patients with end-stage obstructive or restrictive lung diseases and accompanying PH receiving mechanical ventilatory or extracorporeal membrane oxygenation support.

Specific Aspects of Sarcoidosis, Systemic Sclerosis, and Rare Lung Diseases

The prevalence of pulmonary hypertension in sarcoidosis (PH-SA) was approximately 5% in the only series of unselected patients (73). However, PH was reported in 47% of sarcoidosis patients with exertional dyspnea disproportionate to pulmonary function test results, with low PaO_2 and low DLCO levels, indicating the presence of PH (74) and, in up to 74% of sarcoidosis patients, listed lung transplantation (75). PH-SA has a 5-year survival of ~60% (76), with PH being an independent, poor prognostic determinant. PH may occur with little or no evidence of interstitial lung disease (75), reflecting considerable pathophysiologic heterogeneity. Mechanisms contributing to the pathogenesis of PH-SA include fibrotic ablation of the pulmonary vasculature, extrinsic compression of the central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, pulmonary veno-occlusive disease, left ventricular dysfunction, portopulmonary hypertension, and an intrinsic sarcoid vasculopathy caused by granulomatous invasion of pulmonary vessels (76). The management of PH-SA includes treatment of the underlying sarcoidosis, reversal of resting hypoxemia, and referral for lung transplantation in selected patients. As to vasoactive therapy, acute and chronic improvements in pulmonary hemodynamics and exercise capacity have been reported for inhaled NO, intravenous epoprostenol, bosentan, sildenafil, and inhaled iloprost (77–79); however, larger controlled trials are missing. Referral of patients with PH-SA to expert centers is strongly recommended, with treatment decisions made on a case by case basis.

Patients with systemic sclerosis occasionally develop both pulmonary fibrosis and PH, with hemodynamic characteristics generally comparable to that of IPAH (80). Whether PH should be classified as group 1 or 3 in this setting is often unclear and should be judged in expert centers. Only retrospective studies regarding PAH therapy are available in patients with systemic sclerosis, PH, and interstitial lung disease, with unclear benefit (81).

For patients with rare lung diseases, in whom any randomized controlled trial is very unlikely to be undertaken in the near future, registries are strongly encouraged to provide reliable data about the prevalence of PH in these populations and to provide a hypothesis as to whether PAH-focused therapy might be of any clinical benefit. Individual responses to treatment with PAH-approved drugs were reported for patients with severe kyphoscoliosis (82), obesity-hypoventilation syndrome (24), Langerhans cell granulomatosis (25,26), and advanced lymphangioleiomyomatosis (27).

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REFERENCES

1. Chaouat A, Bugnet A-S, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:189–94.
2. Andersen KH, Iversen M, Kjaergaard J, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant 2012;31:373–80.
3. Carlsen J, Hasseriis Andersen K, Boesgaard S, Iversen M, Steinbrüchel D, Bøgelund Andersen C. Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. J Heart Lung Transplant 2013;32:347–54.
4. Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. J Heart Lung Transplant 2012;31:557–64.
5. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Hirth C, Roegel E. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 1984;130:993–8.
6. Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. N Engl J Med 1972;286:912–8.
7. Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 1995;107:1193–8.
8. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med 2012;367:913–21.
9. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest 2007;131:650–6.
10. Kimura M, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration 2013;85:456–63.
11. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008;31:1357–67.
12. Minai OA, Santacruz JF, Alster JM, Budev MM, McCarthy K. Impact of pulmonary hemodynamics on 6-min walk test in idiopathic pulmonary fibrosis. Respir Med 2012;106:1613–21.
13. Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respiration 2008;76:288–94.
14. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 2007;30:715–21.
15. Zisman DA, Ross DJ, Belperio JA, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2007;101:2153–9.
16. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129:746–52.
17. Boutou AK, Pitsiou GG, Trigonis I, et al. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. Respirology 2011;16:451–8.
18. Corte TJ, Wort SJ, Wells AU. Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. Sarcoidosis Vasc Diffuse Lung Dis 2009;26:7–19.
19. Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010;35:105–11.
20. Cottin V, Nunes H, Brillet P-Y, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26:586–93.
21. Mejía M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136:10–5.
22. Shlobin OA, Nathan SD. Management of end-stage sarcoidosis: pulmonary hypertension and lung transplantation. Eur Respir J 2012;39:1520–33.
23. Dobarro D, Schreiber BE, Handler C, Beynon H, Denton CP, Coghlan JG. Clinical characteristics, haemodynamics and treatment of pulmonary hypertension in sarcoidosis in a single centre, and meta-analysis of the published data. Am J Cardiol 2013;111:278–85.
24. Friedman SE, Andrus BW. Obesity and pulmonary hypertension: a review of pathophysiologic mechanisms. J Obes 2012;2012:505274.
25. Le Pavec J, Lorillon G, Jaïs X, et al. Pulmonary Langerhans Cell Histiocytosis associated pulmonary hypertension: clinical characteristics and impact of pulmonary arterial hypertension therapies. Chest 2012;142:1150–7.
26. Kiakouama L, Cottin V, Etienne-Mastroïanni B, Khouatra C, Humbert M, Cordier JF. Severe pulmonary hypertension in histiocytosis X: long-term improvement with bosentan. Eur Respir J 2010;36:202–4.
27. Cottin V, Harari S, Humbert M, et al. Pulmonary hypertension in lymphangioleiomyomatosis: characteristics in 20 patients. Eur Respir J 2012;40:630–40.
28. Berger RMF, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537–46.
29. Manika K, Pitsiou GG, Boutou AK, et al. The impact of pulmonary arterial pressure on exercise capacity in mild-to-moderate cystic fibrosis: a case control study. Pulm Med 2012;2012:252345.
30. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735–40.
31. Fisher MR, Criner GJ, Fishman AP, et al. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 2007;30:914–21.
32. Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med 2006;173:744–50.
33. Corte TJ, Wort SJ, Gatzoulis MA, et al. Elevated brain natriuretic peptide predicts mortality in interstitial lung disease. Eur Respir J 2010;36:819–25.
34. Nathan SD, Cottin V. Chapter 12. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Eur Respir Monogr 2012;57:148–60.
35. Olschewski H, Ghofrani HA, Walmrath D, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 1999;160:600–7.
36. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 2002;360:895–900.
37. Blanco I, Ribas J, Xaubet A, et al. Effects of inhaled nitric oxide at rest and during exercise in idiopathic pulmonary fibrosis. J Appl Physiol 2011;110:638–45.

38. Roger N, Barberà JA, Roca J, Rovira I, Gómez FP, Rodriguez-Roisin R. Nitric oxide inhalation during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;156:800–6.

39. Boerrigter BG, Bogaard HJ, Trip P, et al. Ventilatory and cardiocirculatory exercise profiles in COPD: the role of pulmonary hypertension. Chest 2012;142:1166–74.

40. Hoeper MM, Andreas S, Bastian A, et al. Pulmonary hypertension due to chronic lung disease: updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011;154 Suppl 1:S45–53.

41. Weinmann GG, Chiang Y-P, Sheingold S. The National Emphysema Treatment Trial (NETT): a study in agency collaboration. Proc Am Thorac Soc 2008;5:381–4.

42. Horn M, Ries A, Neveu C, Moser K. Restrictive ventilatory pattern in precapillary pulmonary hypertension. Am Rev Respir Dis 1983;128:163–5.

43. Burke CM, Glanville AR, Morris AJ, et al. Pulmonary function in advanced pulmonary hypertension. Thorax 1987;42:131–5.

44. Spiekerkoetter E, Fabel H, Hoeper MM. Effects of inhaled salbutamol in primary pulmonary hypertension. Eur Respir J 2002;20:524–8.

45. Meyer FJ, Ewert R, Hoeper MM, et al. Peripheral airway obstruction in primary pulmonary hypertension. Thorax 2002;57:473–6.

46. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1985;131:493–8.

47. Voswinckel R, Reichenberger F, Enke B, et al. Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension. Pulm Pharmacol Ther 2008;21:824–32.

48. Network TIPFCR, Zisman DA, SM, Anstrom KJ, Collard HR, Flaherty R, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010;363:620–8.

49. Günther A, Enke B, Markart P, et al. Safety and tolerability of bosentan in idiopathic pulmonary fibrosis: an open label study. Eur Respir J 2007;29:713–9.

50. King J, Talmadge E, Behr J, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:75–81.

51. King J, Talmadge E, Brown KK, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:92–9.

52. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 2013;158:641–9.

53. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 2007;131:897–9.

54. Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest 2013;143:1699–708.

55. Seeger W, Pullamsetti SS. Mechanics and mechanisms of pulmonary hypertension-Conference summary and translational perspectives. Pulm Circ 2013;3:128–36.

56. Dumitrascu R, Weissmann N, Ghofrani HA, et al. Activation of soluble guanylate cyclase reverses experimental pulmonary hypertension and vascular remodeling. Circulation 2006;113:286–95.

57. Ghofrani H, D'Armini A, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a randomized, double-blind, placebo-controlled phase 3 study (CHEST-1). N Engl J Med 2013;369:319–29.

58. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled phase 3 study (PATENT-1). N Engl J Med 2013;369:330–40.

59. Ghofrani HA, Hoeper MM, Halank M, et al. Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study. Eur Respir J 2010;36:792–9.

60. Grimminger F, Weimann G, Frey R, et al. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur Respir J 2009;33:785–92.

61. Hoeper MM, Halank M, Wilkens H, et al. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. Eur Respir J 2013;41:853–60.

62. Cottin V. Clinical case: combined pulmonary fibrosis and emphysema with pulmonary hypertension—clinical management. BMC Res Notes 2013;6 Suppl 1:S2.

63. Barbera JA, Blanco I. Pulmonary hypertension in patients with chronic obstructive pulmonary disease: advances in pathophysiology and management. Drugs 2009;69:1153–71.

64. Boeck L, Tamm M, Grendelmeier P, Stolz D. Acute effects of aerosolized iloprost in COPD related pulmonary hypertension—a randomized controlled crossover trial. PLoS One 2012;7:e52248.

65. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. Eur Respir J 2008;32:619–28.

66. Valerio G, Bracciale P, Grazia D'Agostino A. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. Ther Adv Respir Dis 2009;3:15–21.

67. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am J Respir Crit Care Med 2010;181:270–8.

68. Rietema H, Holverda S, Bogaard HJ, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Respir J 2008;31:759–64.

69. Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. COPD 2012;9:268–75.

70. Blanco I, Santos S, Gea J, et al. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial. Eur Respir J 2013;42:982–92.

71. Rao RS, Singh S, Sharma BB, Agarwal VV, Singh V. Sildenafil improves six-minute walk distance in chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. Indian J Chest Dis Allied Sci 2011;53:81–5.

72. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med 2012;185:763–8.

73. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. Chest 2006;129:1246–52.

74. Baughman RP, Engel PJ, Meyer CA, Barrett AB, Lower EE. Pulmonary hypertension in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2006;23:108–16.

75. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J 2005;25:783–8.

76. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. Thorax 2006;61:68–74.

77. Baughman RP. Pulmonary hypertension associated with sarcoidosis. Arthritis Res Ther 2007;9 Suppl 2:S8.

78. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension. A two-center experience. Chest 2009;135:1455–61.

79. Baughman RP, Judson MA, Lower EE, et al. Inhaled iloprost for sarcoidosis associated pulmonary hypertension. Sarcoidosis Vasc Diffuse Lung Dis 2009;26:110–20.

80. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179:151–7.

81. Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis and Rheum 2011;63:2456–64.

82. Hosokawa Y, Yamamoto T, Yabuno Y, et al. Inhaled nitric oxide therapy for secondary pulmonary hypertension with hypertrophic obstructive cardiomyopathy and severe kyphoscoliosis. Int J Cardiol 2012;158:e20–1.

Key Words: combined pulmonary fibrosis and emphysema ■ COPD ■ exhausted circulatory reserve ■ exhausted ventilatory reserve ■ lung fibrosis ■ pulmonary hypertension in chronic lung disease.